

Coming Full Circle: The Development, Rise, Fall, and Return of the Concept of
Anticipation in Hereditary Disease

by

Judith Ellen Friedman
B.Sc., University of Alberta, 1994
B.A. University of Alberta, 1995
M.A. University of Alberta, 1997

A Dissertation Submitted in Partial Fulfillment of the
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ABSTRACT

This dissertation examines the history of the creation and development of the concept of anticipation, a pattern of heredity found in several diseases (e.g. Huntington's disease and myotonic dystrophy), in which an illness manifests itself earlier and often more severely in successive generations. It reconstructs major arguments in twentieth-century debates about anticipation and analyzes the relations between different research communities and schools of thought. Developments in cutting-edge medicine, biology, and genetics are analyzed; many of these developments were centered in Britain, but saw significant contributions by people working in France, Germany, Switzerland, the Netherlands and North America.

Chapter one traces precursor notions in psychiatric and hereditarian thought from 1840 to the coining of the term 'anticipation' by the ophthalmologist Edward Nettleship in 1905. Key roles in the following chapters are played by several figures. Prior to World War II, these include: the neuropathologist F.W. Mott, whose advocacy during 1911-

1927 led to anticipation being called “Mott’s law”; the biometrician and eugenicist Karl Pearson, who opposed Mott on methodological and political grounds; and two politically and theoretically opposed Germans – Ernst Rüdin, a leading psychiatrist and eugenicist who came to reject anticipation, and Richard Goldschmidt, a geneticist who offered a peculiar Mendelian explanation. The British psychiatrist and human geneticist, Lionel Penrose, makes a first interwar appearance, but becomes crucial to the story after World War II due to his systematic dismissal of anticipation, which discredited the notion on orthodox Mendelian grounds. The final chapters highlight the contributions of Dutch neurologist Christiaan Höweler, whose 1980s work demonstrated a major hole in Penrose’s reasoning, and British geneticist Peter Harper, whose research helped demonstrate that expanding trinucleotide repeats accounted for the transgenerational worsening without contradicting Mendel and resurrected anticipation as scientifically legitimate. Reception of the concept of anticipation is traced across the century through the examination of textbooks used in different fields.

This dissertation argues against established positions regarding the history of the concept, including claims that anticipation’s association with eugenics adequately explains the rejection of the notion after 1945. Rejected, in fact, by many eugenicists from 1912, anticipation was used by physicians until the 1960s.

Table of Contents

Supervisory Committee	ii
Abstract	iii
Table of Contents	v
Acknowledgements	vi
Dedication	viii
Introduction	1
Chapter One: Anticipating Anticipation (1840-1910)	12
Chapter Two: A Natural Law (1910-1930)	35
Chapter Three: Seeking to Define a Mechanism (1930-1945)	72
Chapter Four: Refuting the Concept of Anticipation (1945-1970)	147
Chapter Five: Gradually Re-Conceptualizing Anticipation (1970-1990)	210
Chapter Six: Anticipation Redeemed – Discovering Expanding Trinucleotide Repeats (1991-1994)	240
Conclusion	261
Bibliography	265

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down sources both obscure and mundane. I would also like to extend my thanks to those who very kindly agreed to be interviewed for this dissertation—most especially Dr. Peter Harper, Dr. Christiaan Höweler, and Dr. Keith Johnson—and those who were interviewed for stages of the project that did not come to fruition in this dissertation. Without their recollections and comments this would have been a much poorer dissertation.

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Dedication

This dissertation is dedicated to those who encouraged me along the way but, unfortunately, did not live to see the final results of this project.

“The Gimli Girls”
Ethel, Ada, and Eva Greenberg

Dr. Morris H. W. Friedman

Dr. Robert K. Merton

Introduction

In a finding that adds a strange new twist to traditional genetics, scientists have discovered that the most common form of muscular dystrophy is caused by a gene that gradually grows bigger each time it is inherited. And the bigger it gets, the worse the disease.

The discovery about the form called myotonic dystrophy, made at the same time by three separate groups of scientists, brings to light a novel mechanism of inheritance, involving a sliding scale of genetic damage that gets more severe with subsequent generations.

This is in distinct contrast with the prevailing concept that genes are handed down through generations essentially unchanged and that either a gene is normal or that it is not...

It means, for example, that a genetic counselor may have to advise patients that they are carrying a gene that will not affect them or their children but that may cause a deadly disease in their great-great-grandchildren.

“This opens up moral social and ethical problems that were totally unanticipated,” said Dr. David Housman a molecular geneticist at the Massachusetts Institute of Technology who is a member of one of the groups that made the discovery.

Three papers describing the findings are being published today in *Nature*, a British science journal.

Geneticists describe the finding as a complete surprise.¹

New York Times 6 February 1992

This dissertation is an intellectual and social history of approaches to anticipation in hereditary disease. It covers the subject from nineteenth-century precursor notions of degeneration to the current early twenty-first century iteration involving a mutation in an unstable region of DNA. Although anticipation—the concept that in succeeding generations a disease will appear at an earlier age and often in a more severe form—has never been central to the study of heredity and medicine in the past two hundred years, examining the history of anticipation and its relationship to these disciplines throws light

¹ Gina Kolata, “Geneticists find defect worsens over generations,” *New York Times*, February 6, 1992, page A1.

on significant aspects of the development of these fields and on the diverse ways changes in “the best and most current science” can affect how a particular physical phenomenon is understood and interpreted.

The history of research on anticipation is complex and somewhat atypical in the history of scientific and medical studies of pathology. The story is unusual in that the concept itself has remained virtually unchanged since it was first clearly defined by the English ophthalmologist Edward Nettleship in 1905. However, the reception of the concept by various groups within different scientific and medical communities has varied tremendously over time. The scope of the idea of anticipation, the interpretation of evidence supporting or contradicting the existence of such a biological phenomenon, and the explanations for its possible existence or absence changed several times over the last century as prevailing scientific norms and social attitudes changed. Rather than being a completely novel subject, as the quotation from a MIT geneticist suggests, anticipation is a concept that has raised a variety of concerns for over a century.

Many Distinct, Overlapping, and Shifting Research Communities

Due to its breadth and depth, this study traces the development of anticipation through a range of research communities, some distinct and some overlapping, and over an extended period of time as these communities emerged, grew and in some cases died. This variation of research communities—many with their own approach to the question of anticipation—was caused by several factors, including: developments in science; transformations in institutions and the research programmes pursued within them; related changes in government and philanthropic funding goals; and changes in societal norms and political priorities. Interdisciplinarity is therefore inherent to this study and is inescapable in pursuing it.

During the nineteenth century, notions of directional heredity interested two main groups—psychiatrists, who assumed that degenerate heredity was caused by genetic change originating in a variety of moral and environmental factors, and scientists, some of whom felt that the concept of directional heredity might apply to good traits as well as bad ones. The early years of the twentieth century saw the concept of anticipation applied to explain a range of specific disorders from ophthalmologic diseases to mental

illness and diabetes and to explain patterns of heredity in Huntington's disease and myotonic dystrophy—two diseases with which it has remained associated until the present. Researchers examining these specific diseases also formed distinct communities, although membership in these sometimes overlapped because certain individuals researched more than one specific illness.

During the first half of the twentieth century, British psychiatrists formed one notable research community that tended to support the concept of anticipation. Their assertions that anticipation was a means by which Nature could “end or mend” a broken stock and that relatives of those with mental illness who had reached the age of twenty-five without showing signs of the disease should be free to marry and procreate drew the ire of the British biometricians who argued that the notion of anticipation was based on a statistical fallacy. Within the psychiatric community those who favoured the eugenic strategy of sterilizing the mentally deficient were at odds with those who argued that sterilization legislation was unnecessary because of anticipation.

From the mid-1930s through to the 1990s, there was also a divide between physicians and medical specialists, on the one hand, who were inclined to believe in the idea of anticipation when faced with evidence supporting it, and those with genetic training, on the other, who were unable to believe that any form of degenerate heredity could have a biological basis. In the period preceding the Second World War, the communities of geneticists and eugenicists overlapped, but after the discovery of the uses to which eugenics was put by the Nazis, geneticists gradually turned away from eugenics. Moreover, after the Second World War the field of genetics experienced a wave of great scientific change and expansion. That expansion and the concomitant series of new genetic discoveries contributed to the creation, institutionalization, and rapid development of the new fields of human, medical, and clinical genetics, all of which grew from a small and eclectic core of researchers trained in the earlier period. Each of these research communities, distinct and overlapping, had its own approach to the concept of anticipation. As these communities developed and changed over time so too did their approaches to anticipation. For this reason, in order to cover them all, the present study spans the conventional boundaries of the history of science and the history of medicine

Historiographical Perspectives and Conceptual Artefacts

Just as the story of anticipation cannot be fully circumscribed within the bounds of either the history of science or the history of medicine, so too have drawn on tools and approaches from a variety of historiographical and methodological traditions. This dissertation is the first extended historical study of the concept of anticipation in hereditary disease. It presents and analyzes a great deal of information that has been left out of the story of anticipation by scientific-medical researchers and by sociologists of science and medicine. Previous examinations of the subject have been constrained either by the short temporal period examined or by the restricted design and content of the study. The story of the concept of anticipation reaches across more than one hundred and fifty years and crosses through the fields of psychiatry, biology, medicine, eugenics, and genetics. For this reason my primary approach has been a medical, scientific, social, and intellectual history of the subject contextualized against the background of the relevant scientific, medical, institutional, social, and political events of the period. Because the story of anticipation extends into the very recent past, chapters five and six, which deal with the most recent periods, are affected by difficulties common to the study of contemporary history—i.e. lack of archival or documentary material against which to check memory-based accounts, few published retrospectives, and little primary and secondary historical material to draw on.

One of the difficulties posed by examining concepts of hereditary disease over such a lengthy time period is that even the names and the definitions of concepts and the disciplines have undergone significant and far-reaching changes conceptually and institutionally. Even the names of the diseases examined have undergone significant changes. For example, as Hans-Jörg Rheinberger and his colleagues have shown, our modern concept of heredity did not exist before the mid-nineteenth century. Furthermore, there was considerable overlap, both in terms of the researchers involved and in terms of the concepts used between the “fields” of eugenics and genetics during the first half of the twentieth century. Indeed, the shift in nomenclature used by those engaged in the study of human heredity after the Second World War—even if a wholesale change in their opinions did not occur—remains to be fully examined by historians. In any event, the temptation to treat eugenics as a pseudoscience because of

the uses to which it was put obscures a whole range of important issues including the extent to which cutting-edge scientists in the first half of the twentieth century endorsed one aspect or other of the eugenics programme. Indeed, Pauline Mazumdar has gone so far as to argue, with good reason, that even those who opposed eugenics were forced to work within what she terms the “eugenics problematic.”

Members of a wide variety of sometimes overlapping medical and genetic specialties and sub-specialties engaged in the study of diseases associated with anticipation. This dissertation mentions the fields of human and medical genetics—two closely related fields with a sometimes overlapping membership. The former emphasises the study of the genetics behind hereditary disease while the latter engages more in clinical diagnosis and treatment. Indeed, as will be seen in chapters four and five clinical specialization could have a distinct impact upon an individual’s acceptance or rejection of the concept of anticipation. Individuals who were trained in clinical specialties such as ophthalmology or neurology were generally more accepting of the concept of anticipation than those whose training or orientation was primarily genetic in nature.

Even the very names of the diseases studied have changed over time. For example, the term *dementia praecox* has been succeeded by schizophrenia; Huntington’s chorea is now known as Huntington’s disease; and *Dystrophia myotonica* is now commonly called myotonic dystrophy although the contraction DM is sometimes still used in the literature.

One of the most important features of this study is its revelation of a nuanced model of scientific change. The story of the concept of anticipation shows that, rather than being a linear process based mainly on logical progression and successive scientific and medical discoveries, scientific change in this case involved a spiral process of falsification and resurrection in which the reception of the concept of anticipation was repeatedly affected by a combination of scientific and social factors. Finally, this study shows that the presence or absence of an established explanatory mechanism played an important role in the acceptance or rejection of the concept of anticipation.

Constructing the Narrative

In order to provide a coherent narrative, I have taken care when constructing the chapters to provide the reader first with an overview of the communities involved in the study of anticipation during the time period in question. I then move on to examine the developments taking place within those communities that might affect the reception of the concept. A central part of each chapter is the ensuing discussion of the main theoretical developments concerning the concept of anticipation. Finally, I analyze the reception of anticipation within the scientific and medical literature of the time. This last section of each chapter usually contains two sections. One section is comprised of a fairly detailed discussion of exactly how the concept of anticipation was being received and used in the study of diseases with which it was then being associated. Since the pathologies associated with anticipation have changed over time, the diseases discussed will vary from chapter to chapter. Only two diseases, myotonic dystrophy and Huntington's disease, have been associated with anticipation for almost the entire period treated in this study. Other diseases, most notably schizophrenia and diabetes, were associated with anticipation early in the twentieth century and again became associated with it after the discovery of anticipation's biological basis in the early 1990s. The second section in these chapters details the reception of anticipation within textbooks used most commonly in pure genetics and human, medical, and clinical genetics, but in the first half of the dissertation they also include psychiatric textbooks which examined the question of mental deficiency.

Due to the complex nature of the history of anticipation, I structured my narrative temporally rather than thematically—although thematic discussions do appear within each chapter. The first chapter covers the years from 1840 to 1910 and examines the important precursor notions to anticipation and the naming and definition of the concept by Edward Nettleship. The second chapter concentrates on the development and popularization of anticipation by other early twentieth-century researchers: it begins in 1910 when Nettleship suggested the idea of anticipation to the British neuropathologist Frederick Walker Mott, who became the idea's strongest advocate. Chapter three covers the period between 1930 and 1945. In 1930 anticipation underwent its second period of theoretical examination and discussion. The boundary between chapter three and chapter

four is the return of Lionel Penrose from Canada to Britain to take up the Galton Chair of Eugenics at the University of London. As chapter four details, between 1945 and 1970, Penrose's opinion of rejecting anticipation rose to dominance following the publication in 1948 of his pivotal study on anticipation in myotonic dystrophy. The period between 1970 and 1990 saw a gradual re-conceptualization of anticipation. This change was driven in part by Dutch neurologist Christiaan J. Höweler whose detailed examinations pointed out fatal flaws within Penrose's hypothesis, and in part by the discovery of inexplicable patterns of heredity in diseases with which anticipation had been associated. However, without the identification of a biological mechanism to explain these findings, anticipation remained a dubious concept. It regained legitimate scientific status in 1991 when the underlying genetic mechanism that causes anticipation—expanding trinucleotide repeats—was discovered. Chapter six details the complicated process of this discovery and traces detailed developments until 1995.

Chapters five and six differ from the earlier chapters in that changes treated in them were not as fully contextualized against social, political, and institutional developments as their predecessors. This is in large part due to the fact that comparable primary (e.g. archival) and secondary (historical) sources are yet not available in quantity. For this reason, there is a greater reliance on published papers and discussions concerning anticipation. Although most of the principles involved in these discoveries are still living—which has meant that interview material is available—it was not possible to analyze their accounts against contemporary archival sources, and much material which previous generations might have deposited in archives has, unfortunately, been destroyed. Moreover, attempting to provide a more thorough and nuanced discussion of the scientific discoveries of the 1980s that enabled the sequencing of the disease genes and the institutional developments that drove these changes would be so complex and cumbersome as to detract significantly from the primary narrative.

Synopsis of Dissertation Chapters

Chapter one explores the origins of anticipation. The idea that certain diseases run in families has ancient origins. In the mid-nineteenth century, during a period of general concern about social and medical degeneration, the French psychiatrist Prosper Lucas

noted the tendency for various diseases to manifest earlier in succeeding generations within certain families. This idea was taken up by later psychiatrists (Bénédict Morel and Henry Maudsley) who applied it to mental illness and various other diseases, while leading authorities on heredity (Charles Darwin, Francis Galton, and August Weismann) were also influenced by Lucas' ideas. In 1905, the British ophthalmologist Edward Nettleship drew on both of these research streams when he formulated the concept of anticipation. Nettleship, whose work analysing pedigrees for hereditary diseases was respected by biometricians and Mendelians alike, sought to popularize this concept. Of the various researchers who adopted the notion of anticipation the most important was Frederick W. Mott.

Chapter two examines how F. W. Mott developed and popularized the concept of anticipation. This British neuropathologist had already been studying heredity in mental illness using the psychiatric conception of the degeneration of weak family lines as propounded by Morel and Maudsley. Nettleship's concept of anticipation provided Mott with a mechanism to explain his finding that mental illness sometimes appeared earlier in succeeding generations. Beginning in 1911, Mott published prolifically on anticipation, presenting it first as a "rule" and then as a "law" of heredity. Mott's application of his "law of anticipation" to cases of hereditary insanity, however, annoyed some prominent eugenicists. While Mott declared that if individuals from afflicted families reached a certain age they might safely marry, many eugenicists, including the biometrician Karl Pearson, felt that this was foolhardy advice. As early as 1912, first Pearson and then his student David Heron put forth arguments treating anticipation as merely a statistical fallacy. In spite of these complaints, Mott and a variety of other researchers continued over the following years to apply the concept of anticipation to a variety of illnesses including Huntington's disease, myotonic dystrophy, diabetes, cataract, and schizophrenia.

Discussions prompted by the British Eugenics Society's campaign for voluntary sterilization legislation beginning in 1930 provided the framework for the next set of theoretical discussions concerning anticipation; these are examined in chapter three. In the early 1930s, a group of unlikely bedfellows was arguing against anticipation. Eugenicists, including Pearson and members of the British Eugenics Society such as the

psychiatrist Arthur Paterson, continued to argue vociferously against anticipation, citing the same kinds of statistical errors and fallacies that had been levelled against anticipation over fifteen years earlier. At this time, anti-sterilization activists used Mott's conception of anticipation to argue against the proposed legalised sterilization of the unfit that the Eugenics Society supported. These anti-eugenicists held that Nature was already working to end or mend degenerate stocks by means of anticipation. Opposition to sterilization was widespread. A. F. Tredgold, who normally supported the eugenic programme, was leery of legislating sterilization, for a variety of reasons. Not surprisingly, both Labour and religious groups, particularly Catholics, were also concerned about the proposed legislation as were members of the new Left-leaning group of mathematically trained Mendelians that was beginning to rise to scientific prominence.

The strongly anti-eugenicist Lionel Penrose began what became a decades-long campaign against anticipation in the early 1930s. Penrose viewed the concept of anticipation as one of many outdated modes of inheritance advocated by eugenicists. He sought to raise the standard of human genetics by introducing ideas based on the new analytical techniques offered by mathematical Mendelism, which had recently been introduced to England. Various researchers attempted to explain anticipation within the new context of mathematical Mendelism, but none was successful. Despite the arguments raised against anticipation by the unlikely threesome of Pearson, Paterson, and Penrose, physicians continued to invoke the notion to diagnose and treat certain disorders.

The return of Penrose to England to take up the Galton Chair of Eugenics at the end of the Second World War marked a major turning point in the story of anticipation, as chapter four explains. Called "the greatest living authority on human genetics" by no less an authority than J. B. S. Haldane, Penrose found himself in a uniquely influential position to put forward his ideas dismissing anticipation after the war. At the same time, the eugenicists and anti-eugenicists who had once been interested in anticipation because of how they thought it affected the campaign to sterilize the unfit, faced a new political reality. In the wake of the Second World War, public discussions of sterilization and related topics became less frequent, though the scientific issues involved remained alive. Penrose marshalled and honed his arguments against anticipation over the next few years.

This work culminated in his influential 1948 paper in which, using data from studies of myotonic dystrophy—long associated with anticipation—he argued that the appearance of anticipation was merely an experimental artefact and not a real biological phenomenon. Couched in the language of Mendelian inheritance, backed up by extensive mathematical and statistical analyses, and flawlessly logical (if not entirely supported by experimental evidence), Penrose's arguments dismissing perceptions of anticipation soon came to function as a paradigm for researchers, particularly in the growing fields of human and medical genetics. A few individuals who had been educated before the war continued to advocate for the biological reality of anticipation. In general, however, researchers increasingly explained away observations that had once been seen as evidence of anticipation in conditions such as Huntington's disease and myotonic dystrophy.

By the late 1960s and early 1970s, improvements in medical technology led to the increased recognition of congenital or juvenile forms of Huntington's disease and myotonic dystrophy. Chapter five examines the ways in which these discoveries forced the re-conceptualization of anticipation between 1970 and 1990. In the 1970s, congenital and early onset forms of Huntington's disease and myotonic dystrophy became increasingly well characterized, and a quirk was noted that did not seem to fit in with generally accepted notions of heredity. It was found that only one parent transmitted the forms of both diseases with the earliest age of onset; the father in the case of Huntington's disease and the mother in the case of myotonic dystrophy. When these findings could no longer be explained away as being caused by ascertainment bias or as an experimental artefact, a variety of genetic and other mechanisms were postulated as explanations. These included the existence of separate mutations, the influence of an additional gene or genes, the expression of maternal factors including cytoplasmic and mitochondrial inheritance effects, the operation of intra-uterine factors, and the influence of genomic imprinting or methylation. The work of the Dutch physician and researcher Christiaan Höweler became vital in leading to the reappraisal of anticipation as a real biological condition. In his multi-generational analysis of several families with myotonic dystrophy, Höweler was able in the early 1980s to lay to rest arguments that had been used to dismiss anticipation since the time of Penrose. A few geneticists, such as the

influential British geneticist Peter Harper, then came to embrace Höweler's assertion that anticipation was a real biological phenomenon. However, without a mechanism to explain how anticipation worked biologically, this idea remained controversial within the scientific community.

The discovery of this genetic mechanism in the early 1990s is covered in detail in chapter six. The great breakthrough in the acceptance of anticipation occurred when technological developments in the late 1980s and early 1990s made possible the isolation and sequencing of genes associated with various diseases. When the gene for fragile-X syndrome (a genetic form of mental retardation in which anticipation had been noted) was sequenced in 1991, the mutation was found to be an expanding trinucleotide repeat. Essentially, the larger the repeat the worse the manifestation of the disease; and, as an unstable region of DNA, the trinucleotide repeat domain tended to expand over successive generations. Finally, a mechanism had been found that explained anticipation within a Mendelian framework. The ensuing discovery of similar expanding trinucleotide repeats in other disorders that had been associated with anticipation, principally myotonic dystrophy and Huntington's disease, cemented scientific acceptance of this unusual form of heredity. Anticipation quickly moved from the realm of supposition and speculation to the status of fact in the field of human genetics.

Since 1995 anticipation has again entered into the common parlance of medicine. The idea of anticipation in hereditary disease is, however, not without controversy. Anticipation has been associated with mental disease since its origins, and the discovery of expanding trinucleotide repeats within genes associated with various medical conditions in the early 1990s has led some researchers to posit similar mechanisms for conditions such as schizophrenia and diabetes, for which no gene has been so far discovered. These researchers argue that their pedigree results indicate anticipation is occurring within various diseases; others argue, however, that in the absence of a gene containing an expanding trinucleotide repeat, anticipation cannot be affirmed.

With the solid acceptance of anticipation in certain medical disorders, arguments about anticipation in hereditary disease have come full circle in the last century.

Chapter 1: Anticipating Anticipation (1840-1910)

MODERNIZING AN ANCIENT IDEA

Ancient, medieval and early modern medical thinkers all realized that the inheritance of certain diseases had a tendency to run in families. In the early modern period, physicians tended to class diseases that they were unable to treat as hereditary illnesses. Some wrote books advising those seeking to wed to examine the medical histories of their prospective partner's families, so as to avoid marrying into a family with hereditary illnesses. These concerns again rose in the mid-nineteenth century, when political and economic upheavals led to a more general concern that human beings and society alike were degenerating rather than moving forward. French physicians in particular believed that they could contribute to the nation state (and advance their social and political standing) by understanding the causes of and developing treatments for such types of degeneracy. One of these physicians, the alienist Prosper Lucas,¹ produced an encyclopaedic work on heredity that would influence both scientists and physicians interested in questions of heredity for years to come. In it he argued that there was a tendency, in certain cases, for diseases to appear earlier in children than in their parents. His insight became the seed idea for the concept of anticipation.

Lucas' idea that disease could appear earlier in succeeding generations was taken up and developed by two separate groups—physicians interested in psychiatric illness, and scientists interested in the broader questions of heredity. The French alienist Bénédict Augustin Morel developed Lucas' idea within the framework of degeneration into what he termed degenerate heredity. This concept in due course was taken up and expanded upon by later psychiatrists, including Henry Maudsley and Alfred Frank Tredgold, and would be known more widely as the neuropathic diathesis. Lucas' ideas also influenced those who were more interested in general heredity. Charles Darwin,

¹ "Alienist" was the name given to early French psychiatrists. For a recent examination of how the French alienists dealt with the recognition of the hereditary nature of insanity see, Laure Cartron, "Degeneration and 'Alienism' in Early Nineteenth-Century France," in *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870*, Eds., Staffan Müller-Wille and Hans-Jörg Rheinberger, (Cambridge MA: The MIT Press, 2007), 155-174.

Francis Galton, and August Weismann—some of the most influential thinkers on heredity in the late nineteenth and early twentieth centuries—were all affected by Lucas’ work.

In 1905, the British ophthalmologist Edward Nettleship gathered together these different strands of thinking and coined the term *anticipation* to refer to the tendency for certain hereditary diseases to occur earlier in succeeding generations. Although he was unable to explain how anticipation worked by using either Galtonian, Mendelian, or Weismannian modes of heredity, Nettleship eagerly shared his discovery with other researchers examining the relationship between heredity and disease.

EARLY THOUGHT CONCERNING HEREDITARY DISEASES

Ideas about the heritability of certain diseases date back at least to the time of the ancient Greeks. The Hippocratic writings contain several comments concerning the hereditary nature of disease in general, and tuberculosis and asthma in particular.² The physician Galen likewise endorsed this notion and he drew on the writings of Hippocrates and Aristotle to describe various hereditary “constitutions” and their related predispositions to certain diseases.³ Later, medieval rabbinical writers developed formal opinions regarding the inheritance of disease and whether or not affected individuals should be allowed to marry if they risked passing on a disease to their children.⁴ Seventeenth century British medical dictionaries refer to hereditary constitutional illnesses which included gout, consumption (tuberculosis), and the Stone (kidney stones).⁵ The historian J. C. Waller has outlined how, in the eighteenth and nineteenth centuries, British doctors began to write manuals that advised individuals looking to marry to think carefully about their

² G. E. R. Lloyd, ed., *Hippocratic Writings* (London: Penguin Books, 1983), 161-2, 240-2.

³ During the medieval period, the Salerno School elaborated on these ideas and the notion of one’s hereditary diathesis—and the related illnesses associated with it—continued to be part of the medical corpus into the early twentieth century. See for example, R. Bennet Bean, “Human Types in Relation to Medicine,” *American Naturalist* 61 no. 673 (March 1927): 160-172. See also Carlos López-Beltrán, “Forging heredity: From metaphor to cause, a reification story,” *Studies in History and Philosophy of Science* 25 no. 2 (April 1994): 211-212, 214-215. See also, Staffan Müller-White and Hans-Jörg Rheinberger, “Heredity—The Formation of an Epistemic Space,” in *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870*, Eds., Staffan Müller-Wille and Hans-Jörg Rheinberger, (Cambridge MA: The MIT Press, 2007), 3-34.

⁴ The transmission of the bleeding disease now known as hemophilia is discussed in the Talmud and in later rabbinic writings. Prohibitions against marriage into families containing epileptics or lepers were also included in the Talmud. Some commentators even banned marriages between first cousins and between uncles and nieces due to concern about the production of defective offspring. Fred Rosner, “Judaism, Genetic Screening and Genetic Therapy,” *Mt. Sinai Medical Journal* 65 no. 5&6 (1998): 407-409.

⁵ López-Beltrán, “Forging Heredity,” 221-223.

prospective partner and to look at their family to see whether they had any hereditary diseases or predispositions towards particular illnesses.⁶ Once established in a line, these authors suggested, such a hereditary predisposition was almost impossible to remove and difficult or impossible to treat.⁷ At the same time, physicians were likely to class those diseases that they were least able to treat, such as phthisis (tuberculosis) and gout, as hereditary illnesses and therefore inherently untreatable.⁸

Beginning in the late eighteenth century, the European scholars Maupertuis, Buffon, Bonnet, and Haller began researching questions of heredity.⁹ In the nineteenth century, French physicians became more concerned with the role of heredity in disease.¹⁰ The historian Carlos López-Beltrán notes that the increasing number of medical dissertations after 1815 concerned with heredity and disease was followed by a shift in terminology from the adjectival form in “les maladies héréditaires” to the substantive in the phrase “L’Hérédité dans les maladies.”¹¹ From 1830 onwards “hérédité” was a common term in France.¹²

As the nineteenth century progressed, social and economic upheavals in Western Europe contributed to an increasing sense of ambivalence towards progress and to an outright concern among certain groups that the nation-state as well as the individuals who made up the nation were suffering from moral and physical decay. The increasing number of individuals diagnosed as mentally ill was seen to be a hallmark of this decay. Physicians in revolutionary and post-revolutionary France believed that they could use their skills to better the nation-state. The historian Ian Dowbiggin argues that between 1840 and 1890 the development of “the theory of morbid heredity enabled French

⁶ John C. Waller, “Ideas of Heredity, Reproduction and Eugenics in Britain, 1800-1875,” *Studies in History and Philosophy of Biological and Biomedical Sciences* 32 no. 3 (2001): 457-489.

⁷ John C. Waller, “Poor Old Ancestors: The Popularity of Medical Hereditarianism, 1770-1870,” in *A Cultural History of Heredity II: 18th and 19th Centuries*, Preprint 222 (Berlin: Max-Planck-Institut für Wissenschaftsgeschichte, 2003), 131-132.

⁸ John C. Waller, “‘The Illusion of an Explanation’: The Concept of Hereditary Disease, 1770-1870,” *Journal of the History of Medicine* 57 (October 2002): 410-448.

⁹ López-Beltrán, “Forging Heredity,” 218-221.

¹⁰ Matthew Cobb, “Heredity before genetics: a history,” *Nature Reviews Genetics* 7 (December 2006): 957.

¹¹ Carlos López-Beltrán, “Human Heredity 1750-1970; The Construction of a Domain,” (PhD Thesis, King’s College University of London, 1992), 12-13.

¹² López-Beltrán, “Human Heredity 1750-1870,” 12. For a more up to date and condensed version of this argument see, Carlos López-Beltrán, “The Medical Origins of Heredity,” in *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870*, Eds., Staffan Müller-Wille and Hans-Jörg Rheinberger, (Cambridge MA: The MIT Press, 2007), 105-132.

psychiatrists to adapt to changing socio-political circumstances and quell internecine struggle.”¹³ Accordingly, the link between heredity, environment, disease, and mental illness caught the interest to the early French psychiatrists, known as alienists, after 1840.¹⁴

Lucas and Natural Heredity

Prosper Lucas set out to collect and synthesize all previous work on heredity in his two-volume work, *Traité philosophique et physiologique de l'hérédité naturelle* (1847-1850).¹⁵ Lucas took an encyclopaedic approach to the topic, gathering and collating case histories recorded by previous workers. His ideas on heredity in general and on heredity in various illnesses had a great deal of impact on future researchers working both on general heredity (Charles Darwin, Francis Galton, and August Weismann) and on specific disorders including mental illness (B. A. Morel and Henry Maudsley), several of whom would formulate concepts that fed into the idea of anticipation. In fact, López-Beltrán argues, it was principally through the work of Lucas that the term heredity made its way into the work of English naturalists such as Spencer and Darwin.¹⁶

In his discussion of the influence of age, place, and weather on the heredity of morbid diseases, Lucas noted that in certain hereditary illnesses it was common for children to be affected by the disease at the same age as their parents. However, in some cases the child suffered the illness at an earlier age. Lucas thought this earlier onset could be caused either by a predisposition in the child in whom the disease could be accelerated or slowed down (depending on circumstances) or by the actual mode of

¹³ Ian Dowbiggin, “Degeneration and hereditarianism in French mental medicine 1840-90: psychiatric theory as ideological adaptation,” in *The Anatomy of Madness: Essays in the History of Psychiatry*, Volume I: People and Ideas, edited by W. F. Bynum, Roy Porter, and Michael Shepherd, (London: Tavistock Publications, 1985), 188-189, 213-220.

¹⁴ See especially Daniel Pick, *Faces of Degeneration: A European Disorder, c. 1848-1918*, (Cambridge: Cambridge University Press, 1989); Ian Dowbiggin, *Inheriting Madness: Professionalization and Psychiatric Knowledge in Nineteenth-Century France*, (Berkeley: University of California Press, 1991), and Waller (various).

¹⁵ Carlos López-Beltrán, “In the Cradle of Heredity; French Physicians and *l'hérédité naturelle* in the Early 19th Century,” *Journal of the History of Biology* 37 (2004): 62.

¹⁶ López-Beltrán, “Forging Heredity,” 212-213.

transmission of the disease from parent to child.¹⁷ In the section of his book dealing with illnesses of the nervous system Lucas also linked heredity and mental illness.¹⁸

Although his *Traité philosophique et physiologique de l'hérédité naturelle* continued to be referenced as important by scholars for more than 60 years, Lucas' work has been largely ignored by historians of biology and psychiatry alike partly because his ideas were soon superseded by those of more prestigious thinkers such as Darwin on general heredity and Morel on psychiatric heredity.¹⁹ However, Lucas provided a common origin for notions that hereditary diseases can strike earlier in succeeding generations. Such notions were then developed separately by scientists concerned with heredity and physicians concerned with psychiatric illnesses, before the two research streams converged once more in the concept of anticipation.

Morel and Degenerate Heredity

Bénédict Augustin Morel was one of the most influential of the many French physicians and alienists in the mid-nineteenth century who turned their attention to possible connections between heredity and degenerate physical dispositions or mental illnesses.²⁰ Morel was worried by what he saw as the degenerate physical, moral, and emotional states of his working-class patients. His travels to hospitals throughout Europe in the 1840s suggested to him that this phenomenon was widespread and generally incurable.²¹ Drawing on the work of Buffon, as emended by Flourens, and on his own ideas concerning the possible causes of degeneration, Morel in the 1850s attempted to explain as degenerative the changes that he saw taking place around him.²² In his *Traité des dégénérescences de l'espèce humaine* published in 1857, many of what would become

¹⁷ Prosper Lucas, *Traité philosophique et physiologique de l'hérédité naturelle dans les état de santé et de maladie du système nerveux*, vol. 2, (Paris: J. B. Ballière, 1850), 847-854 esp. 851-854.

¹⁸ Lucas, *Traité philosophique et physiologique de l'hérédité naturelle*, 674-823 esp. 756-797.

¹⁹ López-Beltrán, "Cradle of Heredity," 63; Charles Mellon in Prosper Lucas, *Prosper Lucas's "On the Heredity of Mental Illness" [1850]*, edited and with an introduction by Charles David Mellon, translated by Linda Forge Mellon, (New Mexico: Genetics Heritage Press, 1996), 1-3.

²⁰ López-Beltrán, "Cradle of Heredity," 60-61.

²¹ Daniel Pick, *Faces of Degeneration*, 44-47.

²² Rafael Huertas, "Madness and degeneration, I. From 'fallen angel' to mentally ill," Edited by C. M. Winston, *History of Psychiatry* 3 (1992): 395-396. Jean-Christophe Coffin argues that "Morel's works can be viewed as an attempt to unify, within the emerging mental medicine, notions and issues belonging to the natural sciences, medicine and philosophy," Jean-Christophe Coffin, "Heredity, Milieu and Sin: the works of Bénédict Augustin Morel (1809-1873)," in *A Cultural History of Heredity II: 18th and 19th Centuries*, Preprint 222 (Berlin: Max-Planck-Institut für Wissenschaftsgeschichte, 2003), 153.

the hallmarks of the notion of anticipation in hereditary disease were clearly outlined for the first time. For Morel, degeneracy was not merely a matter of morbidity, whether physical or moral, but had a hereditary component that he found especially disturbing.²³

Morel believed that certain families were subject to a sort of progressive degeneration—physical, moral, and intellectual—that could, over the course of a several generations, affect the afflicted so severely as to render them sterile and incapable of transmitting their condition.²⁴ For Morel degeneracy stemmed from a variety of causes: intoxication, famine, social milieu, proximity to industry, unhealthy professions, misery, pathological genetic transformations, bad morals, congenital or acquired infirmities, and, of course, heredity.²⁵ Morel urged physicians to take a prophylactic and hygienic approach to stopping degeneration, and he warned repeatedly about the dangers of industrialization, alcoholism, and poor moral behaviour. Unfortunately, Morel believed, once degeneration had occurred the only correct treatment was to place those suffering from the relevant illnesses into an institutional environment where they could be treated and kept from passing their degeneracies along to future generations.²⁶ Morel urged physicians to press for legislation to stem the tide of this social ill. He argued for science-based legislation to prevent marriages between incompatible partners, but he also held that this would be an incomplete solution unless the afflicted were rendered incapable of transmitting their degeneration through institutionalization.²⁷

Morel's second monograph *Traité des maladies mentales*, published in 1860 for a more specialised audience of alienists, reiterated the danger of morbid and progressive heredity.²⁸ He argued that the parents of hysterics, hypochondriacs, and epileptics passed down to their children some sort of in-born taint that made the children susceptible to these illnesses.²⁹ In his view these parents must have had some kind of tendency towards a nervous temperament: irritability, violence, or some other sort of character flaw that, if

²³ B. A. Morel, *Traité des dégénérescences: physiques, intellectuelles et morales de l'espèce humaine et des causes qui produisent ces variétés maladives*, (Paris: J. B. Baillière, 1857. Reprint edition 1976 by Arno Press), 4.

²⁴ Morel, *Dégénérescences*, 4-5.

²⁵ Morel, *Dégénérescences*, 43-65. For a discussion of the importance of “milieu” in Morel's work see Coffin, “Heredity, Milieu and Sin,” 153-164.

²⁶ Morel, *Dégénérescences*, 75-78 also 354-356.

²⁷ Morel, *Dégénérescences*, 595-596.

²⁸ B. A. Morel, *Traité des maladies mentales*, (Paris: Librairie Victor Masson, 1860), ii-iii.

²⁹ Morel, *Maladies Mentales*, 514.

conditions remained unchanged, could induce the same nervous system disorders in their offspring. Again, he thought succeeding generations would eventually become so degenerate as to lead to sterility and the failure to survive.³⁰ The notions of progressive or degenerate heredity discussed in several sections of the text became very influential and were cited in psychiatric texts for more than fifty years.³¹

Darwin, Galton, and Developments in Physical Heredity and Eugenics

In the meantime, research on the general nature of heredity and its causes was advancing dramatically. In 1859 Charles Darwin's influential and controversial *The Origin of Species* opened the floodgates of discussion on connections between heredity, evolution, and natural selection.³² The role of Darwin and his work in the development of the theory of evolution, modern biology, and genetics is much discussed in a vast secondary literature but his contributions to the concept of anticipation though limited to a few references to degenerative and progressive inheritance have gone essentially unnoticed. In *The Origin of Species*, Darwin's discussion of this topic is limited to remarks such as the following:

A much more important rule, which I think may be trusted, is that, at whatever period of life a peculiarity first appears, it tends to appear in the offspring at a corresponding age, though sometimes earlier. . . . But hereditary diseases and some other facts make me believe that the rule has a wider extension, and that when there is no apparent reason why a peculiarity should appear at any particular age, yet that it does tend to appear in the offspring at the same period in which it first appeared in the parent. I believe this rule to be of the highest importance in explaining the laws of embryology. These remarks are of course confined to the first *appearance* of the peculiarity, and not to its primary cause, which may have acted on the ovules or the male element.³³

³⁰ Morel, *Maladies Mentales*, 514-516.

³¹ Morel, *Maladies Mentales*, see esp. 541-545, 637-639. Mark Lubinsky, "Degenerate Heredity: The History of a Doctrine in Medicine and Biology," *Perspectives in Biology and Medicine* 37 no. 1 (1993): 78.

³² Charles Darwin, *The Origin of Species by Means of Natural Selection* (1859), edited and with an introduction by J. W. Burrow, (London: Penguin Books, 1985).

³³ Darwin, *Origin*, 76.

Darwin expanded these ideas in his two-volume work *The Variation of Animals and Plants Under Domestication* first published in 1868. In this text, Darwin referred often and positively to Lucas' *Traité philosophique et physiologique de l'hérédité naturelle*.³⁴ Darwin also drew on the work of earlier authors and modern acquaintances alike for evidence to support his ideas regarding inheritance. Darwin cited evidence that in several disorders, including cataract and cancer, the disease could present earlier in succeeding generations.³⁵ Although this concept was mentioned in *Origin of Species* and treated at more length in *Variation*, it was not discussed in Darwin's most controversial book on human heredity, *The Descent of Man* (1871).³⁶

Francis Galton, Darwin's cousin and the man often referred to as the father of eugenics, frequently wrote on human heredity beginning in the mid-1860s when he published a two-part article "Hereditary Talent and Character" in *Macmillan's Magazine*.³⁷ His ideas were expanded in the book-length study *Hereditary Genius* (1869) that laid the groundwork for his later work on human heredity, statistics, and eugenics (the term he would coin in 1884). Galton's writings and patronage helped to establish the discipline of eugenics in Britain. This field was soon widely disseminated and adapted to cultural conditions elsewhere in Europe, North America, and other parts of the globe.³⁸

Galton's extensive published works had wide reaching significance, but for the purposes of this discussion must be confined mainly to passages that relate directly to the development of anticipation. Galton's seminal *Hereditary Genius* is often referenced as a crucial early source for arguments relating to anticipation. Lionel Penrose, who in the

³⁴ For example, he refers to the length of Lucas' work in the introduction to his chapter on inheritance. Charles Darwin, *The Variation of Animals and Plants Under Domestication*, 2 vols., (New York: D. Appleton and Company, 1896), vol. 1, 445.

³⁵ Darwin, *Variation*, vol. 1, 452-453, Vol. 2, 56-57.

³⁶ Charles Darwin, *The Descent of Man, and Selection in Relation to Sex*, in 2 vols., (London: John Murray, 1871); Charles Darwin, *The Descent of Man, and Selection in Relation to Sex*, 2nd ed. revised, (New York: D. Appleton and Company, 1883).

³⁷ Francis Galton, "Hereditary Talent and Character," *Macmillan's Magazine* 12 no. 68 (1865): 157-166, 318-327.

³⁸ There is significant literature on the history of the field of eugenics; see among others: on England Pauline Mazumdar, *Eugenics, Human Genetics and Human Failings: The Eugenics Society, its sources and its critics in Britain*, (London: Routledge, 1992); on eugenics in an Anglo-American context see Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity*, (Cambridge Mass.: Harvard University Press, 1995); for a comparison of eugenics in a continental European context see Mark Adams, ed., *The Wellborn Science: Eugenics in Germany, France, Brazil, and Russia*, (New York: Oxford University Press, 1990); on eugenics in Latin America see Nancy Leys Stepan, "*The Hour of Eugenics*" *Race, Gender and Nation in Latin America*, (Ithaca NY: Cornell University Press, 1991).

1930s became a leading opponent of the concept, went so far as to have passages of this text typed up, underlined, and starred for his own notes.³⁹ Galton's *Hereditary Genius* applied the new science of statistics to heredity and argued that mankind could take control of its own evolution by a process of selective reproduction analogous to that which was carried out by animal breeders.⁴⁰ Those who could contribute the most to society should be encouraged to breed more prolifically while those who would be a drain on society should be encouraged to have fewer children or to emigrate.⁴¹

When it came to the question of the intensification of hereditary characteristics Galton did not confine himself to the negative aspect that had been noted by previous authors. He argued that "the sons of gifted men are decidedly more precocious than their parents I do not care to quote cases, because it is a normal fact, analogous to what is observed in diseases, and in growths of all kinds, as has been clearly laid down by Mr. Darwin."⁴² For Galton it was also a well-known fact that the most gifted men rarely left many offspring due in part, he felt, to the tendency for these men to find roles within Church or University that denied them the ability to marry and have children.⁴³ Even when they did marry, he calculated, these men had fewer offspring, and he applied Prosper Lucas' comment that giants and dwarves were less fertile than normal men to draw the conclusion that the same held true at the extremes of intelligence, whether genius or imbecility.⁴⁴

Galton used his personal wealth to fund research into eugenics and founded the Eugenics Record Office (ERO) in 1905 at University College London. While it was initially separate from Professor Karl Pearson's Biometrical Laboratory, in 1906 the ERO

³⁹ Penrose Papers, University College London Archive, 77/2, no date.

⁴⁰ Francis Galton, *Hereditary Genius: An Inquiry into its Laws and Consequences*, 2nd ed. reprinted. (London: Macmillan and Co., Ltd., 1914), 1.

⁴¹ Galton, *Hereditary Genius*, 343, 346-347. Of course, Galton's notions of who might and might not be useful to society were firmly rooted in his social and economic class and his concerns about heredity were shaped by his own family tree, which included the Darwins and the Wedgewoods, as well as by his own infertile marriage. However influential they came to be, when first published Galton's ideas were by no means met with universal approval. A study of reviews written immediately after the publication of the first edition of *Hereditary Genius* reveals that Galton's ideas were generally liked by scientists, disliked by religious individuals, and felt to be impractical if interesting by general reviewers. Emil Gokyigit, "The Reception of Francis Galton's *Hereditary Genius* in the Victorian Periodical Press," *Journal of the History of Biology* 27 (1994): 215-240.

⁴² Galton, *Hereditary Genius*, 320.

⁴³ His comments regarding the clergy and divines got Galton into hot water with the religious portion of his audience. Galton, *Hereditary Genius*, 343-344.

⁴⁴ Galton, *Hereditary Genius*, 320-321.

became the Galton Laboratory for National Eugenics with Pearson as the director. The new lab was endowed from Galton's estate after his death in 1911. While Galton did not play a role in the formation of the Eugenics Education Society (1907), he did accept the post as its Honorary President in 1908.⁴⁵ The creation of these institutions and related funding bodies helped to promote what historian Pauline Mazumdar has called the "eugenics problematic" in England—a set of scientific, political, and social concerns regarding the reproductive habits of the poorest (and most prolific) members of society and the concomitant desire to enact legislation to change that pattern before it led to the downfall of (polite) society.⁴⁶

Psychiatry, Pathology, Degenerate Heredity and the Neuropathic Diathesis

During the last quarter of the nineteenth century and into the twentieth century, various psychiatrists and physicians continued to pursue the question of the contribution of heredity to mental illness. One of the most influential of these authors was the English medical psychologist Henry Maudsley. In his study *The Pathology of Mind* (1879), Maudsley clearly expressed the view that the roots of insanity in an individual might have their cause in previous generations.⁴⁷ He believed that hereditary predisposition, aggravated by life experience, was likely what lay at the root of insanity.⁴⁸ He felt that these hereditary tendencies had been recognized by ancient scholars but were often forgotten by modern men who believed that nurture could overcome the effects of nature.⁴⁹ In cases where insanity seemed to have appeared out of nowhere, e.g. in a family with no history of the illness, Maudsley argued that the parents, while themselves apparently normal, "may, by reason of their mental or bodily characters, be as unfitted to breed together successfully as if they were positively insane."⁵⁰ Maudsley called this inborn susceptibility to insanity the *neurotic diathesis* and saw links between this

⁴⁵ The Eugenics Education Society was renamed the Eugenics Society in 1926. In order to avoid confusion, I refer to this group as the Eugenics Society throughout following the convention laid out by Mazumdar. Kevles, *Eugenics*, 114; Mazumdar, *Eugenics*, throughout.

⁴⁶ Mazumdar, *Eugenics*, 1-3.

⁴⁷ Henry Maudsley, *The Pathology of Mind. Being the third edition of the second part of the "Physiology & Pathology of Mind," Recast, Enlarged, and Rewritten*, (London: Macmillan and Co., 1879), 84.

⁴⁸ Maudsley, *Pathology*, 87.

⁴⁹ Maudsley, *Pathology*, 88-90.

⁵⁰ Maudsley, *Pathology*, 95.

hereditary disposition and physical diseases including tuberculosis and diabetes.⁵¹ He thus judged Morel's example of degeneration of a family line through four generations "an instructive example of a retrograde movement of the human kind, ending in so wide a deviation from the normal type that sterility ensues."⁵²

The Scottish asylum physician Thomas Clouston, who co-edited the *Journal of Mental Science* with Maudsley, published his own text on mental disease in 1883.⁵³ In his *Clinical Lectures of Mental Diseases*, Clouston too advocated the notion of the neurotic diathesis which he felt was inherited from parent to offspring. "The facts of nature," Clouston wrote, "compel the physician to see that purely mental qualities and mental defects are transmissible from parent to child, and prepare him for the great part that heredity plays in psychological development and in mental disease."⁵⁴ Temperament and diathesis, he felt, was inherited in sons from their mother and in daughters from their father.⁵⁵ Depression was among the mental diseases that Clouston believed was strongly influenced by heredity.⁵⁶ Clouston followed Morel and Maudsley in his description of the insane diathesis, which he argued was hereditary and most likely to be exhibited in the children of insane or neurotic parents.⁵⁷

Other physicians also integrated these ideas about degeneration into their work. In 1892, the Hungarian-born newspaper correspondent and later physician Max Nordau wrote his work on degeneracy, published in English as *Degeneration* in 1895.⁵⁸ This influential critique of late-nineteenth century decadence was published in several editions in Europe and North America and was translated into a variety of languages.⁵⁹ Nordau noted that several physicians and psychiatrists, Morel among them, were concerned with "degeneration (degeneracy) and hysteria, of which the minor stages are designated as

⁵¹ Maudsley, *Pathology*, 108, 112-113.

⁵² Maudsley, *Pathology*, 113-114.

⁵³ Thomas Clouston, *Clinical Lectures on Mental Diseases*, (London: J. & A. Churchill, 1883).

⁵⁴ Clouston, *Clinical Lectures*, 10-11.

⁵⁵ Clouston, *Clinical Lectures*, 35-36.

⁵⁶ Clouston, *Clinical Lectures*, 131.

⁵⁷ Clouston, *Clinical Lectures*, 351-353.

⁵⁸ George L. Mosse, "Introduction," in Max Nordau, *Degeneration*, translated from the second edition of the German work, with an introduction by George L. Mosse (New York: Howard Fertig, 1968), xvi.

⁵⁹ Mosse, "Introduction," xvi-xvii.

neurasthenia.”⁶⁰ As part of his discussion, Nordau drew on the work of Morel and particularly on his argument that poisoning from recreational drugs and industrial and organic sources could cause progressive degeneracy in the descendants of those so affected.⁶¹ That these sorts of poisons existed in abundance in *fin de siècle* Europe was without question, he argued.⁶²

Another researcher influenced by Morel’s ideas about degeneration within families was the German pathologist Ernst Ziegler whose textbook, *General Pathology*, influenced not only German thinking but also contributed to discussion in the English-speaking world through an English translation. In the section of *General Pathology* that dealt with the inheritance of disease, Ziegler too referred to Morel’s four-generation degeneration pattern from nervous temperament and moral depravity to congenital idiocy and malformations.⁶³ His work became an important reference for later researchers interested in hereditary degeneration.

The physician Arthur Frank Tredgold, who provided Britain and North America with a series of textbooks on mental deficiency (later mental retardation) during the first two-thirds of the twentieth century, also believed in the importance of heredity to mental illness.⁶⁴ In his own research, he found “that over 80 per cent. of persons suffering from the severer grades of amentia were the descendants of a pronounced neuropathic stock.”⁶⁵ Tredgold also believed that “neuropathic diathesis” in a family stock would worsen over succeeding generations. Like Maudsley and Morel before him, he held that this

⁶⁰ Max Nordau, *Degeneration*, translated from the second edition of the German work, with an introduction by George L. Mosse (New York: Howard Fertig, 1968), 15; see also 16-33.

⁶¹ Nordau, *Degeneration*, 34.

⁶² Nordau, *Degeneration*, 34-36.

⁶³ Ziegler’s work went through several editions in German and was translated into English in the United States. Ernst Ziegler, *General Pathology*, Translated and Updated by Aldred Scott Warthin. (New York: William Wood and Co., 1908), Originally published as *Allgemeinen Pathologie* 11th ed., (Jena: Gustav Fisher, 1905), 54.

⁶⁴ The *Lancet*’s 1952 obituary of Tredgold called the 1908 edition of *Mental Deficiency* “easily the most comprehensive work on the subject which had ever appeared” and noted, moreover, that “a comparison of the eight editions of Tredgold’s textbook enables the reader to obtain a fairly complete picture of the progress made in the study of mental deficiency during the last fifty years.” I will examine a succession of editions of *Mental Deficiency* to detail the evolution in the reception of the concept of anticipation in the field of psychiatry. Although Tredgold held to his own hypothesis of *blastophthoria* (germ corruption) as the source of mental defect, as his obituary notes “he incorporated the latest findings [in the field] with admirable impartiality, in the successive volumes.” Anonymous, “Obituary: Alfred Frank Tredgold M.D. Durh., F.R.C.P., F.R.S.E.,” *Lancet* 260 no. 6735 (27 September 1952): 642.

⁶⁵ A. F. Tredgold, *Mental Deficiency (Amentia)*, (London: Ballière, Tindall and Cox, 1908), 16-17.

hereditary failing could be caused by a variety of ills including alcoholism and “consumption” (tuberculosis) and would steadily worsen over three succeeding generations until it produced full-blown mental deficiency.⁶⁶

In addition to his strictly medical work, Tredgold joined the ranks of those concerned about the supposed social danger posed by the feeble-minded, also known as the so-called “social problem group.”⁶⁷ As a member of the Eugenics Society, he was concerned that “degenerate families” were having children (often illegitimate ones) at almost twice the rate of the national average. He believed that improvements in medicine and social welfare stopped the action of natural selection and that, rather than breeding simply with other degenerates until a point of sterility was reached, “these degenerates mate with the *healthy* members of the community and thereby constantly drag fresh blood into the vortex of disease and lower the general vigour of the nation.”⁶⁸ To remedy this, Tredgold advocated the setting up of a series of “suitable farm and industrial colonies” in which “the feeble-minded would not only be happy, far happier in fact amid companions like themselves than in the outside world, but they would also contribute to their own support.”⁶⁹ In this way “society would thus be saved a portion, at least, of the cost of their maintenance, and, more important, it would be secure from their depredations and the danger of their propagation.”⁷⁰ Tredgold’s arguments are fairly representative of the ones used by other members of the Eugenics Society and by the Society as a whole when advocating for the adoption of better legislation for the control and care of the mentally deficient.⁷¹

Competing Ideas about Heredity: Galton, Weismann, and Mendel

During the last third of the nineteenth century, Francis Galton, August Weismann, and Gregor Mendel proposed three major theories of heredity, and by the first decade of the

⁶⁶ Tredgold, “The Feeble-Minded—A Social Danger,” *Eugenics Review* 1 (1909): 98-99.

⁶⁷ See for example Tredgold, “Feeble-Minded,” 97-104.

⁶⁸ Tredgold, “Feeble-Minded,” 100-102.

⁶⁹ Tredgold, “Feeble-Minded,” 104. For a discussion of developments concerning the colony project see Mathew Thomson, “Sterilization, segregation and community care: ideology and solutions to the problem of mental deficiency in inter-war Britain,” *History of Psychiatry* 3 no. 12 (1992): 473-498.

⁷⁰ Tredgold, “Feeble-Minded,” 104.

⁷¹ Mazumdar, *Eugenics*, 2.

twentieth century these three were competing for scientific dominance.⁷² Older ideas such as that of degenerate heredity were, in this context, reconfigured in order to adapt to differing perspectives offered by these new theories. The hostility of the different camps could clearly be seen in Britain where Galtonians, known as biometricians, and Mendelians fought bitterly before and during the First World War.

In the first decade of the twentieth century the three main competing theories of heredity were the Galtonian theory of ancestral inheritance, Weismannian germ-plasm theory, and Mendelian theory of unit characteristics.⁷³ At this point none of these theories had yet gained dominance over the others and some scientists actually argued that all three should be combined. Galton's theory of ancestral inheritance had as its basis the idea that each parent contributed equal amounts of genetic material to their offspring but did not hold that the hereditary material was made up of unit traits. This view allowed one to calculate mathematically the contributions of the parental, grandparental, and great-grandparental generations and so on, each ancestor contributing in specific amounts to the offspring. Galtonian heredity also lent itself to the use of statistics for the examination of blended traits such as height and tended to be adopted by statistically-minded researchers. Weismann's germ-plasm theory argued that the hereditary material consisted of particles that were located in the germ cells (eggs and sperm). At conception, the hereditary particles were combined equally from both parents in their offspring. Weismann believed that since these hereditary particles were segregated in the germ-plasm from an early point in development that the effects of the environment upon heredity were limited. Because of this genetic fixity Weismannian heredity was sometimes called "hard" heredity. Mendelian heredity—rediscovered by Hugo De Vries in 1900—was also particulate: it was based on a notion of unit characteristics which determined that hereditary traits always come in pairs and might be either dominant or recessive in nature. An inherited trait would appear dominant when

⁷² The work of each of these authors has been studied extensively by historians. This study is confined to a general description of their contributions to the field of heredity and a discussion of their direct contributions (if any) to the concept of anticipation. A historiographic analysis of works concerning these authors would seem to be a diversion from the topic at hand.

⁷³ For an older but still well respected discussion of the various theories of heredity in the late nineteenth and early twentieth centuries, see Franklin Portugal and Jack S. Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*, (Cambridge, Mass.: The MIT Press, 1977), 90-136.

the pairs are made of two dominant particles or a dominant and a recessive particle; a trait would appear recessive only when two recessive particles are present. One major difference between these last two theories was that whereas the Galtonian conception of heredity held that all ancestors contributed an equal proportion of their genetic material to their offspring, according to Weismannian and Mendelian heredity it was possible for remote ancestors to contribute no genetic material to their descendents—i.e. because of the particulate nature of hereditary traits it was possible that specific particles from particular ancestors would not be passed along to their descendents while other particles would. These new ideas did not entirely supplant older ideas of heredity, for example the idea that like begets like. Indeed, historian Pauline Mazumdar has argued that the Eugenics Society's use of pedigree research as their experimental model relied upon the continued use of this older notion of heredity.⁷⁴ Additionally, other conceptions of heredity, such as Lamarck's theory of inheritance of acquired characteristics, also remained in play.

Degeneration and Disease

Regardless of which mode of heredity they advocated, if any, several authors during this period noted the intensification of disease processes through succeeding generations. For example, the British physicians Henry Bence Jones and Frederick Pavy noted that diabetes tended to run in families and that the earlier the age of onset of the disease, the worse the outcome.⁷⁵ Xavier Galezowski, who was born in Russia but practiced ophthalmologic surgery in Paris, observed that while in *most* instances cataract appeared at the same time from generation to generation, in *some* families the cataract could appear earlier in succeeding generations.⁷⁶ The American physician Sanger Brown noted earlier ages of onset in succeeding generations in certain families with hereditary ataxia.⁷⁷ At a meeting of the London Clinical Society in 1893, Claude Wilson and Douglas Stanley

⁷⁴ Mazumdar, *Eugenics*, 3.

⁷⁵ Henry Bence Jones, "Lectures on Chemical and Mechanical Diseases and their Relationship," *Medical Times and Gazette* I (1865): 58; Frederick W. Pavy, *Researches on the Nature and Treatment of Diabetes*, 2nd ed. (London: John Churchill & Sons, 1869), 196-200.

⁷⁶ Xavier Galezowski, "De l'étiologie de la cataract," *Recueil d'Ophthalmologie* 4 (1882): 730-731.

⁷⁷ Sanger Brown, "On Hereditary Ataxy, with a series of twenty-one cases," *Brain* 15 (1892): 250-268; Ormerod and Bernhardt, "Remarks on Dr. Sanger Brown's Cases," *Brain* 15 (1892): 268-282; Sanger Brown, "The Morbid Anatomy of a Case of Hereditary Ataxy," *Brain* 20 (1897): 276-289.

described a family with hereditary enlargement of the spleen in which the symptoms appeared earlier in each of three succeeding generations.⁷⁸ In his 1903 study of several families with Huntington's disease in Germany, Heilbronner significantly noted that the disease appeared earlier in succeeding generations; consequently he classified it as a form of progressive heredity of the sort studied by Morel—i.e. a form of degenerate heredity.⁷⁹ Three years later, Dr. F. Lange from the medical clinic at the University of Tübingen noted a similar case of progressive heredity in Huntington's disease where the child was affected at an earlier age than the parent.⁸⁰ This was confirmed again in 1908 when Dr. Hans Curschmann related similar findings of progressive degeneration across generations in his study of a previously unexamined family suffering from Huntington's disease in Mainz.⁸¹ Many of these hereditary diseases, most notably diabetes, cataract, and Huntington's disease, continued to be associated with this notion of degenerative or progressive heredity until the mid-twentieth century.

Life insurance companies had also taken note of the role that heredity played not only in what they called constitutional maladies (e.g. gout, cancer, rheumatism, diabetes etc.), but also in familial dispositions to epidemic diseases (e.g. syphilis and tuberculosis).⁸² In the 1889 edition of the *Medical Handbook of Life Assurance*, readers were assured that the inheritance of both phthisis (tuberculosis) and insanity were caused by “an accumulation of heredity in several ancestors.”⁸³ Both of these illnesses were held to strengthen over succeeding generations with the disease often appearing in the children before the parents.⁸⁴ Twenty-five years after the German physician Robert Koch proved

⁷⁸ Claude Wilson and Douglas Stanley, “A Sequel to some cases showing Hereditary Enlargement of the Spleen,” *Transactions of the Clinical Society of London* 26 (1893): 163-171.

⁷⁹ E. Heilbronner, “Ueber eine Art progressiver Heredität bei Huntington'scher Chorea,” *Archiv für Psychiatrie Und Nervenkrankheiten* 36 (1903): 889-894.

⁸⁰ F. Lange, “Ueber chronische progressive Chorea (Huntington) im jugendlichen Alter,” *Berliner Klinische Wochenschrift* 43 no. 6 (5 February 1906): 153-156.

⁸¹ Hans Curschmann, “Eine neue Chorea-Huntington-Familie,” *Deutsche Zeitschrift für Nervenheilkunde* 35 (1908): 293-305.

⁸² James Pollock and James Chisholm, *Medical Handbook of Life Assurance*, 2nd ed., (London: Cassell & Company, Limited, 1889), 45-60.

⁸³ Pollock and Chisholm, *Medical Handbook*, 60.

⁸⁴ Pollock and Chisholm, *Medical Handbook*, 48-50.

in 1882 that tuberculosis had its origin in infection, the *susceptibility* of family members was still considered to be hereditary and liable to worsen over several generations.⁸⁵

In his 1907 statistical study of tuberculosis, Karl Pearson, the head of the Galton Laboratory, argued that “the discovery of the possibility of phthisical (tuberculosis) infection has led, I think, to underestimation of the hereditary factor” because most individuals could not “escape an almost daily risk of infection under urban conditions.”⁸⁶ As part of his statistical analysis of material from the Crosley Sanatorium, Frodsham, Pearson examined cases in which family histories recorded instances of tuberculosis in several generations.⁸⁷ There were several difficulties in carrying out such an analysis, Pearson noted.⁸⁸ The completeness and quality of the record always posed a difficulty.⁸⁹ Then the issue of analyzing families in which all individuals had not yet passed the “danger zone” of infection needed to be considered, as this could mean that those who might later contract the disease might be falsely recorded as healthy. This could be countered, Pearson argued, by using only completed family histories i.e. families in which all members had either died or passed the critical age.⁹⁰ One might get around this, he suggested, by studying the ancestors of individuals with tuberculosis. This, however, posed its own set of problems, most notably that “we have made a *selection* of the tuberculous individuals in the grandparental generation, namely, those in whose stocks the tuberculous diathesis was sufficiently strong for at least one grandchild to manifest tubercule.”⁹¹ Pearson also discussed the issue of earlier age of onset of tuberculosis in succeeding generations. He concluded that “the probably earlier age of onset, at least in certain cases of family history, as compared to those cases without

⁸⁵ Karl Pearson, *Drapers' Company Research Memoirs: Studies in National Deterioration II. A First Study of the Statistics of Pulmonary Tuberculosis*, (London: Dulau and Co., 1907), 24-25. Robert Olby discusses the controversy that arose in the nineteenth century between hereditarians who believed in the tubercular diathesis and the bacteriologists who argued that the disease had an external (bacterial) cause. Robert Olby, “Mendelism and the Theory of Hereditary Diathesis,” in *The History & Development of Human Genetics: Progress in Different Countries, Washington, DC, 6 October 1991*, edited by Krishna Dronamraju, (Singapore: World Scientific, 1992), 257-258.

⁸⁶ Pearson, *Statistics of Pulmonary Tuberculosis*, 3.

⁸⁷ Pearson, *Statistics of Pulmonary Tuberculosis*, 5.

⁸⁸ Pearson's analysis is discussed here in some detail because the issues that he mentioned in his 1907 study are similar to those that he raised in his 1912 criticism of F. W. Mott's utilization of the concept of anticipation. The dispute between Pearson and Mott will be covered in chapter two.

⁸⁹ Pearson, *Statistics of Pulmonary Tuberculosis*, 5.

⁹⁰ Pearson, *Statistics of Pulmonary Tuberculosis*, 6.

⁹¹ Pearson, *Statistics of Pulmonary Tuberculosis*, 6.

family history, cannot at present be definitely asserted as to be due to parental infection.”⁹² He believed that:

the earlier age of onset in the children is probably associated with the same tendency to earlier inheritance noted in cases of cancer and defective vision and possibly gout, rheumatic fever and diabetes, where the question of infection hardly arises.⁹³

While Pearson *accepted* the notion of earlier age of onset in succeeding generations at this time and within this context, by 1912, he came to disagree vehemently with the argument that insanity could be inherited with decreasing age of onset over succeeding generations.

DEVELOPING ANTICIPATION: THE WORK OF EDWARD NETTLESHIP

It was in this scientific, social, and medical context that the British ophthalmologist Edward Nettleship began his studies of heredity in the early years of the twentieth century after retiring from active practice as an ophthalmic surgeon at the Royal London Ophthalmic Hospital and St. Thomas’s Hospital in 1902.⁹⁴ Nettleship was one of those individuals who had little investment in the three major conceptions of inheritance then competing for dominance. In his quest to learn more about hereditary disease, he managed to befriend both the statistician Karl Pearson and the geneticist William Bateson who were the leaders of strongly opposed forces in the ongoing Biometric-Mendelian dispute.⁹⁵ Nettleship was thus able to adopt ideas from both the biometric (Galtonian) and Mendelian (particulate) models of heredity. In fact, he stated in 1910 that “there seems to me to be no necessary antagonism between Galton’s Law and a particulate

⁹² Pearson, *Statistics of Pulmonary Tuberculosis*, 24.

⁹³ Pearson, *Statistics of Pulmonary Tuberculosis*, 25.

⁹⁴ William Marshall, “Mr. Edward Nettleship, F.R.S.,” *Eugenics Review* 5 (April 1913): 353.

⁹⁵ Peter Harper, “William Bateson, human genetics and medicine,” *Human Genetics* 118 (2005): 145-146; Alan Rushton, “Nettleship, Pearson and Bateson: The Biometric-Mendelian Debate in a Medical Context,” *Journal of the History of Medicine and Allied Sciences* 55 (2000): 134-157; Robert Olby, “The Dimensions of Scientific Controversy: The Biometric-Mendelian Debate,” *British Journal of the History of Science* 22 (1988): 299-320. Olby argues that Bateson was instrumental in transmitting Mendelian ideas to British medical men. Olby, “Mendelism and Hereditary Diathesis,” 259-261.

inheritance such as is required by Weismann's germ plasm and Mendel's 'unit characters.'"⁹⁶

Nettleship began his work on heredity with his mind focused on those diseases with which he was most familiar—diseases of the eye. In his 1905 paper “On Heredity in the Various Forms of Cataract” he first coined the term *anticipation* in relation to the condition of hereditary cataract. Nettleship examined the pedigrees of families in which “the following cases appear to show earlier incidence or ‘anticipation’* in the younger generation.”⁹⁷ He explained the starred term “anticipation” in a note at the bottom of the page with the following definition:

* “Anticipate;” the term used in describing cases of ague in which the attack begins at an earlier hour in the day than did the attack that immediately preceded it. ... The term may be used in the present connection by substituting years for hours and, for successive attacks, persons of successive generations.⁹⁸

Nettleship had observed several instances of cataract developing earlier in succeeding generations as, he noted, had other physicians.⁹⁹ In his 1909 Bowman Lecture, he expanded upon his views about anticipation. He drew on the findings of previous researchers as well as on his own observations to affirm that anticipation seemed to be a phenomenon in the inheritance of Leber's disease, tuberculosis, diabetes, hereditary jaundice, and in at least one pedigree of hereditary ataxia.¹⁰⁰ He also discussed the difficulties involved in gathering data for and interpreting human pedigrees.¹⁰¹

⁹⁶ Edward Nettleship, “Some points in relation to the Heredity of Disease,” *St Thomas's Hospital Gazette* (March 1910): 39.

⁹⁷ Edward Nettleship, “On Heredity in the Various Forms of Cataract,” *The Royal London Ophthalmic Hospital Reports* 16 (October 1905): 190.

⁹⁸ Nettleship, “Heredity in Cataract,” 190. Nettleship adapted the term from John Bristowe, *A Treatise on the Theory and Practice of Medicine*, 7th ed., (London: Smith, Elder, 1890), 288. The *Oxford English Dictionary Online*, 2nd ed., s.v. “Anticipate.”

⁹⁹ Nettleship, “Heredity in Cataract,” 190-199.

¹⁰⁰ Edward Nettleship, *The Bowman Lecture on Some Hereditary Diseases of the Eye*, (London: Adlard and Son, 1909), 72-73. This article was also published as Edward Nettleship, “On Some Hereditary Diseases of the Eye. Being the Bowman Lecture, Delivered on Thursday, June 10th, 1909,” *Transactions of the Ophthalmological Societies of the United Kingdom* 29 (1909): 52-198.

¹⁰¹ Nettleship, *Bowman Lecture*, 78.

By 1910, Nettleship felt confident enough to discuss heredity and disease more generally before the St. Thomas's Hospital Medical and Physical Society.¹⁰² In this lecture, he acknowledged that the study of heredity in disease was complex and could be examined from a variety of points of view—the biometrical/statistical, the embryological, and the experimental. The latter, which included clinical study, was the perspective to which he felt most drawn, but he argued for a harmonization of the three main modes of heredity that were then in contestation (Galtonian, Weismannian and Mendelian). While Mendelian heredity served very well to answer many of the questions regarding hereditary diseases, Nettleship noted that there were complexities in human pedigrees with which the theory was not yet able to cope.¹⁰³ It was in this context that he discussed anticipation in cataract, Leber's disease, cystinuria, diabetes, and familial jaundice.¹⁰⁴ Although he realized that some might believe anticipation was being caused by the transmission of an acquired characteristic, Nettleship argued that:

it may probably be explained as well, or better, by assuming that certain defects, taints or vices of the system, say of the blood, are not only hereditary in the true or germinal sense, but able to produce toxic agents in the embryo which have an evil influence upon all its cells, and thus so lower their power of resistance that the innate hereditary factor has freer play and is likely to manifest itself earlier. There may also be toxic agents in the embryo that have no relation to the hereditary vice, but yet may, and probably do, act in a similar manner as excitants of the hereditary disease.¹⁰⁵

Nettleship continued his research into hereditary disease until his death in 1913.¹⁰⁶ His work in this domain was recognized by his colleagues as exemplary and set a high standard for those wishing to use pedigree analysis to examine the question of heredity in

¹⁰² Nettleship sent a copy his Bowman Lecture to F. W. Mott to introduce him to the idea of anticipation. Given Mott's work in popularizing the concept of anticipation, it is this paper, if any, of Nettleship's that is referenced by later scholars of anticipation. The 1905 paper in which he actually coined the term was not referenced by later supporters or enemies of anticipation, but only by Nettleship himself. Nettleship, "Some Points," 37.

¹⁰³ This included what would later be come known as X-linked diseases such as haemophilia in which only men suffered from a disease carried by women with no outward signs of illness. Nettleship, "Some Points," 40-48.

¹⁰⁴ Nettleship, "Some Points," 59-61.

¹⁰⁵ Nettleship, "Some Points," 61.

¹⁰⁶ Shortly before his death, Nettleship took and passed the Eugenics Society's course on "The groundwork of eugenics" which covered biology, Mendelism, and biometry. He then joined the Society's Research Committee, along with A. F. Tredgold. Mazumdar, *Eugenics*, 73-77.

disease. For this work that Nettleship was elected a Fellow of the Royal Society in 1912.¹⁰⁷ Even Karl Pearson, who would later be a severe critic of the notion of anticipation as popularised by Frederick Walker Mott, wrote favourably about Nettleship's contributions to research into hereditary diseases and expressed his hope that future researchers would show as much care with their work on human heredity as Nettleship had.¹⁰⁸

An Idea in Transition

Nettleship took an active role in spreading his ideas about heredity in disease. In addition to lecturing and publishing articles, he worked with other researchers and shared his knowledge, pedigrees, and offprints. Unsurprisingly, other ophthalmologists who saw a similar pattern in a variety of disorders, e.g. hereditary glaucoma, took up Nettleship's concept of anticipation relatively quickly.¹⁰⁹ The most important researcher with whom Nettleship communicated about anticipation, however, was the neuropathologist Frederick Walker Mott. Mott's enthusiasm in championing the idea was so energetic that later scholars were led to perceive Mott rather than Nettleship as the "father" of the idea of anticipation—a mistake that continues to this day.¹¹⁰

¹⁰⁷ Among those who proposed Nettleship for election to the Royal Society were F. W. Mott and William Bateson. Nettleship, Edward, Certificate of a Candidate for Election, EC/ Royal Society Library and Archive, Royal Society of London.

¹⁰⁸ Karl Pearson, "On the Inheritance of Mental Disease," *Annals of Eugenics* 4 (1931): 363. Pearson dedicated the second volume of his *Treasury of Human Inheritance* as the *Nettleship Memorial Volume*: "In this way the monument to Nettleship's inspiration and research will reach a wider audience and be of a more permanent character, for it shows not alone what Nettleship did but what he inspired other men to do as well." Karl Pearson, "Prefatory Note," in Julia Bell, *The Treasury of Human Inheritance*. Vol. 2. *Anomalies and Diseases of the Eye: Nettleship Memorial Volume. Part 1: Retinitis Pigmentosa and Allied Diseases Congenital Stationary Night-Blindness Glioma Retinae*, with a Memoir of Edward Nettleship by J. B. Lawford, (Cambridge: Cambridge University Press, 1922), vi.

¹⁰⁹ J. B. Lawford, "Examples of Hereditary Primary Glaucoma," *Royal London Ophthalmic Hospital Records* 17 (1907): 57-58, 60.

¹¹⁰ For example, in their historical discussions of anticipation both Penrose (1948) and Harper (1992) refer to Mott rather than Nettleship as the source of the notion of anticipation. Lionel Penrose, "The Problem of Anticipation in Pedigrees of Dystrophia Myotonica," *Annals of Eugenics* 14 (1948): 125; Peter Harper, Helen Harley, William Reardon, and Duncan Shaw, "Anticipation in Myotonic Dystrophy: New Light on an Old Problem," *American Journal of Human Genetics* 51 no. 1 (July 1992): 10. This incorrect historical view continues to appear in both scientific and historical literature. See for example, Russell L. Margolis, Melvin G. McInnis, Adam Rosenblatt, Christopher A. Ross, "Trinucleotide Repeat Expansion and Neuropsychiatric Disease," *Archives of General Psychiatry* 56 no. 11 (November 1999): 1019-1031; Edgar Jones and Shahina Rahman, "Framing Mental Illness, 1923-1939: The Maudsley Hospital and its Patients," *Social History of Medicine* 21 no. 1 (2008): 108. The belief that Mott discovered the 'law' of anticipation likewise appears in discussions of anticipation in the artistic community. See Rebecca Gordon Nesbitt,

In 1910, Mott gave the Huxley Lecture on “The Hereditary Aspects of Nervous and Mental Diseases” at the opening of the winter session series at Charing Cross Hospital in London.¹¹¹ Although this paper does not mention anticipation and apparently predates Nettleship’s communications with Mott, it has been cited as an article in which the concept of anticipation was first developed.¹¹² In this widely published lecture, Mott acknowledged that a great deal of work was being done in the field of heredity by biometricians and Mendelians alike.¹¹³ Galton’s work, Mott felt, was best suited to examine the population as a whole while Mendel’s work could be applied to individual lineages.¹¹⁴ In the case of mental illness, Mott agreed with the general notion that what was inherited was a *neuropathic tendency* and that the character of the disease (e.g. insanity, epilepsy, drunkenness, criminal behaviour etc.) was determined by the exciting cause. For this reason, he was happy to produce pedigrees linking all of these traits and showing them all as hereditary.¹¹⁵ Several hereditary studies of particular diseases (including Huntington’s disease and myotonia congenita) with neurological and often mental complications had been completed. Mott thought these offered support for more general conclusions.¹¹⁶ In his pedigrees, he dealt with examples of what he called “bad stock”:

A bad stock is where we find degeneracy, insanity, drunkenness, and criminality in the pedigree . . . , or a general low standard, mental and physical, in both stem and branches of the family tree. The general tendency is for insanity not to proceed beyond three generations, and I have only three such records. As a rule, there is either a regression to the normal or the stock dies out. Not infrequently the stock dies out by the inborn tendency to

“It’s fascinating, it’s beautiful, it’s aesthetic, it’s gorgeous; but, in the end, people are dying,” in *Tomorrow Belongs to Me*, Jacqueline Donachie and Darren G. Monckton, (Glasgow: University of Glasgow, 2006), 12.

¹¹¹ Almost immediately following Mott’s lecture, the text was published (in essentially the same format) in Britain’s two leading medical journals, *The British Medical Journal* and *The Lancet*. All future references will be to *The Lancet* article. F. W. Mott, “The Huxley Lecture on Hereditary Aspects of Nervous and Mental Diseases,” *The British Medical Journal* 2 (1910):1013-1020; F. W. Mott, “The Huxley Lecture on The Hereditary Aspects of Nervous and Mental Diseases,” *The Lancet* 176 no. 4545 (8 October 1910): 1057-1064.

¹¹² Harper *et al.*, “Anticipation,” 10.

¹¹³ Mott, “Huxley Lecture,” 1057.

¹¹⁴ Mott, “Huxley Lecture,” 1058.

¹¹⁵ Mott, “Huxley Lecture,” 1058-1059, 1062-1064.

¹¹⁶ Mott, “Huxley Lecture,” 1058.

insanity manifesting itself in the form of congenital imbecility or insanity of adolescence—dementia praecox. ... Such patients are especially prone to die from tuberculosis; thus “rotten twigs are continually breaking off the tree of life.”¹¹⁷

These ideas expressed by Mott were commonly held by Eugenicists and social Darwinists who were likewise concerned with the health of the nation.¹¹⁸ What Mott lacked was a hereditary explanation of this tendency. This explanation came in the form of Nettleship’s concept of anticipation. Nettleship either attended or read Mott’s Huxley lecture and sent a copy of his 1910 *St. Thomas’s Hospital Gazette* paper to Mott shortly thereafter.¹¹⁹ The idea of anticipation as formulated there would in turn galvanize Mott who would embrace it, first as a “rule” and then as a “natural law,” in a series of papers over the next few years. These papers disseminated and popularized the idea of anticipation broadly within the eugenics community.

FROM DEGENERATION TO ANTICIPATION

During the nineteenth century, ancient concepts of heredity and disease had been developed within a period of social, political, and economic unrest to reflect concerns that degeneration was becoming increasingly common as the century passed. Physicians and scientists concerned with heredity worried that industrial pollution, adulterated foods, physical illnesses such as tuberculosis and syphilis, and social ills such as drink, drugs, and promiscuity were having a negative effect on the population and through the population on the nation-state. Between 1905 and 1912, Edward Nettleship drew together ideas from the fields of medicine and heredity to create the new concept of anticipation which posited that in certain hereditary diseases the illness appears at an earlier age and often more harshly in succeeding generations. In this way, Nettleship transformed, or framed, an older concept to suit the new scientific culture of the early twentieth century. His enunciation of the concept in his own special field was soon generalized to a wide range of conditions by F. W. Mott.

¹¹⁷ Mott, “Huxley Lecture,” 1062.

¹¹⁸ Peter J. Bowler, *Biology and Social Thought: 1850-1914*, (Berkeley: Office for History of Science and Technology University of California, 1993), 61-86.

¹¹⁹ F. W. Mott, “Heredity and Insanity,” *Eugenics Review* 2 (January 1911): 269-271.

Chapter 2: A Natural Law (1910-1930)

A CONTROVERSIAL BEGINNING

The years between 1910 and 1930 were pivotal ones for the spread of the concept of anticipation. Early in this period, Edward Nettleship personally introduced the concept of anticipation to two members of the Eugenics Society, Frederick W. Mott who extended and popularized the concept, and Ernest Lidbetter who applied the concept of anticipation to his own research programme, which aimed to prove that pauperism was hereditary and a source for greater social ills. Some British eugenicists then used anticipation as a plank in their arguments for a legislative solution to the problem of pauperism—that is, for legislated sterilization and/or segregation of those deemed unfit. Others would use the same concept to argue that sterilization was simply unnecessary because anticipation operated as a natural law that would eventually effect the eradication of the affected families over time.

This chapter will show, however, the idea of anticipation was not well received even by all members of the eugenics community. The biometrical statisticians Karl Pearson and David Heron, who *did* believe in eugenics and *were* in favour of a programme of sterilization, did *not* like the concept of anticipation. Despite the fact that Pearson felt great respect for Nettleship's scientific work, he and other researchers at the Galton Laboratory felt that the idea of anticipation, as outlined and used by Mott, was inherently flawed. In addition to questioning Mott's statistics, they felt that the apparent finding of anticipation over successive generations was caused by the selection of families in which the disease manifested late in early generations as these individuals lived long enough to marry and have children, rather than the operation a concrete genetic factor or factors with some biological reality. Charles B. Davenport, an ardent Mendelian who headed up the Eugenics Record Office in the United States, examined and then quickly discarded the concept of anticipation. The German eugenics community initially accepted anticipation, but, by the 1920s, influential members, including Ernst Rüdin and Fritz Lenz, had turned against it. In the meantime, the notion of anticipation would nonetheless continue to be adopted by both psychiatrists engaged in the study of

mental defect and by physicians who used the concept to explain odd modes of heredity that they observed in specific disorders, such as Huntington's disease and myotonic dystrophy.

EUGENICS, GENETICS, AND ANTICIPATION

By the beginning of the second decade of the 20th century, research into eugenics and genetics was well underway.¹ Several forms of heredity: Darwinian, Galtonian, Weismannian, Mendelism, biometry, and even forms of Lamarckism, were all under consideration by researchers.² During this period, it was almost impossible to differentiate between geneticists and eugenicists because the communities overlapped to

¹ The history of eugenics as a complex and varied enterprise has been well examined by a number of historians. I do not intend to replicate their work here, particularly since anticipation goes unmentioned in all of these works, barring Mazumdar (1992). However, certain members of these eugenics communities contributed research towards the concept of anticipation or used anticipation in their arguments. It is the work of these individuals that I examine, rather than that of the eugenics community as a whole. The history of genetics during this period has also been examined by historians. Given the central importance that DNA eventually played, many historians have concentrated their work on this area. Unsurprisingly, anticipation was not discussed in these narratives either.

For a review of literature on eugenics see: Lyndsay Farrall, "The History of Eugenics: a Bibliographical Review," *Annals of Science* 36 (1979): 111-123. In recent years many authors have concentrated on how eugenics developed within national contexts, see below. Regionally comparative studies include: Mark Adams ed., *The Wellborn Science: Eugenics in Germany, France, Brazil, and Russia*, (New York: Oxford University Press, 1990); Mark Adams, Garland E. Allen, and Sheila Faith Weiss, "Human Heredity and Politics: A Comparative Institutional Study of the Eugenics Record Office at Cold Spring Harbor (United States), the Kaiser Wilhelm Institute for Anthropology, Human Heredity, and Eugenics (Germany), and the Maxim Gorky Medical Genetics Institute (USSR)," *Osiris* 20 (2005): 232-262; Ian Dowbiggen, *Keeping America Sane: Psychiatry and Eugenics in the United States and Canada, 1880-1940*, (Ithaca NY: Cornell University Press, 1997); Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity*, with a new preface, (Cambridge, Mass.: Harvard University Press, 1995); Nancy Lays Stepan, "*The Hour of Eugenics*" *Race, Gender and Nation in Latin America*, (Ithaca NY: Cornell University Press, 1991).

For literature on genetics see: Elof Axel Carlson, *The Gene: A Critical History*, (Philadelphia: W. B. Saunders, 1966); Donald Chambers, ed., "DNA: The Double Helix: Perspective and Prospective at Forty Years," *Annals of the New York Academy of Sciences* 758 (1995); Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, Expanded edition, (Planesview NY: Cold Spring Harbor Laboratory Press, 1996); Maxim Frank-Kamenetskii, *Unravelling DNA: The Most Important Molecule of Life*, (Reading, MA: Addison-Wesley, 1997); Lily Kay, *Who Wrote the Book of Life? A History of the Genetic Code*, (Stanford CA: Stanford University Press, 2000); Evelyn Fox Keller, *The Century of the Gene*, (Cambridge, MA: Harvard University Press, 2000); Robert Olby, *The Path to the Double Helix: The Discovery of DNA*, (New York: Dover Publications, Inc., 1994); Franklin Portugal and Jack S. Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*, (Cambridge MA: MIT Press, 1977); A. H. Sturtevant, *A History of Genetics*, introduction by Edward B. Lewis, (Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2001); N. A. Tiley, *Discovering DNA: Meditations of Genetics and a History of Science*, (New York: Van Nostrand Reinhold Company, 1983); Bruce Wallace, *The Search for the Gene*, (Ithaca: Cornell University Press, 1992).

² See for example, S. Herbert, *The First Principles of Heredity*, (London: Adam and Charles Black, 1910).

such a great extent.³ Eugenics as a field of research developed with distinct regional variations.⁴ British eugenics was concerned especially with the “uncontrolled breeding” of “the pauper class”; American eugenics focused on the fecundity of recent immigrants from the Mediterranean and Eastern Europe, and German eugenics fixated on the degeneration of “the race.” In Britain, the Eugenics Society embarked on a systematic programme of research designed to support their argument that legislation should be used to remedy the problem of the pauper class.⁵ At the Galton Laboratory for National Eugenics in London, biometricians led by Karl Pearson used statistics to examine questions concerning the inheritance of diseases (or predispositions thereto).⁶ In the United States, Charles Davenport headed up the Eugenics Record Office at Cold Spring

³ See among others: G. R. Searle, *Eugenics and Politics in Britain 1900-1914*, (Leyden: Noordhoff International Publishing, 1976), 3-19; Daniel J. Kevles, “Genetics in the United States and Great Britain, 1890-1930: A Review with Speculations,” *Isis* 71 no. 3 (September 1980): 441-455; Daniel J. Kevles, “Genetics in the United States and Great Britain 1890-1930: A Review with Speculations,” in *Biology, Medicine and Society 1840-1940*, ed., Charles Webster, (Cambridge: Cambridge University Press, 1981), 193-215; Peter J. Bowler, *Biology and Social Thought: 1850-1914*, (Berkeley: Office for History of Science and Technology, University of California at Berkeley, 1993), 61-92.

⁴ Britain: Richard Soloway, *Demography and Degeneration: Eugenics and the Declining Birthrate in Twentieth-Century Britain*, (Chapel Hill NC: University of North Carolina Press, 1990); Pauline Mazumdar, *Eugenics, Human Genetics and Human Failings: The Eugenics Society, its sources and its critics in Britain*, (London: Routledge, 1992); Canada: Angus McLaren, *Our Own Master Race: Eugenics in Canada, 1885-1945*, (Toronto: Oxford University Press, 1990); America: Edwin Black, *War Against the Weak: Eugenics and America's Campaign to Create a Master Race*, (New York: Four Walls Eight Windows, 2003); Elof Axel Carlson, *The Unfit: A History of a Bad Idea*, (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2001); Mark Haller, *Eugenics: Hereditarian Attitudes in American Thought*, (New Brunswick NJ: Rutgers University Press, 1963); Wendy Kline, *Building A Better Race: Gender, Sexuality, and Eugenics from the Turn of the Century to the Baby Boom*, (Berkeley: University of California Press, 2001); Christine Rosen, *Preaching Eugenics: Religious Leaders and the American Eugenics Movement*, (Oxford: Oxford University Press, 2004); Germany: Peter Weingart, “German Eugenics between Science and Politics,” *Osiris* 5 (1989): 260-282; Jonathan Harwood, *Styles of Scientific Thought: The German Genetics Community, 1900-1933*, (Chicago: Chicago University Press, 1993); France: William Schneider, *Quality and Quantity: The Quest for Biological Regeneration in Twentieth-Century France*, (Cambridge: Cambridge University Press, 1990); Scandinavia: Gunnar Broberg and Nils Roll-Hansen, eds., *Eugenics and the Welfare State: Sterilization Policy in Denmark, Sweden, Norway, and Finland*, (East Lansing, MI: Michigan State University Press, 1995).

⁵ See among others: G. R. Searle, “Eugenics and Class,” in *Biology, Medicine and Society 1840-1940*, ed., Charles Webster, (Cambridge: Cambridge University Press, 1981), 217-242; John Macnicol, “In Pursuit of the Underclass,” *Journal of Social Policy* 16 no. 3 (July 1987): 293-318; Soloway, *Demography*; Mazumdar, *Eugenics*.

⁶ Bernard J. Norton, “Karl Pearson and Statistics: The Social Origins of Scientific Innovation,” *Social Studies of Science* 8 no. 1 (February 1978): 3-34; Donald A. Mackenzie, *Statistics in Britain 1865-1930: The Social Construction of Scientific Knowledge*, (Edinburgh: Edinburgh University Press, 1981), 73-93; Lionel Penrose, “The Galton Laboratory: Its Work and Aims,” *Eugenics Review* 41 no. 1 (1949): 17-27.

Harbor, New York and was hard at work applying Mendelian genetics to a variety of diseases, from Huntington's disease to feeble-mindedness.⁷

In Germany, a mathematical form of Mendelism called *Vererbungsmathematik* was founded in the first decade of the twentieth century by the Jewish-descended physician Wilhelm Weinberg.⁸ This form of genetics was initially well accepted in Germany, and was quickly adopted by those engaged in the new science of human blood group research, but did not become well known in the English-speaking world until 1930.⁹ German research in eugenics and genetics would further deviate from the Anglo-American stream in the wake of the First World War. The Swiss-born German

⁷ See for example: Kenneth Ludmerer, "American Geneticists and the Eugenics Movement: 1905-1935," *Journal of the History of Biology* 16 (1969): 337-362; Garland E. Allen, "The Eugenics Record Office and Cold Spring Harbor, 1910-1940: An Essay in Institutional History," *Osiris* 2 (1986): 225-264; Jan A. Witkowski, "Charles Benedict Davenport, 1866-1944," in *Davenport's Dream: 21st Century Reflections on Heredity and Eugenics*, Eds., Jan A. Wikowski and John R. Inglis, (Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2008), 35-58; Elof A. Carlson, "The Eugenic World of Charles Benedict Davenport," in *Davenport's Dream: 21st Century Reflections on Heredity and Eugenics*, Eds., Jan A. Wikowski and John R. Inglis, (Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2008), 59-76; Maynard V. Olson, "Davenport's Dream," in *Davenport's Dream: 21st Century Reflections on Heredity and Eugenics*, Eds., Jan A. Wikowski and John R. Inglis, (Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2008), 77-98.

⁸ Although Weinberg was a practicing physician and obstetrician, he was still able to make considerable contributions to the field of genetics. In 1908, Weinberg and the British mathematician G. H. Hardy independently discovered a key principle of population genetics (that—unless disturbed—the different genotypes within a population remain in equilibrium with one another over generations; this idea is one of the cornerstones of the field of population genetics). The English biometrician Karl Pearson knew of Weinberg's work—which prefigured much of the groundbreaking work on population genetics published independently by R. A. Fisher in 1918—but dismissed him and his criticisms of English biometry. Weinberg's contributions to the field of mathematical genetics did not become widely known in the English-speaking world until Curt Stern (who, as a Jew, was unable to return to Germany after the completion of his second Rockefeller Foundation fellowship in 1933) published a 1943 paper in *Science* where he suggested the discovery should be known as the Hardy-Weinberg Law. By this time, however, the field of population genetics had already surpassed Weinberg's contributions. James Crow, "Hardy, Weinberg and Language Impediments," *Genetics* 152 (July 1999): 821-825; Ute Deichmann, *Biologists under Hitler*, trans. by Thomas Dunlap, (Cambridge MA: Harvard University Press, 1996), 14-15, 21-22; A. W. F. Edwards, *Foundations of Mathematical Genetics*, 2nd ed., (Cambridge: Cambridge University Press, 2000); James V. Neel, "Curt Stern, 1902-1981," *Annual Review of Genetics* 17 (1983): 4; Karl Pearson, "Darwinism, Biometry, and Some Recent Biology," *Biometrika* 7 (1910): 381; William B. Provine, *The Origins of Theoretical Population Genetics*, (Chicago: The University of Chicago Press, 1971), 134-137; Curt Stern, "The Hardy-Weinberg Law," *Science* 97 no. 2510 (5 February 1943): 137-138; Edith Zerbin-Rüdin and Kenneth Kendler, "Ernst Rüdin (1874-1952) and His Genealogic-Demographic Department in Munich (1917-1986): An Introduction to Their Family Studies of Schizophrenia," *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 (1986): 333.

⁹ In 1930, Lancelot Hogben introduced the concepts of *Vererbungsmathematik* to England and, in the early 1930s, several scholars familiar with the technique (many of them either Jewish or of Jewish descent) were forced to flee Germany in the wake of the rise of the Nazis. They took their knowledge of *Vererbungsmathematik* with them. See Pauline Mazumdar, "Two Models for Human Genetics: Blood Grouping and Psychiatry in Germany between the World Wars," *Bulletin of the History of Medicine* 70 no. 4 (1996): 609-657.

psychiatrist and eugenicist Ernst Rüdin was one of the initial supporters of *Vererbungsmathematik* and used its techniques in his own seminal work on schizophrenia in 1916.¹⁰ By the 1920s, however, Rüdin was advocating his own, more qualitative technique of *empirische Erbprognose* (empirical genetic prognosis) which was being used by his large and influential research group in Munich.¹¹ He had also come to reject the concept of anticipation in hereditary disease, referring to it as a statistical fallacy, as will be discussed in detail later.¹²

¹⁰ Ernst Rüdin, *Studien über Vererbung und Entstehung geistiger Störungen. I. Zur Vererbung und Neuentstehung Der Dementia Praecox*, (Berlin: Verlag von Julius Springer, 1916). Rüdin established the so-called Munich school of psychiatric genetics. He was at the German Institute for Psychiatric Research in Munich from its founding in 1917 as head of the Genealogical-Dermographic Department, until he left this position in 1925 to take up a professorship at the University Hospital of Neurology and Psychiatry in Basel. Rüdin returned to Munich Institute in 1928 and remained engaged in his programme of racial hygiene until 1945, when the Allied occupation removed him from the institute for detention and de-Nazification. Although he had held dual Swiss-German citizenship, he lost his Swiss citizenship after he was removed as head of the institute after the end of the Second World War. Rüdin did not join the Nazi party until 1937, but his ideas were already being used by others, such as Fritz Lenz became one of the architects of Nazi eugenics policy. Rüdin did support existing German sterilization legislation in the Weimar era and played a key role in 1933 in drafting the Nazi compulsory sterilization legislation for which he became responsible for enforcing during the Nazi period. Rüdin died in Munich in 1952. His daughter Edith Zerbin-Rüdin still works at the institute, renamed the Max Plank Institut für Psychiatrie, Munich. Matthias Weber, "Psychiatric research and science policy in Germany. The history of the *Deutsche Forschungsanstalt für Psychiatrie* (German Institute for Psychiatric Research) in Munich from 1917 to 1945," *History of Psychiatry* 11 (2000): 235-258; Irving I Gottesman and Askel Bertelsen, "Legacy of German Psychiatric Genetics: Hindsight Is Always 20/20," *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 (1996): 317-322; Matthias Weber, "Ernst Rüdin, 1874-1952: A German Psychiatrist and Geneticist," *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 (1996): 323-331; Zerbin-Rüdin and Kendler, "Ernst Rüdin," 332-337.

¹¹ The fact that Rüdin used Weinberg's mathematical techniques in analyzing his own schizophrenia data in 1916 is unquestioned. However, historians seem somewhat divided on when Rüdin deviated from *Vererbungsmathematik* to form his own method of "empirical genetic prognosis" (*empirische Erbprognose*). Mazumdar argues that Rüdin developed this methodology during the 1920s while Weber states that Rüdin was already using it "which involved a combination of three already extant techniques" (including Weinberg's mathematical analysis) at the time of his 1916 study on schizophrenia. Mazumdar, "Two Models," 609-657; Weber, "Rüdin," 326.

¹² In Germany, anticipation was first rejected as a statistical fallacy by Weinberg, who identified many possible sources of experimental errors due to ascertainment bias (non-random or incomplete sampling of the population) and selection bias (faulty method of sampling the population). These two concepts are often used fairly interchangeably in the literature. Two papers that he published in 1914 pointed out that anticipation could be explained by the fact that, by virtue of being well enough to marry and have children, members of the parental generation were being selected for late onset or less severe disease. This selective pressure was not acting on the offspring, so their disease began at an earlier age. Rüdin and Lenz followed suit, both publishing rejections of anticipation in the 1920s on the grounds that it was caused by statistical error. Wilhelm Weinberg, "Auslesewirkungen bei biologisch-statistischen Problemen. I," *Archiv für Rassen und Gesellschafts Biologie* 10 no. 4 (1914): 417-451; Wilhelm Weinberg, "Auslesewirkungen bei biologisch-statistischen Problemen. II," *Archiv für Rassen und Gesellschafts Biologie* 10 no. 5 (1914): 557-581; Ernst Rüdin, "Über Vererbung geistiger Störungen," *Zeitschrift für die Gesamte Neurologie und Psychiatrie* 81 (1923): 459-496; Fritz Lenz, *Menschliche Erblerehre und Rassenhygiene. Band 2, Menschliche Auslese und Rassenhygiene*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz, (Munich: J. F.

Mott's Conceptualization of Anticipation—Creating a Natural Law

As we have seen, Nettleship's concept of anticipation and his general ideas about heredity had a very powerful influence on Fredrick Walker Mott. As the Director of the Laboratory and Pathologist to the London County Asylums, Physician to Charing Cross Hospital, and a member of the Eugenics Society and its Research Committee, Mott was in a position to spread his ideas widely. However, like many other social Darwinists and eugenicists, his conclusions more reflected upper-middle class economic and social fears rather than showing any real understanding of the underlying genetic processes.¹³ By 1910, he was examining questions of heredity and disease, discussing different modes of heredity, and arguing that he had evidence that degeneration of the type discussed by Morel and Maudsley was occurring within families that suffered from hereditary forms of insanity.¹⁴ When Nettleship contacted Mott in late 1910 and sent him a copy of his *St. Thomas's Hospital Gazette* paper, he introduced Mott to the concept of anticipation and provided a mechanism that explained his findings concerning the inheritance and apparent worsening of mental illness over succeeding generations.¹⁵ Galvanized by the idea of anticipation, Mott developed the concept, first as a rule and then as a natural law over the following years in a series of papers published in Britain and America. These papers spread and popularized the idea of anticipation broadly within the eugenics community.

By January 1911, Mott had begun integrating Nettleship's concept of anticipation with the older ideas of degenerative heredity espoused by Morel and with Maudsley's notion of neurotic diathesis, which were well known within the psychiatric community.¹⁶ He examined parents and offspring who had been in the London County Asylums and felt that anticipation "almost invariably occurs" in cases where both parent and child suffered

Lehmanns Verlag, 1923); Fritz Lenz, *Menschliche Erblere und Rassenhygiene*. Band 2, *Grundriß der menschlichen Erblere und Rassenhygiene*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz, (Munich: J. F. Lehmanns Verlag, 1923). See also Crow, "Hardy, Weinberg," 823.

¹³ Peter Harper, Helen G. Harley, William Reardon, and Duncan J. Shaw, "Anticipation in Myotonic Dystrophy: New Light on an Old Problem," *American Journal of Human Genetics* 51 no. 1 (1992): 10.

¹⁴ F. W. Mott, "The Huxley Lecture on the Hereditary Aspects of Nervous and Mental Diseases," *Lancet* 176 no. 4545 (October 8, 1910): 1057-1064.

¹⁵ Edward Nettleship, "Some Points in Relation to the Heredity of Disease," *St. Thomas's Hospital Gazette* (March 1910): 37-65; F. W. Mott, "Heredity and Insanity," *Eugenics Review* 2 (January 1911): 269-271.

¹⁶ Nettleship's earlier work had traced a similar path in the development of anticipation, but Mott introduced the idea to new audience. Nettleship, "Some Points," 37-65; Mott, "Heredity and Insanity," 269-272, 275-277.

from insanity.¹⁷ Anticipation now became a “rule, whereby the offspring suffers at a much earlier age than the parent.”¹⁸ In May 1911, Mott raised anticipation from a “rule” to a “law” with the publication in the prominent medical journal *The Lancet* of a lecture he had originally given in February at the Royal Institution.¹⁹ In this lecture, Mott again used this new law as an explanation for his old arguments. He remained concerned, as he had been in 1910, that children were being born “freely to the feeble-minded, to the pauper, to the alien Jew, to the Irish Roman Catholic, to the thriftless casual labourers, to the criminals and others generally the denizens of one-roomed tenements of our great cities.”²⁰ Like many other eugenicists, he felt that if left unchecked, this unrestricted breeding of the unfit could lead to the degeneration of the nation. Therefore, he stated that:

the proper attitude to take up in this question as regards the perpetuation of poor types, according to a well-known journalist, is that laid down by Huxley: ‘We are sorry for you, we will do our best for you (in so doing we elevate ourselves, since mercy blesses him that gives and him that takes), but we deny you the right to parentage. You may live, but you must not propagate.’ To no class of people does this principle apply with greater force than to the mentally defective or feeble-minded.²¹

Mott did not discount the influence of environment or poverty on health, but he felt that inborn weakness was a more important factor for making people vulnerable to alcoholism, tuberculosis, and insanity.²² When examining pedigrees of several families,

¹⁷ Mott, “Heredity and Insanity,” 273.

¹⁸ Mott, “Heredity and Insanity,” 280.

¹⁹ F. W. Mott, “A Lecture on Heredity and Insanity,” *Lancet* 177 no. 4576 (May 13, 1911): 1251-1259. This lecture is frequently cited as the one in which the concept of anticipation was first developed. See for example, Harper *et al.*, “Anticipation,” 10.

²⁰ Mott, “Lecture,” 1251. Mott was not alone in these opinions. The British socialist Sidney Webb published almost identical remarks in the *Fabian Tract* in 1907: “In Great Britain at this moment, when half, or perhaps two-thirds, of all the married people are regulating their families, children are being freely born to the Irish Roman Catholics and the Polish, Russian and German Jews, on the one hand, and to the thriftless and irresponsible—largely the casual laborers and the other denizens of the one-roomed tenements of our great cities—on the other. Twenty-five per cent. of our parents, as Professor Karl Pearson keeps warning us, is producing 50 per cent. of the next generation. This can hardly result in anything but national deterioration; or, as an alternative, in this country gradually falling to the Irish and the Jews.” Sidney Webb, *The Decline in the Birth-Rate*, (London: The Fabian Society, 1907. Fabian Tract No. 131), 16-17.

²¹ Mott, “Lecture,” 1251.

²² Mott, “Lecture,” 1252-1255.

Mott was particularly struck by the “general tendency for insanity not to proceed beyond three generations.”²³ This proved to him that anticipation was taking place among sufferers of insanity and he felt that it was “a strong argument of heredity transmission, possibly hereditary transmission of an acquired character.”²⁴ It must be remembered that in the early years of the twentieth century several modes of heredity including Darwinian, Galtonian, Mendelian, Weismannian, and even neo-Lamarckian, were under consideration by the scientific community. While the Mendelian approach to heredity was on the rise, it had not yet completely displaced these competing ideas. The strong adherence of the American scientific community to Mendelism (however well or poorly construed) may explain the poor reception given to the idea of anticipation in America by Davenport, who might otherwise have been expected to embrace such a concept.²⁵ In any case, Mott believed that his observations of anticipation were likely caused by a progressive degeneration of the germ plasm.²⁶ At first he counselled that the only ways to halt the degenerative process, short of social intervention was “by marriage into sound stocks” or “by anticipation or ante-dating leading to congenital or adolescent mental disease terminating the perpetuation of the unsound elements of the stock.”²⁷ Yet while he first called for society to prevent the breeding of affected groups, after further consideration Mott came to believe that if a member of an afflicted family reached the age of 25 without showing any signs of illness, that person could safely marry and have children.²⁸ He repeated these ideas in lengthy papers published in both *The Medical Chronicle* and *Brain*.²⁹

²³ Mott, “Lecture,” 1255.

²⁴ Mott, “Lecture,” 1259.

²⁵ Davenport’s response to the notion that anticipation might be taking place in Huntington’s disease will be discussed below.

²⁶ The figure that Mott used to illustrate transmission by germinal determinants was taken from Nettleship’s 1910 *St. Thomas’s Hospital Gazette* paper. Mott, “Lecture,” 1253-1255.

²⁷ Mott, “Lecture,” 1259.

²⁸ The idea that it was safe to have children after reaching some arbitrary age without showing signs of illness was taken up by others in the psychiatric community. However, this idea angered some pro-sterilization legislation members of the eugenics community as sterilization campaigners used it in their (successful) battle against sterilization legislation in Britain. This will be discussed later in this chapter and in chapter three.

²⁹ These papers paralleled Nettleship (1910) in their discussion of the various modes of heredity and their application as well as in the discussions of previous workers. Mott continued to quote Maudsley and his dictum that Nature would seek to either end or mend an insane stock. He also continued to discuss Darwin’s recognition of the occurrence of disease at an earlier age in succeeding generations and he emphasised that his own observations showed that the insane offspring of insane parents were usually

In 1912, Mott's thinking on the question of heredity and insanity underwent important changes. In a lecture given to the Royal Sanitary Institute in April he continued to reiterate the points outlined above.³⁰ However, he added something new to his conclusions. Specifically, he began to discuss the issue of "social surgery of the insane" i.e. sterilization. Having observed from his data that by the time most of the parents were committed to the asylum, they had already married and had children, he argued that "sterilization would therefore be applicable to relatively few parents admitted to asylums."³¹ Moreover, he thought, the insane children of these parents "would be disqualified for propagation by marriage by an incurable mental affection in a large number of instances" and therefore they would not need to be sterilized.³² The eugenic danger to society, Mott felt, lay in "the higher grade imbeciles and moral defectives."³³ These views on the question of sterilization—that is, his opposition to it—would shortly set him at odds with other members of the eugenics movement.

By the time of the First International Eugenics Congress held in London July 24-30 1912, Mott's ideas concerning heredity and insanity and his thoughts on the question of sterilization had undergone further development.³⁴ In his presentation to the Congress Mott reiterated most of his previous discussions on modes of heredity and eugenics.³⁵ He laid out the results of his research into heredity and insanity, explaining why he thought the number of insane individuals merely *appeared* to be increasing. Rather than calling for sterilization, he argued that correcting the environment in which the pauper class lived

affected at an earlier age and more severely than their affected parent. F. W. Mott, "Hereditary Transmission of Disease Especially in Relation to Anticipation," *Medical Chronicle* 22 (1911): 63-92; F. W. Mott, "The Inborn Factors of Nervous and Mental Disease," *Brain* 34 no. 1 (1911): 73-101.

³⁰ Mott once again quoted Maudsley, referenced Darwin, and stated that his own observations showed "that there is a signal tendency for the insane offspring of insane parents to be born imbeciles or become insane at a much earlier age than the parent, and to suffer with a more intense form of mental disease." F. W. Mott, "Sanity and Insanity. A Lecture Delivered to the Royal Sanitary Institute on Wednesday, April 24th, 1912," *Journal of the Royal Sanitary Institute* 33 (1912): 247.

³¹ Mott, "Sanity and Insanity," 251.

³² Mott, "Sanity and Insanity," 251.

³³ Mott, "Sanity and Insanity," 251.

³⁴ The papers were collected and published by the Eugenics Society. F. W. Mott, "Heredity and Eugenics in Relation to Insanity," in *Problems in Eugenics: Papers communicated to the First International Eugenics Congress*, (London: Eugenics Society, 1912), 400-428. Despite the controversy that certain aspects of the paper engendered between Mott and those at the Galton, the Eugenics Society reprinted and circulated Mott's paper in a stand-alone form. F. W. Mott, *Heredity and Eugenics in Relation to Insanity*, (London: Eugenics Education Society, 1912).

³⁵ Mott, "Heredity and Eugenics," 400-404.

would go a long way to correct their character defects.³⁶ Mott re-emphasised his belief that neuropathic inheritance lay at the root of cases of insanity and that the tainted stock could contain “individuals possessing the melancholic, suspicious, brooding, self-centred, hypochondriacal temperament,” with associated tendencies to “chronic alcoholism, dipsomania, hysteria, hypochondriasis, exophthalmic goître, neurasthenia, psychasthenia, migraine, *petit mal* [seizures], or neuroses of an epileptic character.”³⁷ The recent discovery of a test for syphilis, however, showed that general paralysis of the insane—which formed a substantial number of asylum cases—was caused by syphilitic infection, and news of a possible cure raised the hope of a possible end to this sort of preventable insanity.³⁸ This discovery led Mott and others to question the causes of feeble-mindedness. If syphilis was the cause of general paralysis, and these inmates formed a substantial number of asylum cases, what was to become of the arguments that mental defect was caused by atavism or to the idea put forward—particularly by the Americans Davenport and Goddard—that mental defect was a trait with Mendelian hereditary characteristics.

In his new discussion of anticipation, Mott thus put forward the idea, supported by Galton’s *Natural Inheritance*, of “the coalescence or crystallization out of the unsound germinal determinants into a few of the offspring, leaving the germ-plasm of the other free.”³⁹ This idea in due course drew criticism from both Mendelians and biometricians. Nevertheless, Mott thought such a mechanism “would not only purify the stock by segregation but by concentration in one or two offspring; it would lead to intensification and anticipation of the disease. The diseased offspring would be unfit for the struggle for

³⁶ Mott, “Heredity and Eugenics,” 404-409. The question of the importance of environment vs. heredity in insanity led to a “nature vs. nurture” dispute that preoccupied psychiatrists and eugenicists into the 1940s. See also chapter three.

³⁷ Mott, “Heredity and Eugenics,” 411-421.

³⁸ Mott, “Heredity and Eugenics,” 409-411. For a typical contemporary view see: H. C. Stevens, “Environment v. Heredity in Feeble-mindedness,” *Eugenics Review* 9 (1917): 373-374. Mott was among the first British researchers to connect syphilitic infection with general paralysis of the insane. His paper on the subject was referred to as “epoch making.” Mott dedicated substantial time over the following years to elucidating the causative effect of syphilis on a variety of types of mental illness. Anonymous, “Frederick Mott, K.B.E., M.D., F.R.C.P. Lond., LL.D. Edin., F.R.S.,” *Lancet* 207 no. 5364 (19 June 1926): 1229; F. W. Mott, “The Pathology of Syphilis of the Nervous System in the Light of Modern Research (Morison Lectures, 1909),” *Archives of Neurology and Psychiatry* 4 (1909): 13-57

³⁹ Mott, “Heredity and Eugenics,” 422.

existence and propagation.”⁴⁰ He followed this argument with statistical data generated from his genealogical studies. Perhaps most interestingly, Mott ended this discussion with a distinct note of caution concerning the use of sterilization as a solution for the control of the insane:

When *hereditary health* as shown by longevity, fertility, and mental stability in a stock is regarded as a greater asset for happiness in the family and the nation than hereditary wealth, then will be the time for the rich and comparatively prosperous to suggest the desirability of the sterilization of the insane *pauper*. For no one supposes that it would be carried out in all classes.⁴¹

This warning against the project of class discrimination marks a significant shift in Mott’s thinking on the issue of sterilization, particularly when compared to the Malthusian nature of his 1910 statements about the poor living in the slums of London.

These comments made at the 1912 Eugenics Congress drew the ire of the biometricians upon Mott, perhaps because they were unaware of the particulars of his work before this time, or perhaps because Mott was now expressing a distinct uneasiness with the creation and application of the sterilization legislation that many of them advocated.⁴² In any event, the assumptions behind his argument and his experimental technique would soon come under severe criticism from this branch of the scientific community. In addition, certain other components of his argument—most notably the idea of the intensification of illness by means of the segregation of the affected hereditary particles within certain individuals—were considered heretical by biometricians and Mendelians alike. While this attack got underway however, other individuals, with Mott’s encouragement, began to make their own studies relating to the question of

⁴⁰ Mott, “Heredity and Eugenics,” 422. Interestingly, a 1994 study by C. E. M. Die-Smulders *et al.* examined an extended family suffering from myotonic dystrophy over several generations. They found a tendency for the disease to be eliminated from the family after a number of generations through a combination of infertility on the part of males suffering from the disease and the childlessness of those suffering from early onset forms of the disease. C. E. M. Die-Smulders, C. J. Höweler, J. F. Mirandolle, H. G. Brunner, V. Hovers, H. Brüggewirth, H. J. M. Smeets, and J. P. M. Geraedts, “Anticipation resulting in elimination of the myotonic dystrophy gene: a follow up study of one extended family,” *Journal of Medical Genetics* 31 (1994): 595-601.

⁴¹ Mott, “Heredity and Eugenics,” 423-428.

⁴² A lack of money halted to the Eugenics Society’s first attempt to advocate sterilization legislation. When the programme was resumed in 1929, the old arguments concerning Mott’s law were revived. That phase of the debate will be covered in chapter three.

heredity in insanity. Some of these studies found evidence of anticipation across generations.⁴³ Some came to similar conclusions to Mott's regarding the lack of any need for wholesale sterilization, since individuals who were likely to be affected were expected to be stricken early and thus have reduced fertility if they married at all, while their siblings would likely escape the hereditary taint.⁴⁴

Eugenics, Class, and the Sterilization Debate

A key part of the British eugenic problematic, as defined by historian Pauline Mazumdar, was the quest for the creation of legislation to control the rapidly breeding members of the pauper class.⁴⁵ The declining birth rate among the middle and upper classes, coupled with reduced overall mortality due to improving medicine, led to fears that the "pauper class" would shortly out-breed and socially overtake the middle and upper classes thereby lead to the degeneration of the nation.⁴⁶ The Eugenics Society sought, unsuccessfully, to encourage the passage of legislation aimed to curb the procreation of the "pauper class" which they believed was inferior biologically (by a tendency toward mental and physical defect) as well as economically (by their low economic position and reliance on the Poor Law).⁴⁷ In order to provide scientific support for this endeavour, the Eugenics Society's Research Committee undertook a study of pauper pedigrees, searching for links between heredity and poverty.⁴⁸ Additionally, the Eugenics Society and its journal *The Eugenics Review* took on the role of advocating eugenic policy measures to the public and lobbying

⁴³ See for example: Hill Wilson White, "The Investigation of Twenty-Five Pedigrees of Insane Persons," *Archives of Neurology and Psychiatry (London)* 6 (1914): 99, 125.

⁴⁴ See for example: J. C. Wootton, "The Investigation of a Number of Family Histories of Patients in Cane Hill Asylum," *Archives of Neurology and Psychiatry (London)* 6 (1914): 127, 137-138.

⁴⁵ Mazumdar, *Eugenics*, 1-6.

⁴⁶ See for example: W. C. D. Whethem, "Heredity and Destitution," *Eugenics Review* 3 (1911): 140-142. This issue has been much discussed by historians. See for example: Bowler, *Biological*, 37-86; Mazumdar, *Eugenics*, 1-145; Searle, *Eugenics*; Soloway, *Demography and Degeneration*, 1-335;

⁴⁷ For a contemporary examination of the British Eugenics Society's viewpoint of the Majority and Minority Reports of the Royal Commission on the Poor Law (1909) see: C. S. Loch, "Eugenics and the Poor Law: The Majority Report," *Eugenics Review* 2 no. 3 (October 1910): 229-232; Sidney Webb, "Eugenics and the Poor Law: The Minority Report," *Eugenics Review* 2 no. 3 (October 1910): 233-241. For a review of the history of eugenic sterilization (ca. 1900s-1960s) from the Eugenics Society's point of view see: C. P. Blacker, "The Sterilization Proposals: A History of their Development," *Eugenics Review* 22 no. 4 (January 1931): 239-247; C. P. Blacker, "Voluntary Sterilization: The Last Sixty Years," *Eugenics Review* 54 no. 1 (1962): 9-23. John Macnicol's article provides an informative overview on the social and scientific factors at play in the creation of the concept of hereditary poverty (and its tendency to return cyclically in political discussion). Macnicol, "Underclass," 293-318.

⁴⁸ The pauper pedigree project will be discussed below.

for the passage of eugenic legislation. While they felt that they could combine Galtonian biometrical/statistical methods with Mendelian genetics, in practice the simple pedigree analysis remained their tool of choice until around 1925. At that time, methodologies began to change.⁴⁹ Meanwhile, the Galton Eugenics Laboratory set itself the goal to carry out research in a more impartial and scientific fashion, but its heads, Karl Pearson and R. A. Fisher, were frequently at odds with the Eugenics Society on issues of method, even if they seemed to be largely in agreement as to goals.⁵⁰

In 1910, the editor of *The Eugenics Review* had stated that “it must be the work of the eugenicists in the immediate future to ensure that the underlying principle shall be the discouragement of parenthood on the part of the unfit, and the encouragement of large families on the part of the fit.”⁵¹ The former objective was called “negative eugenics,” and the latter “positive eugenics.” The goals would be achieved by “clearly indicating to our legislators and the general public the light thrown on these problems by recent scientific investigation.”⁵² Accordingly, the Eugenics Society and other eugenicists undertook carrying out several projects meant to achieve these goals, among them a study tracing the pedigrees of pauper families. Meanwhile important statistical work was undertaken by the biometricians at the Galton Laboratory.⁵³ Both the Eugenics Society and the Galton Laboratory hoped with time to see legislation that would control or segregate this class of individuals, as the feeble-minded had been by the Mental Deficiency Acts of 1913.⁵⁴ Eugenic societies in other countries were also looking to

⁴⁹ See Mazumdar *Eugenics*, 96-107, for a discussion of the Eugenics Society’s attempt to cross the Mendelian-Biometrician divide by offering training in both techniques before the reconciliation of the two sides by R. A. Fisher in 1918.

⁵⁰ Galton intended the Galton Laboratory to carry out research independently of the Eugenics Society and knew what he was doing when he appointed Karl Pearson as its first chair. Lionel Penrose kept a typed copy of a letter from Francis Galton to *The Times* on November 3, 1910 that described this as his intention. The Galton’s second chair, R. A. Fisher, had his own quarrels with the Eugenics Society regarding appropriate methodology. Penrose Papers 77/4. See Mazumdar *Eugenics* for a discussion of the ill feeling between many biometricians and the Eugenics Society.

⁵¹ Editor, “Editorial Notes,” *Eugenics Review* 2 (April 1910): 1-2. For discussions on the Eugenics Society’s role in supporting positive and negative eugenics policies see Macnicol, “Eugenics,” 164; Mazumdar, *Eugenics*, 3; Searle, “Eugenics,” 166, 168-169.

⁵² Editor, “Editorial Notes,” 2.

⁵³ Editor, “Editorial Notes,” 2-3. For the studies being carried out at the Galton Laboratory see the paper by Edgar Schuster given before the Eugenics Society in December 1910 and later published. Edgar Schuster, “Methods and Results of the Galton Laboratory for National Eugenics,” *Eugenics Review* 3 (1911): 24. See also Mazumdar, *Eugenics*, 22-57, and others.

⁵⁴ Editor, “Editorial Notes,” 1-3. For discussions concerning the development of the 1913 Mental Deficiency Act, its passage through Parliament, and its application see: Searle, *Eugenics*, 106-111; Mathew

enact legislative solutions to their perceived eugenic problems, and many of these achieved considerably more success than their English counterparts.⁵⁵

However, in the 1920s, the Eugenics Society's programme to limit the size of the pauper class and encourage sterilization of those deemed "unfit" came under attack from both without and within. Any attempt by the Eugenics Society to support sterilization was complicated by the fact that the operation itself was of questionable legality.⁵⁶ Critics from outside of the Eugenics Society, such as G. K. Chesterton, also harshly criticized of the goals of the eugenic movement.⁵⁷ In addition, the campaign to pass sterilization legislation alienated certain notable social commentators, such as William Inge, Dean of St Paul's (1911-1934), who were otherwise supportive of eugenics but rejected sterilization legislation on moral grounds.⁵⁸ The scientific utility of the pedigree came under strong attack by R. A. Fisher, who, although he supported sterilization, nonetheless urged the Eugenics Society to adopt more up-to-date mathematical

Thomson, *The Problem of Mental Deficiency: Eugenics, Democracy, and Social Policy in Britain c. 1870-1959*, (Oxford: Clarendon Press, 1998), 1-205.

⁵⁵ See for example: Harry Laughlin, "Report of the Committee to Study and to Report on the Best Practical Means of Cutting off the Defective Germ-Plasm in the American Population," *Eugenics Record Office Bulletin* 10A (February 1914): 5-64. Eugenic legislation was first passed in the United States with the "Sterilization Bill" and the "Eugenic Marriage Bill" in Wisconsin in 1913. American eugenicists published monographs lauding the success of their sterilization movement. See E. S. Gosney and Paul Popenoe, *Sterilization for Human Betterment: A Summary of Results of 6,000 Operations in California, 1909-1929*, (New York: The Macmillan Company, 1929). The British Eugenics Society continued to return to the issue of other countries' successes, and to its failure, to get such legislation passed several times. See, for example, Daniel Kevles, "Eugenics in North America," in *Essays in the History of Eugenics: Proceedings of a Conference organised by the Galton Institute, London, 1997*, ed., Robert Peel, (London: The Galton Institute, 1998), 208-226; Kevles, *Eugenics*, 99-104; McLaren, *Master Race*, 89-106; Mazumdar, *Eugenics*, 196-214. The Eugenics Society's attempts to sponsor legislation to legalize voluntary sterilization will be discussed in chapter three.

⁵⁶ Under the 1861 Offences Against the Person Act sterilization surgery, even with consent, could be deemed an "unlawful wounding." The 1913 Mental Deficiency Act held that, if the patient was *non compos mentis*, sterilization surgery was definitely illegal, and those who granted permission for the operation could be prosecuted. Macnicol, "Eugenics," 165-166. See also Thomson, *Problem*, 180-205. The 1930s attempt by the Eugenics Society to sponsor sterilization legislation through Parliament will be dealt with in chapter three.

⁵⁷ G. K. Chesterton, *Eugenics and Other Evils*, (London: Cassell and Company, Ltd., 1922).

⁵⁸ Inge's defection from the cause in 1925 was taken badly by Leonard Darwin and R. A. Fisher who discussed it in their correspondence. This marks a departure from Inge's position in 1922 when he favourably discussed eugenics and even the possibility of state intervention to "restrain" the profligate and the "reckless" who "ought not be allowed to procreate." William Ralph Inge, *Outspoken Essays (Second Series)*. Second Impression, (London: Longmans, Green and Co., 1922), 254-275, quotation from 271. J. H. Bennett ed., *Natural Selection, Heredity, and Eugenics: Including selected correspondence of R.A. Fisher with Leonard Darwin and others*, (Oxford: Clarendon Press, 1983), 79-80. On Dean Inge's previous support of the eugenics enterprise see Searle, "Eugenics," 227-228.

methodologies for research and analysis.⁵⁹ Moreover, within the medical establishment, prominent psychiatrist Alfred Frank Tredgold, who generally supported the aims of the Eugenics Society, drew the line at sterilization legislation. As a medical expert to the Royal Commission on the Feeble-Minded, Tredgold was unhappy with the results of the Commission and the failure of the government to enact significant new legislation regarding its findings. Moreover, he was concerned that the proposed legalisation of sterilization would be used as an excuse to cut funding for the care and treatment of the mentally defective.⁶⁰ Tredgold voiced these opinions directly to the members of the Eugenics Society in his 1927 Galton Lecture which was published both in the *Lancet* and in the *Eugenics Review*.⁶¹ In this lecture, Tredgold agreed that it was necessary to restrict the fertility “of those persons who suffer from any form of mental disease due to inheritance.”⁶² However, “after careful consideration,” Tredgold concluded “that the advantages of segregation far outweigh those of sterilisation.”⁶³ In order for sterilization to be eugenically effective, he argued, “it would be necessary to sterilise every carrier of the neuropathic diathesis, which is obviously impossible.”⁶⁴ Moreover, competing biological processes were at work; anticipation acted to extinguish the neuropathic diathesis in some families while environmental stressors acted to produce new instances of the neuropathic diathesis in others.⁶⁵ The real solution, Tredgold argued, was to educate the public and trust that individuals at risk of passing on hereditary disease would choose to restrict their own fertility.⁶⁶

⁵⁹ Mazumdar, *Eugenics*, 122-144.

⁶⁰ Tredgold was a widely-recognized expert on mental deficiency from 1905 until his retirement in 1951. His textbook *Mental Deficiency*, published first in 1908 and regularly revised and reprinted, was “at once accepted as the most authoritative work on the subject” and was “the standard textbook both here [Britain] and in other English-speaking countries.” Anonymous, “Obituary: A. F. Tredgold, M.D., F.R.C.P.,” *British Medical Journal* 2 (27 September 1952): 726-727. Tredgold’s rejection of sterilization seems to date back as far as 1923 and a pamphlet mentioned in a 1926 *Times* editorial which advocated segregation rather than compulsory sterilization. Leslie Scott, A. F. Tredgold, H. B. Brackenbury, Evelyn Fox, “Mental Deficiency. Case For Institutional Treatment.” *The Times* (London), 20 January 1926, pg. 8, Issue 44174, col. D; Macnicol, “Underclass,” 304; Mazumdar, *Eugenics*, 122-144; Scott, Tredgold, Brackenbury, and Fox, “Mental Deficiency,” 8.

⁶¹ A. F. Tredgold, “Mental Disease in Relation to Eugenics,” *Lancet* 209 no. 5401 (5 March 1927): 526-528; A. F. Tredgold, “Mental Disease in Relation to Eugenics,” *Eugenics Review* 19 no. 1 (April 1927): 1-11.

⁶² Tredgold, “Mental Disease,” *Lancet* 527.

⁶³ Tredgold, “Mental Disease,” *Lancet* 527.

⁶⁴ Tredgold, “Mental Disease,” *Lancet* 528.

⁶⁵ Tredgold, “Mental Disease,” *Lancet* 527-528.

⁶⁶ Tredgold, “Mental Disease,” *Lancet* 528.

Moreover, some physicians were concerned that proposed eugenic sterilization measures would go too far in eliminating those deemed unfit or unwanted. A 1925 discussion on “prophylaxis of mental disorder” published in the *British Medical Journal* illustrates these concerns. In his opening paper, Sir Humphrey Rolleston, Regius Professor of Physic at the University of Cambridge and President of the Royal College of Physicians argued that:

Without being reactionary we may wisely hesitate before advocating strict eugenic measures of breeding, which, if carried to their logical conclusions, might seriously impair the future progress of the race; for if the inborn tendency to variation, which is responsible both for mental weakness and for intellectual ability, were thus removed, a dead level of standardized men, like “Robots,” might conceivably result.⁶⁷

Several of the physicians who contributed to the general discussion following this presentation echoed these concerns.⁶⁸ Frederick Mott himself waded into the issue once more in a lecture given at the University of Liverpool which was published in the *British Medical Journal* shortly after his death on 8 June 1926.⁶⁹ In his lecture “Heredity in Relation to Mental Disease and Mental Deficiency,” Mott again urged caution in the face of proposals by eugenicists to involve the state in preventing “procreation by feeble stocks either by segregation or sterilization.”⁷⁰ He urged that “before any such proposal could be the subject of legislation much more information is required regarding heredity in relation to mental deficiency and the influence of education and social reforms.” Educational and social reforms, he felt, particularly in caring for rural populations, were

⁶⁷ Rolleston thanked Mott for his contributions to the field in his opening remarks. Humphry Rolleston, “Discussion of Prophylaxis of Mental Disorder,” *British Medical Journal* 2 (31 October 1925), 781.

⁶⁸ Anonymous, “General Discussion,” *British Medical Journal* 2 (31 October 1925), 784-788.

⁶⁹ Mott’s extensive contributions to the field, including his “Law of Anticipation” were recognized after his death. See, for example: Anonymous, “Frederick Mott,” *Lancet* 207 no. 5364 (19 June 1926): 1228-1230.; C. von Monakow, “Sir Frederick Mott, K.B.E.: His Life and Work,” in *Contributions to Psychiatry, Neurology and Sociology dedicated to the late Sir Frederick Mott, K.B.E. Hon.LL.D., M.D., F.R.C.P., F.R.S. by his colleagues, friends and former pupils.* Ed., J. R. Lord, (London: H. K. Lewis & Co. Ltd., 1929), 386-387.

⁷⁰ In this paper Mott again maintained that Nature would tend to “end or mend” a degenerate stock by means of natural selection and the “law” of anticipation. F. W. Mott, “Heredity in Relation to Mental Disease and Mental Deficiency,” *British Medical Journal* 1 (19 June 1926): 1025.

the best ways to address the problems of mental defect and insanity before they led to further racial deterioration.⁷¹

In 1924 the Board of Education and the Board of Control set up a research committee under the chairmanship of Sir Arthur Wood to examine how well the 1913 Mental Deficiency Act was functioning in providing care and control of those deemed mentally deficient. The *Report of the Mental Deficiency Committee*, also known as the *Wood Report*, was published in 1929 and stirred up a debate on the question of sterilization as a means to control the mentally deficient that would last until the beginning of the Second World War.⁷²

Nettleship, Lidbetter, and the Pauper Pedigree Project

In 1908, the British Royal Commission on the Care and Control of the Feeble Minded—the investigative committee of which included several members of the Eugenics Society—had submitted its report advocating the control of the feeble-minded by institutionalization, to prevent them from breeding and adding more members to the pauper class.⁷³ Some individual members of the Eugenics Society argued quite energetically for the imposition of legislative controls on the feeble-minded. A. F. Tredgold, the influential writer of psychiatric textbooks that will be examined later, was one such individual. In 1911 and 1912, he published several articles in which he advocated the adoption of eugenic controls on marriage and childbirth as a solution to the societal ills of pauperism and mental defect aimed at eugenical and general audiences alike.⁷⁴

The Eugenics Society believed that similar arguments could be made specifically about the “pauper class.” In 1910, the Eugenics Society’s Committee on Poor Law Reform undertook a study looking for a “biological cause” for pauperism that became known as the pauper pedigree project. While the Society’s Committee on Poor Law

⁷¹ Mott, “Heredity in Relation,” 1025-1026.

⁷² The dispute over the passage of legislation to allow voluntary sterilization in Britain (and the role of anticipation in it) will be dealt with in chapter three. Macnicol, “Eugenics,” 156; Macnicol, “Underclass,” 301-303; Mazumdar, *Eugenics*, 197-200.

⁷³ Mazumdar, *Eugenics*, 22-23; Macnicol, “Eugenics,” 154.

⁷⁴ A. F. Tredgold, “Eugenics and the Future Progress of Man,” *Eugenics Review* 3 (1911): 94-117; A. F. Tredgold, “The Study of Eugenics,” *Quarterly Review* 214 no. 432 (July 1912): 43-67; A. F. Tredgold, “Marriage Regulation and National Family Records,” *Eugenics Review* 4 (1912): 74-90.

Reform was divided as to whether charity or economic forces played a larger role in pauperism, its members agreed on the idea that “both were secondary to an inborn biological deficiency.”⁷⁵ It was hoped that a eugenic solution to this problem might be found in restricting the breeding of this segment of society, perhaps under an extension of the Poor Law.⁷⁶

The pauper pedigree project, which was intended to show the relationship between heredity, degeneracy, and poverty, was the next step in the Eugenics Society’s research programme.⁷⁷ Much of the work of collecting and analysing the pedigrees would be done by Ernest Lidbetter, General Relieving Officer of the Parish of Bethnal Green in London.⁷⁸ Like Mott, Lidbetter was introduced to the concept of anticipation by Nettleship. Lidbetter went on to co-author papers with both men. He provided pedigree material to Mott for his 1911 *Brain* article and in 1913 he co-authored a paper with Nettleship on anticipation in mental disease.⁷⁹ In this paper, Lidbetter and Nettleship put forward the idea that anticipation might be caused by an increased susceptibility to toxins over succeeding generations, as posited by John George Adami in 1912.⁸⁰ Lidbetter also

⁷⁵ As part of this study, the Eugenics Society enlisted the help of relieving officers in three of London’s workhouses. One of these relieving officers was Ernest Lidbetter who later made a study of the relationship between heredity and poverty his life’s work. Mazumdar, *Eugenics*, 71-72.

⁷⁶ Mazumdar, *Eugenics*, 73.

⁷⁷ This research was conducted under the auspices of the Eugenics Society’s Research Committee which was founded in 1912 and included among its members both Lidbetter and Tredgold. Mazumdar, *Eugenics*, 77-79.

⁷⁸ Lidbetter had worked for the London Poor Law authority since 1898 and joined the Eugenics Society soon after it was founded in 1909-1910. He was a frequent speaker at their meetings, often on the subject “Eugenics and the Poor Law,” and he took the full slate of courses offered by the Eugenics Society on biology, Mendelism and biometry. Mazumdar describes him as the Eugenics Society’s “own product, both in his Poor Law background and in his genetics.” Mazumdar, *Eugenics*, 73-77.

⁷⁹ Nettleship died in 1913 shortly after the publication of this paper. In this paper, Lidbetter and Nettleship acknowledged the criticism made by Pearson (1912) to Mott’s statistical methods, but made no further comment beyond stating that anticipation had been noted in a wide variety of disorders, not just in the case of mental defect. E. J. Lidbetter, and E. Nettleship, “On a Pedigree Showing Both Insanity and Complicated Eye Disease: Anticipation of the Mental Disease in Successive Generations,” *Brain* 35 no. 3 (February 1913): 195-221.

⁸⁰ Lidbetter and Nettleship, “Pedigree,” 199. The English-born Adami was appointed chair of pathology and bacteriology at McGill University in Montreal. He was concerned that conditions that affected parents could “influence the children even unto the third and fourth generations.” He repudiated the hard-line Weismannian views of heredity that held that germ cells would not be harmed by conditions (illness etc.) that affected the parent. Rather, he argued, there were chemical (e.g. mercury, alcohol) and physical agents (e.g. x-rays) which could affect the germ plasm. He also suspected that diseases such as syphilis, tuberculosis, and other serious bacterial infections could institute a predisposition, or diathesis, in the parents that would affect succeeding generations and he termed this mode of inheritance “somatogenic.” John George Adami, “A Study in Eugenics: Unto the Third Generation,” *Lancet* 180 no. 4653 (2 November 1912): 1199-1204.

wrote a paper of his own on the effects of heredity and environment on the lower classes.⁸¹ Lidbetter's pedigrees were in turn used by other eugenicists who found them of interest for showing "that in many instances not only do the descendants of the insane poor become inmates of our asylums, but also the remainder who are not deemed anti-social help to swell the large number of paupers that fill our workhouses and infirmaries."⁸² The outbreak of the First World War temporarily halted the pauper pedigree project.

In 1923, the Eugenics Society Research Committee started up again with a new membership, this time including R. A. Fisher.⁸³ Fisher was critical of Lidbetter's use of simple pedigree analysis and urged the committee to adopt more up-to-date scientific and statistical methodologies.⁸⁴ In 1925 Fisher managed to gain the support of two committee members, Julian Huxley and Ward Cutler, in a failed attempt to wrest control of the pauper pedigree project from Lidbetter.⁸⁵ In 1926 the Committee's attempts to introduce statistical analyses and sample a broader segment of society failed due to fiscal constraints and the large scale of the proposed project.⁸⁶ Despite methodological changes made in the intervening years, Lidbetter (and the Eugenics Society) continued to look for links between heredity and membership in the "pauper class" or, as it was called after 1929, the "social problem group."⁸⁷ In spite of all the criticism and opposition, Lidbetter persevered with the project, eventually publishing the partial results in his 1933 *Heredity and the Social Problem Group*.⁸⁸

⁸¹ E. J. Lidbetter, "Nature and Nurture—A Study in Conditions," *Eugenics Review* 4 (1912): 54-73. The relationship between Mott and Lidbetter appears to have been a long-lived and congenial one. Mazumdar describes Mott as "one of Lidbetter's most loyal supporters for many years to come" after their participation in the First International Congress of Eugenics (1912). Mazumdar, *Eugenics*, 89.

⁸² Mott, "Heredity and Insanity," 280-281.

⁸³ Mazumdar, *Eugenics*, 124-126.

⁸⁴ Mazumdar, *Eugenics*, 128-133.

⁸⁵ Mazumdar, *Eugenics*, 133-135.

⁸⁶ Mazumdar notes that techniques developed by the German *Vererbungsmathematik* programme could have successfully analyzed the collected pedigree material. However, British researchers were still unaware of the discoveries of their German counterparts. Mazumdar, *Eugenics*, 135-142.

⁸⁷ Unlike many eugenicists, who had come to reject the idea of anticipation by 1930, Lidbetter continued to believe that anticipation played a role in heredity. This will be discussed further in chapter three.

⁸⁸ E. J. Lidbetter, *Heredity and the Social Problem Group*, (London: Arnold, 1933). A further discussion of this project will appear in chapter three.

The Biometricians and their Criticisms of Anticipation—and Mott’s Reply

Meanwhile, at the Galton Laboratory, Karl Pearson was leading his researchers in a parallel, biometrically oriented, series of eugenic studies.⁸⁹ While the official policy of the Eugenics Society was to consider both Galtonian biometric and Mendelian modes of heredity as applicable to eugenic research—and Nettleship and Mott both did so—a rift existed between proponents of these two approaches until R. A. Fisher bridged the divide in 1918.⁹⁰ While they may have been working towards the same goals as the members of the Eugenics Society, Pearson and his followers vocally expressed their concerns over the scientific fuzziness of many eugenicists at home and abroad.⁹¹ A book reviewer observed: “Dr. Heron and his colleagues [at the Galton Laboratory] have frequently expressed their distaste for controversy, but they have never allowed this reluctance to deter them from expressing their opinions with the utmost frankness.”⁹² One particular fight the statisticians at the Galton Laboratory involved themselves in was a crusade against Mott’s use of anticipation. A second fight saw a brutal exchange of opinions with researchers intent on applying Mendelian genetics to the heredity of feeble-mindedness.

Karl Pearson raised the first arguments against anticipation in the wake of Mott’s paper given at the First International Eugenics Congress.⁹³ At that point Pearson recognized rising interest in anticipation. While he noted that it had its roots in some

⁸⁹ Schuster, “Methods and Results,” 24. Pearson’s ideas were published in his book *The Problem of Practical Eugenics*. The first edition was published in 1909 and is uncirculating so I have had to make do with the second edition. Karl Pearson, *The Problem of Practical Eugenics*, 2nd ed., (London: Cambridge University Press, 1912). On the prickly relationship between Pearson and the Eugenics Society see Mazumdar, *Eugenics*, 41-44.

⁹⁰ Fisher’s 1918 paper reconciled the differences between the Mendelians (led by William Bateson and Reginald Punnett) and the biometricians (led by Karl Pearson) by showing that the range of variation noted by the biometricians could be caused by the Mendelian action of a several (not just one or two) genes. Both by Pearson (who couldn’t deal with the genetics) and Punnett (who couldn’t deal with the statistics) rejected the paper for publication by the Royal Society of London; it appeared in the *Transactions of the Royal Society of Edinburgh* only with the intervention of Major Leonard Darwin (Charles Darwin’s son and the president of the Eugenics Society). R. A. Fisher, “The Correlation between Relatives on the Supposition of Mendelian Inheritance,” *Transactions of the Royal Society of Edinburgh* 52 (1918): 399-433; Kevles, *Eugenics*, 180-184; Mazumdar, *Eugenics*, 58-145; Donald Mackenzie, “Sociobiologists in Competition: The Biometrician-Mendelian Debate,” in *Biology, Medicine and Society 1840-1940*. ed., Charles Webster, (Cambridge: Cambridge University Press, 1981), 243-288; Provine, *Origins*, 140-152.

⁹¹ Mazumdar, *Eugenics*, 40-44.

⁹² M. Greenwood Jr., “Heron, David, D.Sc. *Mendelism and the Problem of Mental Defect. Questions of the Day and of the Fray*. No. vii. London. Dulau and Co.; 1913,” *Eugenics Review* 5 (1913): 367.

⁹³ Pearson’s animosity towards the idea of anticipation is even more interesting because he was, in general, extremely complimentary towards the work of Nettleship, whom he considered a friend and an exemplary researcher. There is, in fact, no evidence that he realized Nettleship, and not Mott, was the originator of the concept.

remarks of Charles Darwin and other serious scholars, he declared that he was unable to follow the attempt at a proof set forward by Mott in his paper.⁹⁴ Pearson wrote, “it *appears* to me to depend upon a statistical fallacy, but this apparent fallacy may not be real, and I should like more light on the matter.”⁹⁵ Pearson explicitly admitted that he based his argument on two assumptions: “(1) that there is no antedating at all; [and] (2) that there is no inheritance of age of onset.”⁹⁶ He observed that an appearance of anticipation would rest on the ability of those in the parental generation to live long enough to have offspring.⁹⁷ He offered as proof that Mott had fallen into a fallacy the example of antedating in the case of violent deaths:

Consider now the parents and offspring who die from violent deaths; clearly there would be no representative of death from violence under twenty in the parent generation, and we would have a most marked case of antedating, because the offspring generation would contain all the infantile deaths from violence.⁹⁸

Pearson argued that, by examining diseases which ran in families, researchers were automatically selecting for a later age of onset in the parental generation (by virtue of the parents living long enough to marry and have children) than in the offspring generation when the disease could strike at any age (but would be likeliest seen if it had an early onset). In other words, when studying families suffering from a hereditary disease with a variable age of onset (like insanity), the researcher would only examine those members of the parental generation who happened to live long enough to have children. In the offspring generation the disease could strike at any age, but—given the length of time of the average genetic study—researchers would be most likely to notice (and record) early-

⁹⁴ Karl Pearson, “On an Apparent Fallacy in the Statistical Treatment of “Antedating” in the Inheritance of Pathological Conditions,” *Nature* 90 (1912): 334.

⁹⁵ Pearson, “Fallacy,” 334. The arguments set forth by Mott in his Eugenics Congress paper were somewhat terse, especially when compared to his earlier writing on the subject.

⁹⁶ Pearson, “Fallacy,” 334.

⁹⁷ While Pearson’s argument is valid as far as it goes, it rests on the assumption that anticipation is not a real biological phenomenon. That is, there was no way to ascertain whether a disease was, in fact, appearing at earlier ages in succeeding generations because any appearance of anticipation would be assumed to be due to this process of selection. Given this assumption, I doubt if it would ever have been possible for Mott to defend the general concept of anticipation. Moreover, both the Mendelians and the biometricians found abhorrent Mott’s specific mechanism of anticipation, i.e. the germinal concentration of bad genes within certain members of the pedigree.

⁹⁸ Pearson, “Fallacy,” 334.

onset cases.⁹⁹ Moreover, Pearson noted, in the case of insanity “those who become insane before twenty-five, even if they recover, are far less likely to become parents than those who become insane at later ages—many, indeed, of them, considering the high death-rate of the insane, will die before they could become parents of large families.”¹⁰⁰ This too could contribute to the appearance of anticipation because these individuals would have no children in whom the disease would manifest at a later age than in their parents. Pearson concluded that, although Mott’s research had revealed “a most marked antedating of disease in the offspring” of insane parents, it was “an antedating which is wholly spurious.”¹⁰¹ Pearson mentioned having found “a further grievous fallacy involved in this method of considering the problem” but said that he would wait until his first criticisms were answered before revealing it.¹⁰² To the best of my knowledge, he never published the second fallacy he claimed to have detected.

Mott replied to Pearson in a 1913 lecture given at Johns Hopkins University in Baltimore. Versions of his talk were later published in the *American Journal of Insanity* and in *Archives of Neurology and Psychiatry*.¹⁰³ This lecture contained much of the same information contained in Mott’s other papers outlining his methodology, discussing the history of research on anticipation and the application of the concept to the study of mental illness. Mott restated his finding that “after the age of 25 there is a greatly decreasing liability of the offspring of insane parents to become insane” and therefore those reaching that age unaffected would be safe to marry and have children.¹⁰⁴ This finding, Mott stated, was confirmed by no less an authority than Sir George Savage, the president of the psychiatric section of the Royal Society of Medicine, whose clinical experience agreed with Mott’s findings.¹⁰⁵

⁹⁹ Similar arguments would be later taken up by the British psychiatrist and geneticist Lionel Penrose in his own studies of anticipation. See chapters three and four.

¹⁰⁰ Pearson, “Fallacy,” 335.

¹⁰¹ Pearson, “Fallacy,” 335.

¹⁰² Pearson, “Fallacy,” 335.

¹⁰³ F. W. Mott, “A Study of the Neuropathic Inheritance,” *American Journal of Insanity* 64 no. 4 (1913): 907-938; F. W. Mott, “A Study of the Neuropathic Inheritance especially in Relation to Insanity,” *Archives of Neurology and Psychiatry (London)* 6 (1914):79-98. Although the article published in the *American Journal of Insanity* contains some material not published in the *Archives of Neurology and Psychiatry*, the same arguments appear in both papers.

¹⁰⁴ Mott, “Neuropathic Inheritance,” (1913), 912.

¹⁰⁵ Mott, “Neuropathic Inheritance,” (1913), 912. The meeting that Mott referred to at which Savage confirmed his findings seems to have been the meeting of the Psychiatric Section of the Royal Society of

In discussing Pearson's criticisms, Mott did "not feel myself competent to reply to the opinion of such an eminent authority on mathematics applied to biometrics," however, he stated that:

his criticism does not militate against my conclusions, nor explain away the fact that a large proportion of the insane offspring of insane parents are affected with imbecility or adolescent insanity, for, granting the assumption that there is no antedating at all, we might rightly expect the ages at onset of insane offspring of insane parents to be comparable with the ages at onset of all the admissions to the asylums during the same period. This is by no means the case, for amongst the insane offspring there is a far greater proportion affected early in life.¹⁰⁶

Mott countered Pearson's argument that anticipation was caused by selection bias with the results of his own clinical study which found that many of the children of insane parents suffered from insanity in adolescence or from mental retardation at disproportionate rates when compared to the general population. Unless anticipation was occurring, Mott said, there was no way to explain his findings that the insane children of insane parents were admitted to the London County Asylums at a disproportionately younger age than that of the general population of the insane.¹⁰⁷ In other words, while Mott could only defer to Pearson's statistical expertise, he stood his ground in defence of the substance of his findings and the biological reality of anticipation.

Mott knew that ideas held by "the majority of practising physicians" that "the racial poisons, alcohol, syphilis, and tuberculosis can *per se* cause degeneracy" via a

Medicine on 28 January 1913 at which Mott lectured on "Insanity and the Neuropathic Inheritance." The report of the meeting published in *The Lancet* notes that after describing his study of inmates in the London county asylums "Dr. Mott then proceeded to establish the principle of anticipation or antedating, and nature's means of ending or mending degenerate stock." Savage referred to cases of his own and stated that "marriage between offspring of degenerate parents was not such a serious matter where the contracting parties did not themselves show a neurotic taint as where that did exist." Anonymous, "Medical Societies: Royal Society of Medicine," *Lancet* 181 no. 4667 (8 February 1913): 388-389.

¹⁰⁶ Mott, "Neuropathic Inheritance," (1913), 915.

¹⁰⁷ Mott, "Neuropathic Inheritance," (1913), 916. One of the harshest criticisms that would be levelled against the notion of anticipation by its critics was the argument that late onset cases in the children's generation would likely be missed. Although Mott was not analyzing complete generations (generations in which all of the members had either died or reached an age past that at which disease was likely to manifest itself), membership in the offspring generation included more than just children and young adults. In Mott's study, the age of insane children of insane parents ranged from 0 to 74 years. While the majority of cases were clearly admitted under the age of 35 (71.9%) a not insubstantial number were admitted after that age. By comparison, only 40% of the total admissions were made at under the age of 35.

transmissible “pathological mutation of the germ plasm” were considered to be “a biological heresy.”¹⁰⁸ Nevertheless, he concluded, a large enough collection of pedigrees “would afford the proof required even by biologists” that the observations made by himself and other physicians demonstrated that such degeneration was actually taking place.¹⁰⁹

Mott discussed Pearson’s criticisms once more in his Cavendish Lecture to the West London Medico-Chiurgical Society. This piece was published in the widely circulated medical journal *The Lancet* in July, 1914.¹¹⁰ Mott here went into some detail concerning the role of syphilis in creating mental and nervous disease.¹¹¹ He was concerned that the “race poisons” of “alcoholism, tuberculosis, and syphilis” served as “environmental causes of degeneracy” which itself was known to worsen over succeeding generations, according to Mott, even though such a belief was “a biological heresy.”¹¹² Mott identified the “neuropathic inheritance and disorders of the functions of the sexual glands” as playing “a dominant part in the causation of the true insanities.”¹¹³ Anticipation was often seen in cases where neuropathic inheritance was at work, and in this context Mott once again discussed Pearson’s criticisms of his statistics. Mott, however, argued that he did “not regard this as a question of mathematics, but one of observed facts and experience.”¹¹⁴ His findings of anticipation were supported by British physicians and French alienists alike he declared.¹¹⁵ Even Pearson himself, Mott noted, did not dispute the fact that those stricken with an attack of insanity before the age of twenty-five, even if they later recovered, were unlikely to marry and procreate.¹¹⁶ Moreover, recent studies had shown that in “primary dementia of adolescence” there were often pathological changes in the ovaries that would greatly reduce fertility.¹¹⁷ Mott considered these findings to be “further evidence of “anticipation”.”¹¹⁸ This was Mott’s

¹⁰⁸ Mott, “Neuropathic Inheritance,” (1913), 98.

¹⁰⁹ Mott, “Neuropathic Inheritance,” (1913), 98.

¹¹⁰ F. W. Mott, “A Lecture on The Causes of Insanity,” *Lancet* 184 no. 4741 (11 July 1914): 75-81.

¹¹¹ Mott, “A Lecture,” 75-77.

¹¹² Mott, “A Lecture,” 77-78.

¹¹³ Mott, “A Lecture,” 79.

¹¹⁴ Mott, “A Lecture,” 79.

¹¹⁵ Mott, “A Lecture,” 79-80.

¹¹⁶ Mott, “A Lecture,” 80.

¹¹⁷ Mott, “A Lecture,” 80.

¹¹⁸ Mott, “A Lecture,” 80.

last paper on the subject of anticipation for some time to come. With the outbreak of the First World War he served as a lieutenant-colonel in the Royal Army Medical Corps. His research for the next several years thus centered on the problem of shell shock and its treatment, and he was created a Knight of the British Empire in 1919 in recognition of these contributions.

In 1914, David Heron, who had learned biometric statistics from Pearson before working for him at the Galton Laboratory on his own research into heredity and insanity, joined the discussion on anticipation.¹¹⁹ In a long paper, Heron criticized Mott's concept of anticipation for having "contributed fallacious eugenic rules to those seeking knowledge of the influence of the hereditary factor in insanity."¹²⁰ Heron's criticisms of Mott were lengthy and caustic, especially about the way that Mott's ideas of anticipation were being applied.¹²¹ Rather than discouraging all of those with insane relatives from procreating, Mott would allow them to marry once they passed 25 years of age without showing signs of mental illness. To this, Heron retorted: "it is the obvious duty of the Eugenicist to discourage, rather than to encourage, procreation by the insane and even by those of their offspring who appear to be normal."¹²² Moreover, Mott did not advocate the use of sterilisation as a means of controlling the number of the unfit. Both of these positions ran counter to precepts held by both the Eugenics Society and the biometricians at the Galton Laboratory.

Despite the fact that the concept of anticipation had been strongly rebuked by Pearson and Heron, other researchers in a variety of fields continued to adopt it between 1914 and 1930. Pearson and Heron's scepticism regarding anticipation influenced work at the Galton Laboratory. Their impact is notably evident in the work of Julia Bell, whose own considerable contributions will be discussed later. Bell was always either cautious or dismissive regarding anticipation in her publications. Most of her published comments regarding anticipation appeared in her contributions to the Galton Laboratory's

¹¹⁹ David Heron, "An Examination of some Recent Studies of the Inheritance Factor in Insanity." *Biometrika* 10 (1914): 356-383. For an overview of Heron's study on Heredity and Insanity see Schuster, "Methods and Results," 15-17.

¹²⁰ In the article Heron complained bitterly about how the untrained (meaning Mott) used statistics to back up their theories, arguing that "the day of the amateur in science is gone." David Heron, "Examination," 356-357.

¹²¹ This was apparently not very unusual for him. Greenwood, "Heron, David," 367.

¹²² Heron, "Examination," 381-383.

Treasury of Human Inheritance. These will be discussed later, but her 1928 article in *Annals of Eugenics* very instructively states: “Ante-dating may or may not occur in a variety of diseases. My point is not that it never occurs but that too many investigators have applied quite inadequate statistical methods to demonstrate its occurrence.”¹²³ She approvingly cited Heron’s 1914 *Biometrika* article in support of this view.¹²⁴

The Biological Basis of Mental Defect: A new Biometrical-Mendelian Dispute

The biometricians of the Galton Laboratory also engaged in a heated dispute with those who sought to prove that mental defect was a recessive trait inherited according to the rules of Mendelian heredity. This conflict is mentioned here because it was within the context of discussions about the heredity of mental defect that the dispute concerning anticipation re-surfaced in the 1930s.¹²⁵ Much of the Mendelian work on this question came out of the American eugenics community (although it was adopted by other Mendelians too) and had its basis in the research of Henry Goddard.¹²⁶ Charles Davenport, head of the Eugenics Record Office at Cold Spring Harbor, used his bulletin to publish and republish many papers on Mendelian patterns of heredity in cases of insanity and feeble-mindedness.¹²⁷ Davenport’s books echoed many of the same themes

¹²³ Julia Bell, “The Age of Onset in Hereditary Optic Atrophy,” *Annals of Eugenics* 3 (1928): 274.

¹²⁴ Julia Bell, “Hereditary Optic Atrophy,” 274.

¹²⁵ See chapter three.

¹²⁶ Goddard, Davenport, and other members of the American eugenics community often published their papers in English as well as American journals. For example, one of the papers that began this argument was first published in *American Breeder’s Magazine* in 1910 and republished in the British *Eugenics Review* and the American *Eugenics Record Office Bulletin* in 1911. In fact, most of the papers published in the *ERO Bulletin* were republished from other sources, sometimes with the original page numbers. Henry H. Goddard, “Heredity of Feeble-Mindedness,” *American Breeders Magazine* 1 no. 3 (1910): 165-178; H. H. Goddard, “Heredity of Feeble-Mindedness,” *Eugenics Record Office Bulletin* 1 (1911): 1-14. This particular article was also reprinted in the British *Eugenics Review*. H. H. Goddard, “Heredity of Feeble-Mindedness,” *Eugenics Record Office Bulletin* 1 (1911): 1-14. Further citations will refer to the version published in the *ERO Bulletin*.

¹²⁷ Goddard, “Heredity of Feeble-Mindedness,” 1-14; Gertrude Cannon and A. J. Rosanoff, “Preliminary Report of a Study of Heredity and Insanity in the Light of the Mendelian Laws,” *Eugenics Record Office Bulletin* 3 (May 1911): 1-11; “The neuropathic constitution is transmitted from generation to generation in the manner of a trait which is, in the Mendelian sense, recessive to the normal condition.” (259) A. J. Rosanoff and Florence Orr, “A Study of Heredity in Insanity in the Light of the Mendelian Theory,” *Eugenics Record Office Bulletin* 5 (October 1911): 221-261. In one of the few American papers which discussed the question of anticipation Henry Cotton discussed the work of Mott and Nettleship but was concerned that some individuals might have been missed by the researchers, leading to exaggerated findings. Nevertheless, Cotton felt that Mott’s work “in all probability, represents the best work that has been done by the English in the field.” Henry Cotton, “Some Problems in the Study of Heredity in Mental Diseases,” *Eugenics Record Office Bulletin* 8 (August 1912): 11-12.

in relation to heredity and eugenics.¹²⁸ The British biometricians at the Galton Laboratory took umbrage at what they felt was sloppy science, and they could be quite brutal in expressing their objections. Heron, Pearson, and their colleagues all made their criticisms of this work very plain.¹²⁹ Heron's writing in particular was so vitriolic that a reviewer felt moved to comment extensively on its tone and expressed a hope that he would in the future choose "to formulate his conclusions in studiously moderate terms."¹³⁰ Davenport reserved the whole eleventh issue of the *Eugenics Record Office Bulletin* for articles replying to these British criticisms.¹³¹ Despite, or perhaps because of, the acrimony of the dispute, eugenicists on both sides of the Atlantic continued attempting to apply Mendelian genetics to mental traits.¹³²

APPLYING THE CONCEPT OF ANTICIPATION

Although the demands of the First World War temporarily ended theoretical work on the concept of anticipation, a number of researchers examining a variety of conditions continued to apply the concept. Perhaps it is not surprising, given the lengths to which Mott went to popularize the concept, that the role of anticipation was examined in the

¹²⁸ Charles Davenport, *Heredity in Relation to Eugenics*, (London: Williams and Norgate, 1912); and (New York: Henry Holt and Company, 1913).

¹²⁹ David Heron, *Mendelism and the Problem of Mental Defect: I. A Criticism of Recent American Work*, (London: Dulau and Co., Ltd., 1913). For his part, Pearson discussed questions raised by the application of (Binet-Simon) intelligence testing to normal and "mentally defective" children. His conclusions, unlike those of the Americans, were that the measure of intelligence takes a Gaussian (bell) curve and that mentally defective children merely occupy the lower reaches of the curve. That is, this does not show intelligence to be a simple Mendelian trait. Some of his remarks are quite cutting. Karl Pearson and Gustav A. Jaederholm, *Mendelism and the Problem of Mental Defect: II. On the Continuity of Mental Defect*, (London: Cambridge University Press, 1914).

¹³⁰ Greenwood Jr., "Heron, David," 367.

¹³¹ Charles Davenport, "A Discussion of the Methods and Results of Dr. Heron's Critique," *Eugenics Record Office Bulletin* 11 (1914): 3-24; A. J. Rosanoff, "Mendelism and Neuropathic Heredity: A Reply to Some of Dr. David Heron's Criticisms of Recent American Work," *Eugenics Record Office Bulletin* 11 (1914): 27-43.

¹³² Davenport continued to be an outspoken supporter of the theory that the origins of mental defect could be determined through Mendelian genetics. See for example Charles Davenport, "Heredity of Constitutional Mental Disorders," *Eugenics Record Office Bulletin* 20 (October 1920): 300-310. The historian David Barker has analysed the responses of several Anglo-American geneticists to the theory that mental defect was caused by Mendelian recessive patterns of inheritance. While some geneticists remained supportive of the idea through the 1930s, others, most notably J. B. S. Haldane, moved from accepting the claim (1928) to rejecting it (1935). David Barker, "The Biology of Stupidity: Genetics, Eugenics and Mental Deficiency in the Inter-War Years," *British Journal for the History of Science* 22 (1989): 347-375. On this topic see also Kevles, "Eugenics in North America," 208-226 and Macnicol, "Underclass," 293-318.

case of mental illness and mental defect. The idea, however, was applied to explain patterns of inheritance in neuromuscular, ophthalmologic, and endocrine disorders.

Anticipation and Mental Illness and Mental Defect

The long history of the concept of degeneration as promulgated by Lucas, Morel and Maudsley in the nineteenth century made the medical and psychiatric communities relatively accepting of the concept of anticipation during the first third of the twentieth century. Nevertheless, different national communities treated it differently. The reception of the concept of anticipation in Germany went from favourable to disapproving between 1910 and 1930, while during this time it remained favourably received among psychiatric researchers in Britain, except among the Pearson, Heron and those at the Galton Laboratory.¹³³

Dementia praecox, now known as schizophrenia, was one of the first specific psychiatric disorders with which anticipation was associated. In 1916, the German physician and psychiatrist Ernst Rüdin endorsed the notion of anticipation and traced its antecedents and spread in the literature, in his seminal study of dementia praecox.¹³⁴ In his discussion of anticipation, Rüdin referenced the work of Mott (1911) and took from him the information that the term had been coined by Nettleship. He also referred to the older work of scholars such as Darwin, Lucas, and Bowmann who had seen similar patterns of inheritance in a variety of disorders such as diabetes, tuberculosis, and various forms of insanity.¹³⁵ Other scholars, Rüdin noted, had made similar findings, and these studies were indicated in his bibliography.¹³⁶ However, by 1923 Rüdin had turned away from the concept of anticipation. His 1923 paper on the heredity of mental disorder

¹³³ By 1930, during the debates concerning the adoption of voluntary sterilization in Britain, Pearson and Heron were joined by others who criticised the use of “Mott’s Law” of anticipation as an argument against the passage of such legislation and for allowing marriage and procreation in families with a history of mental illness since, as Mott argued so often citing Maudsley, Nature worked to “end or mend” damaged stocks without the need of outside intervention. This dispute will be dealt with in detail in chapter three.

¹³⁴ Rüdin, *Dementia Praecox*, 123-138. On Rüdin’s schizophrenia studies see also Kenneth Kendler and Edith Zerbin-Rüdin, “Abstract and Review of ‘Studien über Vererbung und Entstehung geistiger Störungen. I. Zur Vererbung und Neuentstehung der Dementia praecox.’ (Studies on the Inheritance and Origin of Mental Illness: I. To the Problem of the Inheritance and Primary Origin of Dementia Praecox.),” 338-342; Weber, “Ernst Rüdin,” 326-327; Zerbin-Rudin and Kendler, “Ernst Rüdin,” 332-337;

¹³⁵ Rüdin, *Dementia Praecox*, 129-130.

¹³⁶ Rüdin, *Dementia Praecox*, 129-130, 170-172.

discussed studies of Huntington's disease that were critical of the idea of anticipation.¹³⁷ Although he recognized that no less an authority than Morel had commented upon the question of degenerate heredity, Rüdin noted that idea of anticipation was now to be rejected on the grounds suggested by Weinberg—that its appearance was due to the researchers' inordinate focus on late onset forms of disease in the parental generation.¹³⁸ Yet long after Rüdin had stopped supporting the notion of anticipation, some researchers continued to associate him with anticipation in schizophrenia due to his 1916 paper.¹³⁹

In the 1920s Mott published a series of papers of his own on the pathology and inheritance of schizophrenia.¹⁴⁰ He discussed his findings as part of his 1921 Maudsley Lecture, which argued that anticipation did occur in instances of schizophrenia and that his observations agreed with those that had been made by Rüdin in 1916.¹⁴¹ He reported similar findings in his 1925 Harveian Oration to the Royal College of Physicians.¹⁴² In this context, he cautioned against the application of Mendelian principles of heredity to the study of mental disease noting that “there are too many complicating factors” in the study of humans as compared to research on animals.¹⁴³ Mott concluded that heredity in mental deficiency was a field of research “which still requires an enormous amount of patient investigation before any definite conclusions” could be arrived at.¹⁴⁴ His final comments on the subject came in his Chadwick Lecture given at the University of Liverpool shortly before his death in 1926. Here he discussed again his “law of anticipation, whereby the offspring of insane parents who become insane do so at an earlier age, and in a more intense form, so that they are segregated and procreation is prevented,” thus ending or mending a “degenerate stock.”¹⁴⁵ This was true of schizophrenia, Mott claimed, because the parents or grandparents of those so afflicted

¹³⁷ Rüdin, “Vererbung Geistiger Störungen,” 473-478.

¹³⁸ Rüdin, “Vererbung Geistiger Störungen,” 492-493.

¹³⁹ See for example, Lionel Penrose, *The Biology of Mental Defect*, with a preface by J. B. S. Haldane., (London: Sidgwick and Jackson Limited, 1949), 66.

¹⁴⁰ Not all of these papers discussed the question of anticipation. Some were more concerned with questions of pathology, e.g. F. W. Mott, “The Pathology of Dementia Praecox,” *British Medical Journal* 2 (20 November 1920): 781-782.

¹⁴¹ F. W. Mott, “Maudsley Lecture,” *Archives of Neurology and Psychiatry (London)* 8 (1922): 48-50.

¹⁴² F. W. Mott, “The Harveian Oration on Heredity in Relation to Mental Disease,” *British Medical Journal* 2 (24 October 1925): 727-731.

¹⁴³ Mott, “Harveian,” 729.

¹⁴⁴ Mott, “Harveian,” 731.

¹⁴⁵ Mott, “Heredity in Relation,” 1025.

were often found to have suffered from “involutional melancholia” or manic depressive insanity.¹⁴⁶

In Britain, successive editions of A. F. Tredgold’s widely used textbook *Mental Defect* provide a good picture of the adoption, integration, and eventual rejection of the concept of anticipation by the medical research community.¹⁴⁷ Tredgold’s approach to the issue in the 1914 edition was somewhat old school, drawing heavily on the writings of Morel, Maudsley and other authors but showing some awareness of Nettleship’s work though this was not overtly discussed.¹⁴⁸ Tredgold promoted the notion that neuropathic diathesis caused much mental defect. The neuropathic diathesis was a hereditary predisposition to mental illness that he thought was triggered by, and could have its origin in, environmental causes.¹⁴⁹ Tredgold did not approve of Davenport’s views that mental defect was caused by dominant or recessive mutations that could be studied according to Mendelian genetics.¹⁵⁰ Instead, following the ideas of Morel and Maudsley, he believed that a progressive psychopathic diathesis existed that, with appropriate environmental triggers, could cause degeneration to occur over a number of generations and lead to a variety of illnesses within the same family.¹⁵¹ These arguments remained essentially unchanged through his third (1920) and fourth (1922) editions but Tredgold discussed anticipation directly in his fifth edition (1929), although his overall analysis of mental deficiency and its causes still remained essentially unchanged.¹⁵² This uniformity of views shows how the new concept was fairly seamlessly integrated into older ideas of degeneration and the hereditary nature of mental illness. Psychiatric researchers often

¹⁴⁶ Mott, “Heredity in Relation,” 1025.

¹⁴⁷ Tredgold’s textbook *Mental Defect* went through multiple editions in several countries. The first of these dated to 1908—that is before the Nettleship began to actively disseminate his concept of anticipation—and new editions continued to appear after Tredgold’s death first by his son and then by other authors. For this reason, I use this text to examine the adoption and eventual rejection of the concept of anticipation. Discussion of it will take place in several chapters.

¹⁴⁸ Tredgold’s textbook was very popular, and several editions were published simultaneously in Britain, Canada, and America. For the sake of consistency, I have tried to acquire all of the London editions but I have not always been successful.

¹⁴⁹ A. F. Tredgold, *Mental Deficiency (Amentia)*, 2nd ed., rev., (Toronto: The Macmillan Company of Canada, Ltd., 1914), 25-26, 39.

¹⁵⁰ Tredgold, *Mental Deficiency* (1914), 28.

¹⁵¹ Tredgold, *Mental Deficiency* (1914), 33-34.

¹⁵² A. F. Tredgold, *Mental Deficiency (Amentia)*, 3rd ed., (London: Baillière, Tindall and Cox, 1920), 23, 26, 34-36, 40; A. F. Tredgold, *Mental Deficiency (Amentia)*, 4th ed., rev., (London: Baillière, Tindall and Cox, 1922), 23, 26, 34-36, 40; A. F. Tredgold, *Mental Deficiency (Amentia)*, 5th ed., largely rewritten, (London: Baillière, Tindall and Cox, 1929), 18, 26-34.

studied Huntington's disease and myotonic dystrophy, the subjects of the next two subsections because psychiatric symptoms were not uncommon in severe cases of each disease.

Anticipation and Huntington's Disease

Acceptance of the concept of anticipation in Huntington's disease was not unanimous among clinical researchers between 1910 and 1930.¹⁵³ Charles Davenport disagreed with Heilbronner's 1903 findings of earlier onset in succeeding generations in Huntington's disease. In 1915, he argued that findings suggesting that the "law of anticipation" was operating in the case of Huntington's disease were "partly, if not wholly, illusory" and that these findings were due to the selection of later age of onset of disease in the grandparental and parental generations (by virtue of their having lived long enough to have children) combined with the fact that the "grandchildren include those in whom the onset is so early in life that they will never marry."¹⁵⁴ The researcher should, he proposed, not compare the age of onset over several generations of a single family, but should rather average the age of onset of succeeding generations of a group of families suffering from Huntington's; "then the evidence for anticipation vanishes."¹⁵⁵ Davenport reiterated these arguments in a 1916 paper co-authored with Elizabeth Muncey.¹⁵⁶ Davenport and Muncey suggested that the appearance of anticipation was caused by a bias in selection such that "the earlier generation are selected for the more advanced age of onset and so they show this advanced age; the later generations are less rigidly selected and so they do not show so advanced an age of onset of the disease."¹⁵⁷ They concluded,

¹⁵³ Psychiatric researchers often studied diseases such as Huntington's disease and myotonic dystrophy because psychiatric symptoms were not uncommon in severe cases of the disease.

¹⁵⁴ Charles Davenport, "Huntington's Chorea in Relation to Heredity and Eugenics," *Proceedings of the National Academy of Sciences of the United States of America* 1 no. 5 (15 May 1915): 284.

¹⁵⁵ Davenport, "Huntington's," 284.

¹⁵⁶ This paper was published in both the *American Journal of Insanity* and in Davenport's *Eugenics Record Office Bulletin*. Charles Davenport, and Elizabeth B. Muncey, "Huntington's Chorea in Relation to Heredity and Eugenics," *American Journal of Insanity* 73 (1916): 195-222; Charles Davenport and Elizabeth Muncey, "Huntington's Chorea in Relation to Heredity and Eugenics," *Eugenics Record Office Bulletin* 17 (October 1916): 195-222.

¹⁵⁷ Davenport and Muncey, "Huntington's Chorea," 207-209.

“there is thus no good evidence that the age of onset of the choreic movements tends to occur earlier in the later generations.”¹⁵⁸

During the 1920s, two papers appeared in Germany which argued that anticipation did not occur in Huntington’s disease. The first was written in 1921 by J. L. Entres, a member of Rüdin’s Munich school.¹⁵⁹ Entres argued that although Heilbronner had found that Huntington’s disease appeared earlier in succeeding generations, a finding later known as “anteponition,” Weinberg had later shown such findings to be the result of selection bias.¹⁶⁰ In 1928 F. Kehrer, the director of the psychiatric and nervous clinic in Munster, published his own monograph on Huntington’s disease.¹⁶¹ Kehrer did not consider whether or not anticipation was due to selection bias, rather he commented that the finding of anticipation was made when the younger generations of a family were found to suffer from forms of Huntington’s disease that were more severe and that manifested at earlier ages in the older generations. Kehrer suggested, as had Davenport, that these were merely variant manifestations of the illness.¹⁶² Later researchers, however, continued to identify signs of anticipation in Huntington’s disease, as we shall see.

Anticipation and Myotonic Dystrophy

Almost from its first recognition as a specific disease in the medical literature, anticipation was synonymous with myotonic dystrophy. Between 1910 and 1930 myotonic dystrophy was first characterized and its generational variation in symptoms and ages of onset recognized. Myotonic dystrophy is an autosomal dominant neuromuscular disease with highly variable symptomology and age of onset. In the first generation, muscles are not usually obviously affected. Instead, the main symptom is cataract development in middle or old age. In the following generation, the disease generally appears in its classic form with muscle weakness and myotonia. The most severe form of the disease occurs congenitally in the offspring of females affected by

¹⁵⁸ Davenport and Muncey, “Huntington’s Chorea,” 209.

¹⁵⁹ Weber, “Ernst Rüdin,” 327; Zerbin-Rüdin and Kandler, “Ernst Rüdin,” 335.

¹⁶⁰ J. L. Entres, *Zur Klinik und Vererbung der Huntingtonschen Chorea, Monographien aus dem Gesemtgebiet der Neurologie und Psychiatrie*. Heft 37. (Berlin: Springer Verlag, 1921), 47.

¹⁶¹ F. A. Kehrer, *Erblichkeit und Nervenleiden, Monographien aus dem Gesemtgebiet der Neurologie und Psychiatrie*. Heft 50. (Berlin: Springer-Verlag, 1928).

¹⁶² Kehrer, *Erblichkeit*, 92-94.

classical myotonic dystrophy.¹⁶³ From the outset researchers acknowledged both the hereditary nature and the extreme variability of the disease. These features consistently attracted the attention of the series of doctors and geneticists who studied the disorder early in the twentieth century.¹⁶⁴ At the same time, the progressive nature of myotonic dystrophy and the fact that children born with the congenital form were usually so severely affected that they could not reproduce made this disease particularly interesting for eugenicists and social Darwinists who saw the disorder as confirmation of their beliefs.¹⁶⁵

In 1911, J. Godwin Greenfield was one of the first researchers to realise the importance of cataract in the earlier generations of myotonic dystrophy.¹⁶⁶ In the family he studied, the existence of patients who developed cataract and myotonia at the same time led him to conclude that “the causes of the two conditions may be in some way related.”¹⁶⁷ Greenfield realised that cataract which manifested in old age without muscular symptoms also existed in earlier generations of the family, members of which now showed signs of myotonia and cataract at a younger age. However, he did not use the term “anticipation” to describe this observation.¹⁶⁸

¹⁶³ The traditional history of anticipation in myotonic dystrophy holds that the high rate of infant mortality in congenital cases resulted in the delay of the recognition of the linkage of maternal transmission and the congenital form of the disease until Harper and Dyken (1972). However, as Harper (2005) remarked recently, the presence of early onset cases, even congenital ones, was noted by Bell in the *Treasury of Human Inheritance* in 1947. However, as will be discussed in chapter four, my research has shown that the recognition that only the children of affected females suffered from the congenital form of the disease was made independently in 1954 by the Swiss geneticist David Klein and the New Zealand neurologists J. E. Caughey and J. Barkley. J. David Brook, Mila E. McCurrach, Helen G. Harley, Alan J. Buckler, Deanna Church, Hiroyuki Aburatani, Kent Hunter, Vincent P. Stanton, Jean-Paul Thirion, Thomas Hudson, Robert Sohn, Boris Zemelman, Russell G. Snell, Shelley A. Flundle, Steve Crow, June Davies, Peggy Shelbourne, Jessica Buxton, Clare Jones, Vesa Juvonen, Keith Johnson, Peter S. Harper, Duncan J. Shaw, and David E. Housman, “Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member,” *Cell* 68 (1992): 799-808; Peter Harper and P. R. Dyken, “Early onset dystrophia myotonica—evidence supporting a maternal environmental factor,” *Lancet* 300 no. 7792 (8 July 1972): 53-55; Peter Harper, “Julia Bell and the *Treasury of Human Inheritance*,” *Human Genetics* 116 (2005): 422-432; David Klein, “Manifestations progressives et extensives d’une dystrophie myotonique dans une famille argovienne,” *Confina Neurologica* 14 (1954): 169-175; J. E. Caughey and J. Barkley, “Dystrophia myotonica and the occurrence of congenital physical defect in affected families,” *Australasian Annals of Medicine* 3 no. 3 (August 1954): 165-170.

¹⁶⁴ Peter Harper, *Myotonic Dystrophy*, 2nd ed., (London: W. B. Saunders Company, 1989), 2-10; 293.

¹⁶⁵ Harper, *Myotonic* (1989), 310.

¹⁶⁶ J. Godwin Greenfield, “Notes, on a family of ‘myotonia atrophica’ and early cataract, with a report of an additional case of ‘myotonia atrophica,’” *Review of Neurology and Psychiatry* 9 (1911): 169.

¹⁶⁷ Greenfield, “Notes,” 169.

¹⁶⁸ Greenfield, “Notes,” 170.

The German ophthalmologist Bruno Fleischer first conclusively proved, in a series of extensive studies published from 1916 to 1923, that the disease showed dominant inheritance and that it involved cataract.¹⁶⁹ Using cataract as an identifying feature, Fleischer was able to trace myotonic dystrophy through different families to show that they had common, and apparently unaffected, ancestors.¹⁷⁰ The accuracy of these genealogical observations was tested and confirmed by several other researchers from 1925 onwards.¹⁷¹ Fleischer noted that although myotonic dystrophy was highly variable, members within the same generation generally had similar symptoms and ages of onset—i.e. the disease showed both homologous and homochronos heredity.¹⁷² He also carefully delineated the way that myotonic dystrophy appeared earlier and in a more severe form in subsequent generations of these families.¹⁷³ Although he was aware of Nettleship's work and referenced Nettleship (1909) in his own 1918 paper, he did not directly use the term 'anticipation' in presenting and explaining his observations. Rather, he placed his observations within the framework of nineteenth-century concepts of inheritance that included the notion of degeneration of family lines; he thus argued that in time the disease would eventually die out in such families.¹⁷⁴ "Degeneration" was in fact the term that Fleischer used, and he compared the degeneration seen in myotonic dystrophy families with that which had been observed in families with Huntington's

¹⁶⁹ Fleischer's 1916 paper identified that cataract was often seen in myotonic dystrophy. His later papers used cataract as a means by which to trace the transmission of the disease through several generations, especially in the early generations when cataract was the only sign of illness. Bruno Fleischer, "Über Myotonia atrophicans und Kataract Bericht," *Versammlung der Heidelberger Ophthalmologisten Gesellschaft* 40 (1916): 441-447; Bruno Fleischer, "Über myotonische Dystrophie mit Katarakt: Eine hereditäre, familiäre Degeneration," *Albrecht Von Graefe's Archiv für Ophthalmologie* 96 (1918): 91-133 (this study referenced Nettleship 1909 but did not refer to anticipation directly); Bruno Fleischer, "Untersuchung von sechs Generationen eines Geschlechtes auf das Vorkommen von myotonischer Dystrophie und anderer degenerativer Merkmale," *Archiv für Rassen und Gesellschafts Biologie* 14 (1922): 13-39; Bruno Fleischer, "Zur Vererbung nervöser Degenerationen," *Zeitschrift für die gesamte Neurologie und Psychiatrie* 84 (1923): 418-425.

¹⁷⁰ Fleischer, "Eine hereditäre, familiäre Degeneration," 91-133.

¹⁷¹ Harper *et al.*, "Anticipation," 11; Christiaan J. Höweler, H. F. M. Busch, J. P. M. Geraedts, M. F. Niermeijrt, and A. Staal, "Anticipation in Myotonic Dystrophy: fact or fiction?" *Brain* 112 no. 3 (June 1989): 780.

¹⁷² Homologous heredity refers to the finding that members of the same generation would suffer from the same variant of the disease. Homochronos heredity refers to the finding that members of the same generation developed the disease at similar ages. Fleischer, "Eine hereditäre, familiäre Degeneration," 129; Fleischer, "Untersuchung von sechs Generationen," 13-39.

¹⁷³ Fleischer, "Eine hereditäre, familiäre Degeneration," 91-133; Fleischer, "Untersuchung von sechs Generationen," 13-39; Fleischer, "nervöser Degenerationen," 418-425.

¹⁷⁴ Fleischer, "Eine hereditäre, familiäre Degeneration," 129; Fleischer, "Untersuchung von sechs Generationen," 13-39; Fleischer, "nervöser Degenerationen," 418-425.

disease.¹⁷⁵ Fleischer's work was so convincing that it led some researchers to conclude that all cases of myotonic dystrophy were familial and found only in affected families.¹⁷⁶

In 1923, W. J. Addie and J. G. Greenfield carried out an extensive study of myotonic dystrophy in England.¹⁷⁷ By tracking the appearance of cataract, they were able to trace the latent transmission of the defect through several generations until the appearance of symptoms of myotonic dystrophy within a single generation. This line of analysis suggested to them that this was a progressive degenerative disease.¹⁷⁸ Addie and Greenfield did use the term anticipation to describe the increasingly early onset of symptoms of the disease in succeeding generations of affected families.¹⁷⁹ The Swiss researcher Hans Frey expanded upon Fleischer's genealogical work on families with myotonic dystrophy and found that, while no muscular disease preceded the first generation to show cataract, after the appearance of cataract the disease would descend through several related family lines. First senile cataract, then pre-senile cataract and mild muscular symptoms, and finally juvenile cataract and severe myotonic dystrophy.¹⁸⁰ In 1927, the German researchers Karl Henke and Siegfried Seeger re-examined Fleischer's pedigree and confirmed Fleischer's findings.¹⁸¹ Henke and Seeger thus acknowledged the validity of "Heilbronner's law" (another phrase used in the literature to refer to what others called anticipation or anteposition) and noted that this progressive pattern of heredity posed a problem that needed to be better understood.¹⁸² They suggested that anticipation might be caused by a process of "phenotypical induction" in which either an outside influence acted on the myotonic dystrophy gene, or some kind of pre-mutation affected the gene that worsened over time.¹⁸³

¹⁷⁵ Fleischer, "Eine hereditäre, familiäre Degeneration," 91-133; Fleischer, "Untersuchung von sechs Generationen," 13-39; Fleischer, "nervöser Degenerationen," 418-425.

¹⁷⁶ See for example, W. J. Addie and J. G. Greenfield, "Dystrophia Myotonica (Myotonia Atrophica)," *Brain* 46 no. 1 (1923): 118. See also, Harper, *Myotonic* (1989), 293.

¹⁷⁷ Addie and Greenfield, "Dystrophia Myotonica," 73-127.

¹⁷⁸ Addie and Greenfield, "Dystrophia Myotonica," 118-119.

¹⁷⁹ Addie and Greenfield, "Dystrophia Myotonica," 112.

¹⁸⁰ Hans C. Frey, "Beitrag zur myotonischen Dystrophie (Myotonia atrophica)," *Archiv für Rassen und Gesellschafts Biologie* 17 (1925): 1-46.

¹⁸¹ Karl Henke and Siegfried Seeger, "Über die Vererbung der myotonischen Dystrophie. Genetischer Beitrag zum Problem der Degeneration," *Zeitschrift für Konstitutionslehre* 13 (1927): 371-415.

¹⁸² Henke and Seeger, "myotonischen Dystrophie," 402-403.

¹⁸³ Henke and Seeger, "myotonischen Dystrophie," 411-413.

Anticipation in Other Disorders

By 1910, as we have seen, Nettleship had noted signs of heredity in such ophthalmological disorders as Leber's disease and cataract, as well as in a variety of other disorders including tuberculosis, cystinuria, diabetes, familial jaundice, and at least one pedigree of hereditary ataxia.¹⁸⁴ In the 1920s other ophthalmologists, including Fleischer added to the findings of anticipation in Leber's disease.¹⁸⁵ Despite these reports, Fritz Lenz, a eugenicist from Munich, would both argue against the concept of anticipation in general—calling it a superfluous notion that was only apparently valid—and question its existence in glaucoma, cataract, and diabetes in particular.¹⁸⁶ American researchers, however, continued to report evidence of hereditary tendencies towards increasingly early onset of disease in diabetes.¹⁸⁷

In 1928, Julia Bell published a study examining the age of onset in Hereditary Optic Atrophy, an offshoot of her work on *The Treasury of Human Inheritance*.¹⁸⁸ As part of her study, she examined the question of anticipation, or rather “antedating” as she called it, in the inheritance of age of onset in hereditary optic atrophy.¹⁸⁹ She took a cautious approach to the possible existence of anticipation, stating that “the hastening of the age of onset in the nephew relatively to that of the uncle may be too readily put forward as an example of ante-dating in the next generation, but this is by no means

¹⁸⁴ Nettleship, *Bowman Lecture*, 72-73; Nettleship, “Some Points,” 59-61.

¹⁸⁵ Leber's disease is a hereditary form of optic atrophy leading to blindness. It is caused by mutations within maternal mitochondria. B. Fleischer and W. Josenhans, “Ein Beitrag zur Frage der familiären Sehnervenatrophie (Leberscher Krankheit,” *Archiv Fur Rassen und Gesellschafts Biologie* 13 (1920): 129-163; R. Kwakami, “Beitrage zur Vererbung der Familiären Sehnervenatrophie,” *Albrecht von Graefes Archiv fur Ophthalmologie*, 116 (March 1926): 568-595.

¹⁸⁶ Lenz, *Rassenhygiene*, 339; Lenz, *Menschliche*, 174-176, 233-236.

¹⁸⁷ N. B. Foster, “Consanguineal Diabetes Mellitus,” *Bulletin of the Johns Hopkins Hospital* 23 no. 252 (1912): 54-55; James Sherrill, “The Diagnosis of Latent Incipient Diabetes,” *Journal of the American Medical Association* 77 no. 23 (3 December 1921): 1779-1785.

¹⁸⁸ Julia Bell's work on *The Treasury of Human Inheritance* covered half a century between 1909 and 1958. She contributed to the first volume and was the major author of volumes two, four, and five. The second volume of the *Treasury* was also known as the *Nettleship Memorial Volume* after the late Edward Nettleship whose collected pedigrees contributed significantly to the volume. A fuller discussion of Bell's work with the *Treasury* will appear in chapters three and four as the volumes dealing with Huntington's disease and myotonic dystrophy were published in 1934 and 1947, respectively. Julia Bell, *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye*, ed., R. A. Fisher, (Cambridge: Cambridge University Press, 1922-1932).; Sarah Budney, “Julia Bell MRCS LRCP FRCP (1879-1979). Steamboat lady, statistician and geneticist,” *Journal of Medical Biography* 4 (1996): 10-11.; Harper, “Julia Bell,” 422-432.

¹⁸⁹ Ante-dating or antedating were alternate terms for anticipation. Bell, “Hereditary Optic Atrophy,” 269-276.

justified from a consideration of the facts.”¹⁹⁰ She believed that only completed pedigrees—those in which all the members had died—could be used to provide solid evidence of anticipation.¹⁹¹ She expanded upon her explanation in a footnote in which she referenced Heron’s 1914 criticisms of the concept and argued while anticipation might or might not actually exist, most of the studies claiming to demonstrate its existence used “quite inadequate statistical methods to demonstrate its occurrence.”¹⁹² This cautious attitude towards anticipation reminiscent of her mentor Karl Pearson continued to mark Bell’s statistical studies on the relationship between heredity and age of onset.

A PERIOD OF DEVELOPMENT AND POPULARIZATION: 1910-1930

The period between 1910 and 1930 saw the notion of anticipation develop from what Nettleship saw as a model of heredity that could explain odd patterns of inheritance to a “rule” and then a “law” of heredity as enunciated by Mott. Over these two decades, the idea was popularized and spread within the scientific and medical communities in Europe and North America where it was used to explain generational differences in ages of onset or severity of disease in a wide variety of disorders. The way that Mott and others applied his “law” of anticipation as a basis for marital advice to individuals with insanity in their families was treated as heretical by eugenicists who thought that members of affected families ought not to reproduce at all and who advocated the sterilization or segregation of affected individuals. Lidbetter utilized Nettleship’s ideas on anticipation as part of his pauper pedigree project that aimed to prove a link between heredity and membership in the poorest economic class in society. Although the project was put on hold due to financial difficulties arising from the First World War, both the pauper pedigree project and the campaign to legislate voluntary sterilization of the mentally unfit were to be resurrected by the Eugenics Society during the depression after 1929. During the 1930s the concept of anticipation would once again come under intense scrutiny. In the meantime, it would continue to be used by physicians, psychiatrists, and other researchers to explain their various findings.

¹⁹⁰ Bell, “Hereditary Optic Atrophy,” 274.

¹⁹¹ Bell, “Hereditary Optic Atrophy,” 274.

¹⁹² Bell, “Hereditary Optic Atrophy,” note 274.

Chapter 3: Seeking to Define a Mechanism (1930-1945)

A TUMULTUOUS TIME

The years between 1930 and 1945 were tumultuous ones for science and society alike. Several social, political, and scientific changes affected the reception of the concept of anticipation in hereditary disease in new, significant and variable ways. Individuals with opposing ideas regarding genetics and eugenics and who took opposing sides in the debate over the sterilization of the mentally deficient could be found on both sides of the discussion concerning the concept of anticipation. Additionally, while most of the theoretical discussions of anticipation took place within the British context, scholars in North America and in continental Europe continued to use the idea.¹ This variation gives the examination of the reception of the concept of anticipation during the years 1930-1945 a kaleidoscopic effect and renders the narrative of the concept's history less than straightforward. This discordance was accentuated by the application of anticipation to a wide range of pathologies: mental (the study of the inheritance of insanity and mental defect), somatic (the study of anticipation in particular diseases), and social (the study of the relationship between biology and poverty).

Although the British Eugenics Society was interested in the question of sterilization legislation in the 1920s, the 1929 report by the Mental Deficiency Committee (also called the *Wood Report*) served to galvanise the Society, and in 1930 the Committee for Legalising Eugenic Sterilization was established as a lobby group. It was in relation to this proposed legislation that most of the theoretical arguments concerning the concept of anticipation emerged in the early 1930s. At the same time, major developments within the field of genetics affected the reception of anticipation—most notably the adoption of the more mathematical and statistical form of Mendelism (*Vererbungsmathematik*) that was introduced to Britain from Germany by Lancelot

¹ In fact, in 1932 an Italian psychiatrist attempted to claim priority of discovery for the concept of anticipation after having had his attention drawn to the subject in the writings of the Canadian medical geneticist Madge Macklin. I have not been able to analyse his claim to priority as the original papers in which he claims to have made the discovery have proven impossible to access. A. Pierraccini, "On the Priority of the Biological Hereditary Law of 'Anticipation'," *Human Biology* 4 no. 4 (December 1932): 554-557.

Hogben in 1930 and later to America by German refugee scientists before World War II.² Caught between the poles of eugenics and the new genetics, the nascent fields of human and medical genetics also began to emerge and define themselves, although their professionalization, sociologically speaking, only came after the Second World War. In the meantime, genetic research continued on several individual disorders with which anticipation was already associated. While many researchers were content with merely noting the presence or absence of anticipation within their pedigrees, others attempted to explain anticipation, or explain it away, according to their abilities, interests, and inclinations.

EUGENICS, GENETICS, HUMAN AND MEDICAL GENETICS 1930-1945

(A) Developments in Eugenics: 1930-1945

The historian of medicine Pauline Mazumdar has argued that much of the work on heredity in Britain during the first half of the twentieth century took place within a eugenic problematic that, as she has described it, “consisted of a group of interrelated claims concerning the nature of the pauper class.”³ In her view, the power and pervasiveness of the eugenics problematic was such that it even shaped the research of the most ardent critics of eugenics.⁴ Issues central to the interests of the Eugenics Society framed much of the discussion of anticipation in the 1930s and 1940s. There have been a wide range of studies on developments within the field of eugenics during the first half of the twentieth century, and it is not my intention to reproduce that information in this study, particularly since anticipation is absent from almost the entire

² *Vererbungsmathematik* had its origins in Germany during the 1910s and 1920s in the study of the inheritance of human blood groups. Many of its proponents were either Jewish or of Jewish ancestry. However, during the 1920s Ernst Rüdin (whose study first noting anticipation in schizophrenia had been one of the first to use *Vererbungsmathematik*) and his large research group turned away from *Vererbungsmathematik* in favour of a more qualitative technique called *empirische Erbprognose* (empirical hereditary prognosis). Rüdin supported existing German sterilization legislation and had a key role in drafting the Nazi compulsory sterilization legislation in 1933. In 1930, the British Eugenics Society contacted Rüdin for advice (which he readily gave) on drafting their own proposed sterilization legislation. See: Mazumdar, *Eugenics*, 204-210; Matthias Weber, “Psychiatric research and science policy in Germany. The history of the Deutsche Forschungsanstalt für Psychiatrie (German Institute for Psychiatric Research) in Munich from 1917-1945,” *History of Psychiatry* 11 (2000): 250-258. On the creation and inter-relationship between *Vererbungsmathematik* and *empirische Erbprognose*, see: Pauline Mazumdar, “Two Models for Human Genetics: Blood Grouping and Psychiatry in Germany between the World Wars,” *Bulletin of the History of Medicine* 70 no. 4 (1996): 609-657.

³ Mazumdar, *Eugenics*, 2-5.

⁴ Mazumdar, *Eugenics*, 2-5.

discussion.⁵ Nevertheless, certain policies and developments in eugenics did influence the reception of the concept of anticipation in hereditary disease. This convergence took place within the context of attempts by the Eugenics Society to sponsor the passage of legislation intended to legalise voluntary sterilization through the British Parliament.⁶ The arguments surrounding the attempt to enact this controversial legislation serve as a prism through which to examine variations in thinking on the subject of anticipation. While one might have expected eugenicists to have endorsed a concept such as

⁵ Developments in eugenics have been examined along several lines. For a bibliographical review of the field up to 1978 see: Lyndsay Farrall, "The History of Eugenics: a Bibliographical Review," *Annals of Science* 36 (1979): 111-123. Since then many authors have concentrated on how eugenics developed within national contexts. On Britain cf.: Richard Soloway, *Demography and Degeneration: Eugenics and the Declining Birthrate in Twentieth-Century Britain*, (Chapel Hill NC: University of North Carolina Press, 1990); Pauline Mazumdar, *Eugenics, Human Genetics and Human Failings: The Eugenics Society, its sources and its critics in Britain*, (London: Routledge, 1992). On Canada see: Angus McLaren, *Our Own Master Race: Eugenics in Canada, 1885-1945*, (Toronto: Oxford University Press, 1990). On the United States cf.: Edwin Black, *War Against the Weak: Eugenics and America's Campaign to Create a Master Race*, (New York: Four Walls Eight Windows, 2003); Elof Axel Carlson, *The Unfit: A History of a Bad Idea*, (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2001); Mark Haller, *Eugenics: Hereditarian Attitudes in American Thought*, (New Brunswick NJ: Rutgers University Press, 1963); Wendy Kline, *Building A Better Race: Gender, Sexuality, and Eugenics from the Turn of the Century to the Baby Boom*, (Berkeley: University of California Press, 2001); Christine Rosen, *Preaching Eugenics: Religious Leaders and the American Eugenics Movement*, (Oxford: Oxford University Press, 2004); On Germany see: Peter Weingart, "German Eugenics between Science and Politics," *Osiris* 5 (1989): 260-282; Jonathan Harwood, *Styles of Scientific Thought: The German Genetics Community, 1900-1933*, (Chicago: Chicago University Press, 1993). On France cf.: William Schneider, *Quality and Quantity: The Quest for Biological Regeneration in Twentieth-Century France*, (Cambridge: Cambridge University Press, 1990). On Scandinavia see: Gunnar Broberg and Nils Roll-Hansen, eds., *Eugenics and the Welfare State: Sterilization Policy in Denmark, Sweden, Norway, and Finland*, (East Lansing, MI: Michigan State University Press, 1995). Regionally comparative studies include: Mark Adams ed., *The Wellborn Science: Eugenics in Germany, France, Brazil, and Russia*, (New York: Oxford University Press, 1990); Mark Adams, Garland E. Allen, and Sheila Faith Weiss, "Human Heredity and Politics: A Comparative Institutional Study of the Eugenics Record Office at Cold Spring Harbor (United States), the Kaiser Wilhelm Institute for Anthropology, Human Heredity, and Eugenics (Germany), and the Maxim Gorky Medical Genetics Institute (USSR)," *Osiris* 20 (2005): 232-262; Ian Dowbiggen, *Keeping America Sane: Psychiatry and Eugenics in the United States and Canada, 1880-1940*, (Ithaca NY: Cornell University Press, 1997); Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity*, with a new preface, (Cambridge, Mass.: Harvard University Press, 1995); Nancy Leys Stepan, *"The Hour of Eugenics" Race, Gender and Nation in Latin America*, (Ithaca NY: Cornell University Press, 1991). Although the literature is extensive, only one text, Mazumdar's *Eugenics*, even mentions anticipation. Mazumdar, *Eugenics*, 140, 218.

⁶ While authors like Soloway and Mazumdar stress the strength and pervasiveness of the eugenics movement, others, most notably Macnicol argue that the inability of the Eugenics Society to get legislation key to its goals passed serves as evidence that the power and influence of the eugenics movement was not what its supporters had hoped. See: Macnicol, "Eugenics," 147-169, and G. R. Searle, "Eugenics and Politics in Britain in the 1930s," *Annals of Science* 36 (1979): 159-169.

anticipation that offered a “law” to explain the degeneration of certain families, the idea’s actual reception was far more complicated.⁷

In Britain, two projects of interest to the Eugenics Society intersected with the study of anticipation in hereditary disease. As we saw in the previous chapter, Nettleship recruited two Eugenics Society members to the study of anticipation: Frederick W. Mott and Ernest Lidbetter each served as a point of origin for distinct research programmes.

Let us consider Mott first. Mott used the concept of anticipation in his study of hereditary insanity. In this he was joined by A. F. Tredgold who applied the concept broadly to the inheritance of what was then known as mental defect. The first field of application, then, was focused on the study of what might be termed mental pathologies. Although Mott and Tredgold both accepted that sterilization might be effective from a eugenic standpoint, both argued against the enactment of sterilization legislation—Mott from as early as 1914 and Tredgold by 1926.⁸ Their point of view had its critics from within the Eugenics Society and outside it. Pearson (1914) and Heron (1916) criticized Mott’s “law” of anticipation not only on statistical grounds but also explicitly on the grounds that it could be used to argue *against* the necessity for sterilization legislation.⁹ These arguments resurfaced in the 1930s in response to the voluntary sterilization campaign.

⁷ This was true not only of the British context but also in Germany where Fritz Lenz, one of the architects of Nazi eugenics policy, argued against the existence of anticipation. He based his argument, ironically, on statistical arguments made against anticipation by the Jewish-descended Wilhelm Weinberg, the originator of *Vererbungsmathematik* and co-discoverer of the Hardy-Weinberg equation that would give rise to the field of population genetics. Lenz’s views on anticipation appeared not only in German texts but also in an English translation, titled *Human Heredity*, published in London and New York in 1931. See: Erwin Baur, Eugen Fischer, and Fritz Lenz, *Human Heredity*, translated by Eden & Cedar Paul, (London: George Allen & Unwin Ltd., 1931), 244; James Crow, “Hardy, Weinberg and Language Impediments,” *Genetics* 152 (July 1999): 821-825; Mazumdar, “Two Models,” 609-657. A. W. F. Edwards, *Foundations of Mathematical Genetics*, 2nd ed., (Cambridge: Cambridge University Press, 2000).

⁸ The article in the *Times* references a 1923 pamphlet by the Central Association for Mental Welfare which further details the arguments of the Association against compulsory sterilization. The Association advocated segregation and treatment instead. Mott, “Heredity and Eugenics,” 423-428; Leslie Scott, A. F. Tredgold, H. B. Brackenbury, Evelyn Fox, “Mental Deficiency. Case For Institutional Treatment.” *The Times* (London), 20 January 1926, pg. 8, Issue 44174, col. D. Tredgold’s negative opinion on the issue of sterilization legislation was cited during the debate over such legislation in Manitoba in the 1930s. McLaren, *Master Race*, 164, 213. Tredgold continued to argue the issue from within the Eugenics Society in the 1930s. Macnicol, “Underclass,” 304.

⁹ See chapter two.

Ernest Lidbetter's "pauper pedigree project," on the other hand, was concerned with what might be deemed social pathologies.¹⁰ As a General Relieving Officer in London, Lidbetter was charged with providing relief (welfare) to those deemed needy under the provisions of the Poor Law.¹¹ During his career Lidbetter noted that certain families appeared on his rolls with great frequency, that these families often intermarried, and that a large proportion of their members appeared to suffer from physical, mental, and moral conditions that, in his view, made them incapable of consistently bettering their economic position.¹² In 1912 he published a paper which examined the relative effects of nature and nurture on the conditions of the lower classes.¹³ Although Lidbetter's work on his pauper pedigree project was temporarily halted by the First World War, he restarted the project in 1923 and spent much of his own time and money on seeing the project to its conclusion.¹⁴ During the 1920s, the methodologies of Lidbetter's project came under attack by critics from within the Eugenics Society, most notably R. A. Fisher, who called for the introduction of a control group and the adoption of statistical analysis to supplement Lidbetter's simple discussions of pedigrees.¹⁵ Despite methodological changes made in the intervening years, Lidbetter and the Eugenics Society continued to look for links between heredity and membership in the "pauper class" which was re-named the "Social Problem Group" after the publication of the *Wood Report* in 1929.¹⁶ The results of Lidbetter's quarter-century long study were eventually published in 1933 as *Heredity and the Social Problem Group*, but only the

¹⁰ The pauper pedigree project was begun in 1912 under the auspices of the Eugenics Society's Research Committee but was mainly carried out by Lidbetter who continued to run the project when it was restarted in 1923 under a re-constituted committee. For a period of almost twenty years, Lidbetter spent most of his time, effort, and personal money on the Eugenics Society's project on pauper pedigrees attempting to demonstrate a connection between heredity and poverty. See chapter two for a more detailed discussion. Mazumdar, *Eugenics*, 73-77, 144.

¹¹ Lidbetter worked for the London Poor Law authority from 1898 and joined the Eugenics Society soon after it was founded in 1909-1910. He spoke frequently at Eugenics Society meetings. Mazumdar, *Eugenics*, 73-77.

¹² Macnicol, "Underclass," 307-310.

¹³ See chapter two. E. J. Lidbetter, "Nature and Nurture—A Study in Conditions," *Eugenics Review* 4 (1912): 54-73.

¹⁴ Mazumdar, *Eugenics*, 143-144.

¹⁵ Kevles, *Name*, 114; Mazumdar, *Eugenics*, 5, 71-89, 124-145, 247-250.

¹⁶ The "social problem group" was itself replaced during the 1940s by the new term "problem families." The desire to uncover a biological and not social explanation for poverty is one that has surfaced periodically in Anglo-American culture. See: John Macnicol, "In Pursuit of the Underclass," *Journal of Social Policy* 16 no. 3 (1987): 293-318. A recent iteration of these ideas is found in Richard Dawkins, *The Selfish Gene*, (new edition, Oxford: Oxford University Press, 1989), 117-118 *et passim*.

first of several anticipated volumes was published and the promised statistical analyses never appeared in print.¹⁷ Unlike many eugenicists, Lidbetter continued to believe that anticipation played a role in heredity. This belief of his will be discussed later.

(i) The Campaign for Voluntary Sterilization Legislation

Since its founding in 1907, the Eugenics Society had sought, unsuccessfully, to legislate limits on the procreation of the “pauper class,” a segment of society that it felt was defined biologically by a tendency towards inborn defects, including insanity and feeble-mindedness, as well as economically by a reliance on the Poor Law.¹⁸ Attempts to encourage population control within this segment of society continued throughout the economically strained period before the Second World War.¹⁹ Other nations, most

¹⁷ E. J. Lidbetter, *Heredity and the Social Problem Group*, Vol. 1. (London: Arnold, 1933). Mazumdar describes the publication as “a Ptolemaic survival in a Galilean world.” Mazumdar, *Eugenics*, 142.

¹⁸ As we saw in chapter two, Mott and Lidbetter, were both introduced to the concept of anticipation by Nettleship and co-authored papers with him. They approached this issue from the two main vantage points of the time. Mott studied families in whom members had been placed in mental institutions. Although Mott was respected as a physician, researcher, and eugenicist, his theories on the relation of mental illness to heredity were subject to controversy, particularly after he argued against the imposition of sterilization legislation. A series of other researchers who continued to examine the relationship between insanity, heredity, and poverty, however, contributed to the drive towards the creation of legislation to sterilize the mentally deficient. For his part, Lidbetter approached the topic by using his position as a poor law relieving officer to collect pedigree material on those who received money from the state. He believed from early on that there was a relationship between heredity and pauperism, and he had published on the subject in the 1910s (see chapter two). Lidbetter’s work was revived during the 1920s and 1930s and will be discussed in more detail below. For an informative overview on the social and scientific creation of the concept of hereditary poverty (and the tendency for belief in the issue to return cyclically in political life), see John Macnicol, “In Pursuit of the Underclass,” *Journal of Social Policy* 16 no. 3 (July 1987): 293-318.

¹⁹ Some eugenicists blamed the high unemployment of the period on genetic defects and urged population control among the working classes and sterilization of the ‘unfit’. Although there were also attempts to support positive eugenics—that is increased breeding among the “right” sorts of individuals from the middle and upper classes—the proposed legislation contained more emphasis on the negative eugenics aspects. It was the issue of access to birth control that drew many reform minded women towards eugenics. Macnicol, “Eugenics,” 164; Mazumdar, *Eugenics*, 3; Searle, “Eugenics,” 166, 168-169. For a review of the history of eugenic sterilization (ca. 1900s-1960s) from the Eugenics Society’s point of view see: C. P. Blacker, “The Sterilization Proposals: A History of their Development,” *Eugenics Review* 22 no. 4 (January 1931): 239-247; C. P. Blacker, “Voluntary Sterilization: The Last Sixty Years,” *Eugenics Review* 54 no. 1 (1962): 9-23. The relationship between the economic depression of this time and the resurgence in interest in the sterilization campaign has been treated differently by various historians. Mazumdar plays down the importance of the depression as a causative agent, suggesting that the sheer numbers of the unemployed in fact undermined the idea that there was some sort of heredity at work. She prefers to concentrate on how scientific developments within the eugenics movement affected the reception of Lidbetter’s pedigrees. Searle, on the other hand, provides evidence that at least a number of eugenicists, though by no means all, believed that the Great Depression was a form of ‘retribution’ visited upon a society that had not corrected its eugenic ills. They thought that the Eugenics Society should move forward in their aims to correct such dysgenic problems. Mazumdar, *Eugenics*, 3, 142-145; Searle, “Underclass,” 300-301; Searle, “Eugenics,” 166. In his analysis, the historian Mathew Thomson argues that the

notably Canada, the United States, and Germany, had begun to pass eugenic marriage, sterilization and immigration legislation. Eugenacists in Britain were jealous of their success.²⁰ As we saw in chapter two, both the science supporting legislation and the ethics of such an act had been under attack from inside and outside the eugenics movement from the mid-1920s.²¹ Additionally, in Britain the questionable legality of sterilization surgery—even when requested by those of sound mind and body for birth-control purposes—posed a significant barrier to any proposed sterilization legislation, voluntary or not, and would continue to do so.²² Nevertheless, a series of governmental

sterilization campaign was so intertwined with ongoing arguments within the eugenics movement concerning professional interests that it cannot just be evaluated based on the success or failure of the proposed legislation or as a mark of support for eugenic social policy. Thomson, *Problem*, 180-205.²⁰ See, for example, Kevles, “Eugenics in North America,” in *Essays in the History of Eugenics: Proceedings of a Conference organised by the Galton Institute, London, 1997*, ed., Robert Peel, (London: The Galton Institute, 1998), 208-226; Kevles, *Eugenics*, 99-104; McLaren, *Master Race*, 89-106; Mazumdar, *Eugenics*, 196-214. American eugenacists published monographs lauding the success of their sterilization movement. See E. S. Gosney and Paul Popenoe, *Sterilization for Human Betterment: A Summary of Results of 6,000 Operations in California, 1909-1929*, (New York: The Macmillan Company, 1929); J. H. Landman, *Human Sterilization: The History of the Sexual Sterilization Movement*, (New York: The Macmillan Company, 1932). An excellent *contemporary* study of the medical and legal aspects of sterilization that offers extensive coverage of the American, British, and German scientific literature (including Goldschmidt’s 1938 article on anticipation) was made by the American neurologist Abraham Myerson. Myerson chaired the American Neurological Association’s committee for the Investigation of Eugenic Sterilization. The committee concluded: 1. That schizophrenia and manic depression had some hereditary basis but that an environmental factor was at play. 2. That for the most part feeble-mindedness had some sort of hereditary origin but that affected individuals came from families that spanned the spectrum intellectually, socially, and economically. 3. That there was some constitutional basis for epilepsy but that it had not been proven to be hereditary. 4. That crime, “one of the conditions which ardent eugenacists expect to be reduced by sterilization[,] is generally non-hereditary in nature.” The committee believed that sterilization was “indicated and desirable” but advocated that only voluntary sterilization be applied and then only to certified cases of rare hereditary neurological diseases, schizophrenia, manic-depressive psychosis, most cases of feeble-mindedness, and epilepsy. Myerson was critical of what he termed “rabid eugenacists,” however, and advocated the creation of a long-term, preferably governmental, research programme to carry out further systematic research into the question. Abraham Myerson. “Certain Medical and Legal Phases of Eugenics Sterilization,” *The Yale Law Journal* 52 no. 3 (1943): 618-633. The success of the sterilization project in other countries moved other British eugenacists to publish monographs arguing for the adoption of similar legislation in Britain. Cora Hodson, *Human Sterilization To-Day: A Survey of the Present Position*, (London: Watts & Co., 1934).

²¹ For example, R. A. Fisher criticized the simplistic analyses of pedigrees used by Lidbetter and others in their studies while William Inge, Dean of St Paul’s (1911-1934), who agreed with many of the principal ideas of eugenics, rejected legislation allowing sterilization on moral grounds. A. F. Tredgold who was otherwise supportive of eugenics drew the line at sterilization legislation and was concerned that it would be used as an excuse to cut funding to the treatment and housing of the mentally deficient. J. H. Bennett ed., *Natural Selection, Heredity, and Eugenics: Including selected correspondence of R.A. Fisher with Leonard Darwin and others*, (Oxford: Clarendon Press, 1983), pp. 79-80; Macnicol, “Underclass,” 304; Mazumdar, *Eugenics*, 122-144; Scott, Tredgold, Brackenbury, and Fox, “Mental Deficiency,” 8.

²² Under the 1861 Offences Against the Person Act sterilization surgery, even with consent, could be deemed an “unlawful wounding.” The 1913 Mental Deficiency Act held that, if the patient was *non*

and scientific reports in the late 1920s and 1930s drew the focus of the Eugenics Society back to the controversial question of sterilization legislation and to the even thornier problem of providing evidence to create a scientific consensus in favour of such legislation. The variety of opinions displayed in these reports reveals just how complicated and controversial the issue and its perceived solution were scientifically, socially, and politically. Moreover, discussions were not limited to eugenicists and politicians. The broader scientific community also engaged actively in this debate in the pages of *Nature*.²³ In addition, attitudes toward the concept of anticipation varied among people arguing for and against the creation of voluntary sterilization legislation. Interestingly, those who *favoured* the sterilization of “mental defectives” were generally critical of anticipation. Some critics of the proposed sterilization legislation used “Mott’s law” as proof that legislation was unnecessary, arguing that Nature would either end or mend afflicted stocks. Others were critical of anticipation on scientific and statistical grounds. Conversely, researchers studying the “social problem group” and the inheritance of “defective” characteristics deemed worthy of sterilization within this group were more inclined to favour the notion of anticipation since they could use it to explain

compos mentis, sterilization surgery was definitely illegal, and those who granted permission for the operation could be prosecuted. Macnicol, “Eugenics,” 165-166.

²³ Throughout this period a series of editorial articles appeared in *Nature* concerning mental deficiency, its causes, and possible solutions. *Nature*’s editor during this period was Sir Richard Gregory; Gary Werskey has argued that his political and scientific beliefs had a large role in propounding a sort of social imperialism in the pages of *Nature* from 1914-1939. This included eugenic ideals and the concern about the increased reproduction of certain elements of the working class. Although the authorship of these lead articles was anonymous, the actual authorship was recorded in *Nature*’s master volumes. Werskey identified the most prolific authors of these editorials (including A. G. Church who introduced the proposed Sterilization Legislation to Parliament in 1931) in his 1969 article. Gary Werskey, “*Nature* and Politics between the Wars,” *Nature* 224 (November 1 1969): 462-472; Gary Werskey, *The Visible College*, (London: Penguin Books Ltd., 1978), 26-37. The most important entries on the subject were: Anonymous, “Mental Deficiency,” *Nature* 129 (February 20, 1932): 287-288; “Social Selection of Human Fertility,” *Nature* 129 (June 18, 1932): 896-897; “Eugenics and Marriage Laws,” *Nature* 131 (April 15, 1933): 540; “State Policies of Eugenic Sterilisation,” *Nature* 132 (August 12, 1933): 221-222; “Eugenic Sterilisation in the United States,” *Nature* (August 12, 1933): 234; “The Eugenic Problem in Great Britain,” *Nature* 132 (October 7, 1933): 540; “Eugenics and Society,” *Nature* 137 (April 11, 1936): 593; “Genetics and Race,” *Nature* 138 (December 12, 1936): 988-989; “Medicine and Eugenics,” *Nature* 141 (February 26, 1938): 382; “Medicine and Eugenics,” *Nature* 142 (July 9, 1938): 68. The discussions of this issue did not confine themselves to the editorial staff. For example, in 1936, several authors weighed in on the debate concerning “the cultivation of the unfit”: E. W. M., “The Cultivation of the Unfit,” *Nature* 137 (January 11, 1936): 44-45.; B. Dunlop, “Cultivation of the Unfit,” *Nature* 137 (February 1, 1936): 188; Joseph Needham, “Cultivation of the Unfit,” *Nature* 137 (February 1, 1936): 188; E. W. M., “Cultivation of the Unfit,” *Nature* 137 (February 1, 1936): 188-189; E. W. M., “Cultivation of the Unfit,” *Nature* 137 (February 15, 1936): 276; H. T. B. Drew, “Cultivation of the Unfit,” *Nature* 137 (February 15, 1936): 276. Searle, “Eugenics,” 164-166.

the increasing severity of a wide range of conditions over several generations of families that had sought economic relief.

The Wood Report (1929)

In 1929 the Board of Education and Board of Control published the *Report of the Mental Deficiency Committee*, also known as the *Wood Report*, after its chairman Sir Arthur Wood. The committee, which included several eugenicists, had been set up in 1924 in order to review how well the 1913 Mental Deficiency Act was working. The *Wood Report* stated that numbers of the mentally deficient were on the rise, due to what it called a “subnormal” or “social problem group.” This group was said to comprise the lowest economic tenth of the population from which a large number of mentally deficient individuals arose. The committee lauded the work being done by eugenicists but noted that a great deal of further study was needed. Sterilization was suggested as a possible remedy, but a highly contentious one that would not likely reduce the future numbers of the mentally defective, and the committee warned that it was not a replacement for the segregation and institutionalization of these individuals.²⁴

The Committee for Legalising Eugenics Sterilization (1930)

The *Wood Report* reinvigorated the Eugenics Society’s interest in the subject of legalizing sterilization and early in 1930 its Committee for Legalising Eugenic Sterilization was formed.²⁵ Committee member Carlos P. Blacker even asked Ernst Rüdin, a leading German eugenicist, for advice on the subject.²⁶ Between 1930 and 1931 the committee produced several propaganda pamphlets including *Eugenic Sterilization*, *The Law as to Sterilization*, and *Better Unborn*, in order to spread their ideas more

²⁴ There was significant concern among certain parties, including Tredgold, that sterilization would somehow come to be thought of as a replacement for the segregation of the insane and mentally deficient. The Eugenics Society was well aware of this concern and tried from the beginning (unsuccessfully) to respond to these criticisms. Blacker, “Sterilization Proposals,” 240-242; Macnicol, “Eugenics,” 156; Macnicol, “Underclass,” 301-303; Mazumdar, *Eugenics*, 197-200.

²⁵ The Committee was chaired by Sir Bernard Mallet. Its membership included, among others, C. P. Blacker, R. A. Fisher, Julian Huxley, E. J. Lidbetter, and A. G. Church (MP) who introduced their proposed legislation to Parliament in 1931. See Blacker, “Sterilization Proposals,” 240-242; Blacker, “Voluntary Sterilization,” 10-11; also Macnicol, “Eugenics,” 156-157; Mazumdar, *Eugenics*, 197-200, 227.

²⁶ Mazumdar, *Eugenics*, 204-208.

widely.²⁷ Several articles also appeared on the subject in the Eugenics Society's journal *Eugenics Review*.²⁸ A parliamentary draftsman was commissioned to write a Sterilization Bill, and on 21 July 1931, A. G. Church, a committee member and rogue Labour MP, attempted to introduce the bill calling for the legalisation of voluntary sterilization to Parliament under the ten-minutes rule but the motion was defeated.²⁹ After this set-back, the campaign was stepped up in an attempt to sway public opinion towards the proposed legislation.³⁰ Part of the campaign included reviving and publishing of material from Lidbetter's pauper pedigree project—now using the new terminology of the “social problem group” in response to concerns raised by the *Wood Report*. The committee also continued editing and publishing leaflets on the issue.³¹ Theoretical arguments concerning the role of anticipation in hereditary disease were made in some of the published articles that appeared as part of the campaign supporting the passage of the proposed voluntary sterilization legislation. These articles will be discussed in detail later.

All-Party Parliamentary Sterilization Committee (1932)

In 1932, another parliamentary supporter of the Eugenics Society, A. W. H. James, formed an all-party Parliamentary Sterilization Committee to consider the issue. According to Blacker, “the unanimous view emerged that there was not the slightest prospect of a Bill of such wide scope being passed; a better hearing, it was said, would be

²⁷ Blacker, “Voluntary Sterilization,” 11-12.

²⁸ Those articles that included a discussion of anticipation as it related to the sterilization legislation will be discussed later in this chapter. Blacker, “Voluntary Sterilization,” 11-12.

²⁹ According to Blacker, a draft bill to legalize sterilization was drawn up in 1929. This draft of the bill was divided into three parts: one concerning mental defect and insanity, one prohibiting the marriage of the mentally defective and insane unless they had been sterilized or were otherwise infertile, and the third dealing with “pauperism and crime.” The bill that was proposed in 1931 was significantly different. According to Blacker, “the Committee was guided by what it held to be desirable on eugenics rather than on tactical grounds.” Despite these claims, it should be noted that the trial legislation called for *voluntary* rather than mandatory sterilization, although it was hoped that in the future the legislation could be updated accordingly at a later date. Three groups were singled out as candidates for voluntary sterilization: 1. mental defectives 2. mental convalescents (those recently recovered from an attack of insanity) and 3. those “suffering from hereditary disease or defect ... impairing mental or physical health or efficiency.” Even at this early stage, Blacker noted, some thought that it would have been expedient to restrict the legislation to only those found to be mentally defective. Blacker, “Sterilization Proposals,” 242-243; Blacker, “Voluntary Sterilization,” 10-13.

³⁰ Blacker, “Voluntary Sterilization,” 13-15; Macnicol, “Eugenics,” 157.

³¹ Lidbetter's findings will be discussed later in the chapter. Blacker, “Sterilization Proposals,” 244-247; Blacker, “Voluntary Sterilization,” 12-13.

given to a Bill limited to mental defectives.”³² The Parliamentary Committee produced a pamphlet which included the Alberta Sterilization Act from Canada as an example of the successful implementation of such legislation. By the time the Parliamentary Committee published its own memorandum in November however, the Brock Committee had been appointed and the Parliamentary Committee decided to wait for its report before taking further action.³³

The Brock Report (1934)

In response to the proposed legislation and to pressures on the government to call a Royal Commission to examine the sterilization question, the Minister of Health set up a Departmental Committee under the leadership of Sir Lawrence Brock in June 1932. The *Brock Report* was released in January 1934.³⁴ Although Brock himself was sympathetic to the idea of voluntary sterilization, he believed that the lack of clear scientific evidence showing the inheritance of mental deficiency would stand in the way of any proposed legislation.³⁵ The *Brock Report* took a somewhat cautious approach to the issue of sterilization legislation. It argued that voluntary sterilization should be encouraged among three groups of people: persons who were mentally defective or insane, persons who suffered from a transmissible physical disability, and persons who were likely to transmit mental or physical defect.³⁶ The report accepted the idea that individuals who were mentally defective were unfit for parenthood and, moreover, accepted the claim that inheritance played a large role in causing such mental deficiency.³⁷ However, the report argued against making sterilization compulsory and built significant safeguards into their proposal, including the suggestions that all sterilization operations would have to be approved by the Minister of Health, that patients be required to grant consent to any such operation and indicate that they clearly understood what they were agreeing to, and that

³² Blacker, “Voluntary Sterilization,” 14.

³³ Blacker, “Voluntary Sterilization,” 14.

³⁴ Macnicol, “Eugenics,” 157.

³⁵ Macnicol, “Eugenics,” 167.

³⁶ Macnicol, “Eugenics,” 158.

³⁷ Macnicol, “Eugenics,” 157-158.

the operations were to take place in hospitals and not mental institutions, so as to remove any stigma from the procedure.³⁸

The BMA Report (1934)

In 1934 a report appeared that underscored what the historian G. R. Searle has called “the division between specialists and experts, on the one hand, and the mass of ordinary G.P.s, on the other.”³⁹ Although the sterilization campaign was supported by the Royal College of Surgeons and the Royal College of Physicians, the British Medical Association would not approve such legislation.⁴⁰ The BMA report was strongly critical of the idea of using sterilization to control the feeble-minded population.⁴¹

Joint Committee on Voluntary Sterilization (1934-1939)

In an attempt to place further pressure on the government, the Eugenics Society helped to set up and fund a Joint Committee on Voluntary Sterilization under the chairmanship of Lord Horder with members from the Central Association for Mental Welfare, the Eugenics Society, the Mental Hospitals Association, and the National Council for Mental Hygiene as well as a representative from the Royal College of Physicians.⁴² In May 1935, a deputation from this Joint Committee approached the Minister of Health, Sir Hilton Young, hoping to get the *Brock Report*'s suggestions implemented. Because the Minister was aware of significant pockets of resistance to the proposed legislation he warned the Committee that the time was not yet right to attempt to present the legislation to Parliament.⁴³ Although the Joint Committee met until the war began in 1939, its activities were essentially fruitless.⁴⁴

³⁸ Macnicol, “Eugenics,” 158; Mazumdar, *Eugenics*, 227.

³⁹ Searle, “Class,” 226.

⁴⁰ Macnicol reports that Blacker was able to get the Royal College of Physicians to investigate the sterilization issue, but not until 1938 and their work ended with the outbreak of war. Macnicol, “Eugenics,” 161; Mazumdar, *Eugenics*, 227; Searle, “Eugenics,” 159-169; Searle, “Class,” 226..

⁴¹ Mazumdar, *Eugenics*, 227 and elsewhere.

⁴² The British Medical Association was notable by its absence and the member from the Royal College of Physicians was merely representative. Blacker, “Voluntary,” 17-19.

⁴³ Macnicol believes that Young was also made cautious due to anticipation of a General Election that took place later that year. Blacker, “Voluntary,” 20-21; Macnicol, “Eugenics,” 158, 167.

⁴⁴ Macnicol, “Eugenics,” 158.

(ii) Resistance to the Proposed Voluntary Sterilization Legislation

In his 1962 retrospective, Blacker identified 1936 as the year in which the tide began turning against the sterilization movement. He identified four main sources for the failure of the campaign.⁴⁵ However, resistance against the campaign for sterilization legislation dates back to its inception.⁴⁶ Opponents of sterilization came from a wide variety of backgrounds, some even from within the eugenics community itself, and the legislation was opposed on a wide variety of grounds: legal, political, ethical, religious, medical, and scientific. The Eugenics Society's attempts to respond to these criticisms, for example by supporting a reformed version of eugenics after 1936 and advocating positive eugenics proposals, were never quite enough to silence their detractors.⁴⁷

The legality of surgical sterilization in Britain was very much in question, even if performed upon those who were judged of sound mind and well able to understand the consequences of the operation. Members of the Eugenics Society asserted that the operation was privately available to the wealthy on Harley Street, but was not publicly available to the poor.⁴⁸ Legal arguments against the operation dated back as far as the 1861 Offences Against the Person Act, under which it might be judged an "unlawful wounding."⁴⁹ The issue was further complicated by the 1913 Mental Deficiency Act under which the sterilization of a *non compos mentis* patient was clearly illegal and even sterilizing one who was *compos mentis* might be so as well.⁵⁰ Two court rulings in 1933 and 1934 added further weight to the argument that sterilization was illegal.⁵¹

Throughout the interwar period lawyers provided conflicting opinions as to the legality of the sterilization operation, and such government departments as the Ministry of Health

⁴⁵ The four causes of failure identified by Blacker were: 1. The refusal of the Minister of Health to attempt to enact the voluntary sterilization legislation. 2. The fact that eugenic legislation enacted in Germany after the rise of the Nazis in 1933 poisoned the air against legislation. 3. The failure of the Joint Committee due to increasing resistance and financial difficulties and 4. The outbreak of war in September 1939. Blacker, "Voluntary," 22-23.

⁴⁶ Mathew Thomson, *The Problem of Mental Deficiency: Eugenics, Democracy, and Social Policy in Britain c. 1870-1959*, (Oxford: Clarendon Press, 1998), 32, 66-70.

⁴⁷ Macnicol, "Eugenics," 151; Searle, "Eugenics," 163-166; Richard Soloway, "From Mainline To Reform Eugenics – Leonard Darwin and C P Blacker," in *Essays in the History of Eugenics: Proceedings of a Conference organized by the Galton Institute, London, 1997*, ed., Robert Peel, (London: The Galton Institute, 1998), 52-81.

⁴⁸ Blacker, "Voluntary," 13; Macnicol, "Eugenics," 165.

⁴⁹ Blacker, "Voluntary," 11; Macnicol, "Eugenics," 165.

⁵⁰ Macnicol, "Eugenics," 165.

⁵¹ Cecil Binney, "Eugenic Aspects of the English Criminal Law," *Eugenics Review* 37 no. 3 (October 1945): 107-108.

and the Board of Control were well aware of the difficulties posed by public opposition to voluntary sterilization legislation, however sympathetic individual members of Parliament or civil servants might be to the idea. Such bodies therefore took a cautious approach to the proposed legislation.⁵²

Although the proposed Voluntary Sterilization Legislation was submitted to Parliament by a Labour MP, in general the Labour Party and others from the political Left (such as the Fabian Society, the Communists, and the ‘New Liberals’) rejected the legislation as essentially anti-working class.⁵³ Socialists, labour unionists, and other members of the Left attacked the campaign for sterilization legislation, fearing—and quite rightly—that it would be directed at the poorer members of society from whom they drew their members.⁵⁴ In addition, the political strength of Catholic opposition to both the sterilization and birth control movements was substantial, despite the limited size of the Roman Catholic population.⁵⁵ Political events in Germany also affected the reception of the proposed sterilization legislation. The realization of the uses to which sterilization legislation was being put by the Nazis from the time of their election in 1933 was a source of increasing political and public resistance to the British sterilization proposals.⁵⁶

⁵² Macnicol, “Eugenics,” 165-166.

⁵³ Macnicol believes that “the real Achilles’ Heel” of the campaign for legalizing voluntary sterilization was the accusation that it was “fundamentally anti-working class.” In his examination of the campaign for voluntary sterilization he argues that Church should not be seen as a typical Labour MP and that Labour’s actual attitude to the legislation was better seen in the arguments raised against the proposed legislation by Dr Hyacinth Morgan, a Catholic and a long-term Labour MP. Macnicol further notes that while the 89 votes supporting the legislation came from all parties (Conservative, Labour, Liberal, and others) Blacker felt that Labour was mainly opposed to the legislation (Blacker’s 1962 retrospective suggests that he felt that the Labour Party was initially divided on the subject but that the “anti-working class” camp gained ground over time). He hoped to break the Labour Party-Roman Catholic coalition while trying to persuade the Left that the proposed legislation would not unfairly target the working class. Blacker, “Voluntary,” 13; Macnicol, “Eugenics,” 160-163; Searle, “Class,” 235. L. J. Ray argues that certain aspects of the eugenics programme appealed to the Fabians and that, in particular, Karl Pearson represents “this merging of Fabian and eugenic views.” L. J. Ray, “Eugenics, Mental Deficiency and Fabian Socialism between the Wars,” *Oxford Review of Education* 9 no. 3 (1983): 213-222.

⁵⁴ Mazumdar, *Eugenics*, 211.

⁵⁵ Macnicol, “Eugenics,” 167.

⁵⁶ As early as August 1933 an editorial appeared in *Nature* stating: “it is impossible to avoid the thought that here is provided a most frightful opportunity for those politically strong at present to outrage the politically oppressed.” Searle identifies the editorialist as C. A. Crew and argues that, in spite of this early warning, it was not until the late 1930s that the anti-Nazi aspect of the anti-sterilization movement became widespread. Some members of the Eugenics Society actually spoke out in favour of the German legislation but this only served to further alienate those they were trying to convince. Anonymous, “State Policies of Eugenic Sterilization,” *Nature* 132 (August 12, 1933): 221-222; Searle, “Eugenics,” 166-168.

From the outset of the Eugenics Society's campaign, religious and ethical arguments were made against the proposed sterilization legislation. Blacker himself later noted that "the opposition on moral grounds was generally similar to the opposition to birth control."⁵⁷ Opponents were concerned as to whether legislation would remain confined to voluntary sterilization and whether the most vulnerable members of society could be protected.⁵⁸ The most vocal block of religious opposition came from the Roman Catholics who were agitating against the proposed legislation even before the publication of the Papal Encyclical *Casti Connubii* on 31 December 1930.⁵⁹ As political events unfolded, the Catholic opposition also feared that sterilization might become compulsory as it had in Germany. They questioned whether the mentally defective could legally consent to being sterilized and argued that encouraging sexual relations or marriage among the mentally defective was improper.⁶⁰ Opposition was not just confined to the Roman Catholics; other religious groups also opposed controls on procreation or attacks on the rights of individuals and lobbied against the proposed sterilization legislation.⁶¹ Even those who had previously supported the Eugenics Society could not accept legalizing sterilization on religious and ethical grounds.⁶²

The medical community was also divided. One notable group of resistance to the legislation were the medical staffs of mental hospitals. Despite assurances to the contrary, these physicians, including the notable A. F. Tredgold, were concerned that the proposed sterilization of the mentally defective would function as an economy measure to

⁵⁷ Blacker, "Voluntary Sterilization," 12-13.

⁵⁸ Macnicol, "Eugenics," 159-160.

⁵⁹ However much individual Catholics might have been sympathetic to the question of sterilization, *Casti Connubii* (On Christian Marriage) represented the Catholic Church's official line on the issue. It argued that sterilization would make individuals ineligible for marriage; that the sterilization of potential parents constituted the punishment by the state for a crime (the production of defective children) that they had not yet committed; and that in any case the individual and the family was sacred and so too was childbearing. Blacker, "Sterilization," 246; Blacker, "Voluntary," 19-20; Claudia Carlen ed., *The Papal Encyclicals: 1903-1939*, (Ann Arbor MI: Pierian Press, 1990), 391-414; Anne Fremantle ed., *The Papal Encyclicals In Their Historical Context*, with an introduction by Gustave Weigel, S. J., (Toronto: The New American Library of Canada Limited, 1963), 235-243; Macnicol, "Eugenics," 161-162.

⁶⁰ Macnicol, "Eugenics," 161-162; Mazumdar, *Eugenics*, 211.

⁶¹ Mazumdar, *Eugenics*, 211.

⁶² The most notable of these was William Inge the Dean of St Paul's who, while he had previously been an ardent supporter of the Eugenics Society, in 1926 found himself arguing against eugenical sterilization on humanitarian grounds much to the dismay of Leonard Darwin and R. A. Fisher. J. H. Bennett ed., *Natural Selection, Heredity, and Eugenics: Including selected correspondence of R.A. Fisher with Leonard Darwin and others*, (Oxford: Clarendon Press, 1983), pp. 79-80. On Dean Inge's previous support of the eugenics enterprise, see Searle, "Class," 227-228.

allow these individuals to make their way within society, rather than keeping them safely segregated and cared for by the state.⁶³ While more elite groups such as the College of Physicians and the College of Surgeons supported the proposed legislation, the British Medical Association responded to the concerns of its liberal and Catholic members and rejected sterilization.⁶⁴ This continued resistance dismayed the Eugenics Society which had hoped that it could bring the physicians around to its point of view correctly educating them in eugenics, statistics, and genetics.⁶⁵

Finally, despite all of their efforts, the Eugenics Society was never able to prove scientifically that sterilization would effectively solve the problem of mental deficiency.⁶⁶ From the very outset, divisions were apparent on the extent of heredity in mental defect. Tredgold suggested that inheritance accounted for only 5 percent of the mentally defective while Fisher argued that the number of mentally defective could be reduced by 17 percent in one generation if sterilization was enacted.⁶⁷ The biological issues and the sterilization campaign were criticized by influential Left-leaning scientists such as Joseph

⁶³ This concern was apparent from the outset of the campaign. As Blacker noted: "If there is such a thing as a professional standpoint, that of the medical staffs of mental hospitals was then opposed [to the proposed legislation]. Opposition was more or less orthodox." Macnicol notes that the Eugenics Society tried repeatedly to assure people that sterilization wasn't intended to replace segregation, but their arguments were ineffective. Blacker, "Voluntary Sterilization," 12-13. Macnicol, "Eugenics," 160.

⁶⁴ Searle, "Class," 227.

⁶⁵ In 1936 the Eugenics Society's Chairman (Lord Horder) urged medical schools to incorporate genetics into their curricula. Searle notes that part of the medical profession's resistance might have been based on the fear that they would be saddled with administering examinations to establish the fitness of individuals to marry (tests that eugenicists had been advocating for years) if eugenic legislation should ever pass. Moreover, many physicians were tired of having the degeneration of the nation placed at their feet by eugenicists who argued that advancements in the medical profession allowed the 'unfit' to live when they would have died in previous centuries. Searle, "Class," 226-228.

⁶⁶ On science and the Eugenics Society, see: Macnicol "Eugenics," 152-153, 158-159; Macnicol, "Underclass," 305-313; Searle, "Eugenics," 164-166; The shift in *Nature's* editorial policy from one relatively favourable towards the sterilization legislation to one opposed is discussed above. Debates over the scientific arguments regarding the inheritance of mental deficiency and related issues also played out in *Nature*. See for example: Lionel S. Penrose and J. B. S. Haldane, "Mutation Rates in Man," *Nature* 135 (June 1, 1935): 907-908; E. W. M., "The Cultivation of the Unfit," *Nature* 137 (January 11, 1936): 44-45.; Joseph Needham, "Cultivation of the Unfit," *Nature* 137 (February 1, 1936): 188; B. Dunlop, "Cultivation of the Unfit," *Nature* 137 (February 1, 1936): 188; E. W. M., "Cultivation of the Unfit," *Nature* 137 (February 1, 1936): 188-189; E. W. M., "Cultivation of the Unfit," *Nature* 137 (February 15, 1936): 276; H. T. B. Drew, "Cultivation of the Unfit," *Nature* 137 (February 15, 1936): 276; J. S. Huxley, "Natural Selection and Evolutionary Progress," *Nature* 138 (October 10, 1936): 603-605; W. Neilson Jones, "Genetics in the University," *Nature* 138 (December 19, 1936): 1058; J. B. S. Haldane, "Mental Defect," *Nature* 141 (April 2, 1938): 575-576; T. Caspersson, and Jack Schultz, "Nucleic Acid Metabolism of the Chromosomes in Relation to Gene Reproduction," *Nature* 142 (August 13, 1938): 294-295; J. I. Cohen, "Intelligence and Birth-Rate," *Nature* 143 (March 18, 1939): 484-485; R. Ruggles Gates, "Human Genetics," *Nature* 144 (November 11, 1939): 821-822.

⁶⁷ Blacker, "Sterilization," 245-246.

Needham, Lancelot Hogben, and J. B. S. Haldane.⁶⁸ Hogben and Haldane especially had an important role in shaping the future direction of genetics. Similarly, as part of his attempt to place the study of mental deficiency on a more sound scientific, mathematical, and Mendelian footing, the psychiatrist and geneticist Lionel Penrose (whose contributions to the study of anticipation will be discussed below) actively undermined the scientific evidence supporting the notion that sterilization could reduce the numbers of the mentally deficient. In a series of published articles and monographs Penrose worked hard to replace the simplistic notion, held by many eugenicists, that mental defect was caused by the action of a recessive gene that followed a Mendelian pattern of inheritance with a more nuanced, scientifically up-to-date, and humane understanding of the subject.⁶⁹ The 1936 study by Sir John Boyd Orr, *Food, Health and Income*, further

⁶⁸ See, for example: Joseph Needham, "The Cultivation of the Unfit," *Nature* 137 (1 February 1936): 188; J. B. S. Haldane, *Heredity and Politics*, (London: George Allen & Unwin Ltd., 1938); Lancelot Hogben, *Dangerous Thoughts*, (London: George Allen & Unwin Ltd., 1939). David Barker analysed the responses of several Anglo-American geneticists to the theory that mental defect was caused by Mendelian recessive patterns of inheritance. While some geneticists remained supportive of the idea through the 1930s, others, most notably Haldane, moved from accepting the theory (1928) to rejecting it (1935). David Barker, "The Biology of Stupidity: Genetics, Eugenics and Mental Deficiency in the Inter-War Years," *British Journal for the History of Science* 22 (1989): 362-363.

⁶⁹ Penrose's contributions on the subject were substantial and important. He believed that the treatment of these individuals reflected the values of society as a whole. He opposed the sterilization of those deemed "unfit" not only on ethical grounds but also on scientific ones, showing that, even if mental defect was somehow inherited according to Mendelian principles, society was in no danger of being overwhelmed by large numbers of the mentally deficient. One of Penrose's most important contributions to disproving the notion that mental defect was caused by a simple Mendelian recessive came in his 1934 *British Medical Journal* article in which he examined a family in which not just consanguinity occurred but also incest. The children of incestuous, mentally defective parents were found to be of perfectly normal intelligence, despite the harsh living conditions of their early years, something that should have not been possible if mental defect was a Mendelian recessive trait as had been suggested by Davenport and others. Additionally, in his textbook *Mental Defect*, Penrose warned against the trend to link various disorders across multiple generations in order to prove genetic defect within a family. He believed that considerable scientific and statistical work would be needed before "one can say, for example, that a woman with an epileptic sister and mother, who marries a man whose aunts are insane, is more likely to have a microcephalic imbecile child than any other prospective mother taken at random." He did argue for the segregation and humane treatment of the mentally defective (the fact that long-term segregation of the mentally defective in government-run institutions was tantamount to sterilization he left unmentioned). In his review of *Mental Defect*, Blacker complained that Penrose was parodying the Eugenic Society's attitudes on the subject of sterilization. However, he acknowledged that Penrose was "unusually well fitted for the task he has undertaken" being "equipped with a knowledge of mathematics and of statistical theory rare among medical men; and he knows enough genetics to appreciate the limitations of this science as well as its possibilities when applied to human material." Blacker concluded: "Dr. Penrose's [hostile] attitude to sterilization is an unimportant feature of this work which, taken as a whole, constitutes a most valuable contribution to the literature on mental deficiency." C. P. Blacker, "Mental Defect," *Eugenics Review* 25 (1933) 267-269. Among Penrose's most important early works are the following: Articles: "Mental Deficiency—II The Sub-Cultural Group," *Eugenics Review* 24 (1932): 289-291; "A Contribution to the Genetic Study of Mental Deficiency," *British Medical Journal* 1 (1934): 10-11; "Autosomal mutation and

complicated discussions of the relation of poverty and inheritance by showing that a significant portion of the poorest members of the British population were existing on a bare subsistence diet and that only the wealthiest third of the population could afford the kind of balanced diet recommended by the new nutritional science.⁷⁰ Penrose's *Colchester Survey*, published in 1938, was the last of the large reports examining mental deficiency. It was jointly instituted and funded by the Medical Research Council and the Darwin Trust in 1930 in response to the *Wood Report*.⁷¹ This landmark survey looked at specific causes of mental deficiency and revealed that the issue was considerably more complex and less amenable to legislative solutions than eugenicists might have wished.⁷²

modification in man, with special reference to mental defect," *Annals of Eugenics* 7 (1936): 1-16; "Eugenic Prognosis with Respect to Mental Deficiency," *Eugenics Review* 31 (1939): 35-37. Books: Penrose, *Mental Defect*, (London: Sidgwick & Jackson, Ltd., 1933) also (New York: Farrar & Rinehart, 1934); Penrose, *The Influence of Heredity of Disease*, (London: H. K. Lewis & Co. Ltd., 1934).

⁷⁰ Controlled studies by this time were showing that adding merely a pint of milk daily to the diet of poor children could result in significant increases in growth over their un-supplemented counterparts. Additionally, scientists were gaining an understanding of the importance of vitamins and minerals in a healthy diet and of the dangers of malnutrition on normal human development. Orr's study noted that only the upper half of the British population was consuming "a diet completely adequate for health." He additionally noted that dietary inadequacy was linked with poorer health amongst the lower income groups. These groups accounted for the largest numbers of children whose health, growth, and education would benefit from an improved diet. The importance of these and other findings did not escape Blacker who warned the Eugenics Society that it was going to have to take environmental and other criticisms much more seriously. This realization contributed to the rise of the 'Nurture' over the 'Nature' camp as seen in a *Nature* editorial from 1935 which stated: "of the two factors which together mould the individual, heredity and environment, modern knowledge is attributing more and more importance to the latter." Anonymous, "Problems of Human Nutrition," *Nature* 135 (1935): 321-322; C. P. Blacker, "Food, Health and Income," *Eugenics Review* 28 no. 3 (1936): 229; C. P. Blacker, ed., *A Social Problem Group?* (London: Oxford University Press, 1937) 4-14; C. P. Blacker, *Eugenics in Retrospect and Prospect: The Galton Lecture, 1945*, 2d ed., (London: The Eugenics Society and Cassell and Company Ltd., 1950); John Boyd Orr, *Food Health and Income: Report on A Survey of Adequacy of Diet in Relation to Income*, (London: Macmillan and Co., Ltd., 1936) 5-11, 38-50; Searle, "Eugenics," 165.

⁷¹ The study is commonly known as the *Colchester Survey* because it examined inmates at the Royal Eastern Counties' Institution, Colchester, and their families. Lionel S. Penrose, *A Clinical and Genetic Study of 1280 Cases of Mental Defect*, (London: His Majesty's Stationary Office, 1938) 1-3.

⁷² Penrose's study made several major discoveries. Penrose showed that intelligence, like height, was not a unit characteristic, but rather a graded one and that there was no sharp line of demarcation between the so-called feeble minded and those with normal intelligence. He also took the time to classify the various types of mentally deficient patients and noted that many had mental conditions caused by illness and other non-hereditary physical causes. He discussed those relatively rare cases in which Mendelian heredity could be ascertained (e.g. phenylketonuria and amaurotic family idiocy—now known as Tay-Sachs) and was among the first to note the importance of maternal age to the incidence of mongolism (now known as Down's Syndrome). He concluded that "the aetiology of mental defect is multiple and a facile classification of patients in the series into primary and secondary, or endogenous and exogenous, cases would only have led to a fictitious simplification of the real problems inherent in the data." The Medical Research Council was left to hope that with further research "other clinical-genetic conditions will emerge from the clinical chaos now designated 'mental deficiency'." Penrose, *Clinical and Genetic*, 1-3, 11-12, 36-37, 49-50, 62-65, 69-70. On the importance of Penrose's *Colchester Survey* see among others, Harry Harris, "Lionel Sharples

(B) Developments in Genetics: 1930-1945

The period between 1930 and 1945 was one of significant change for the field of genetics as well as for eugenics more narrowly.⁷³ It was a time of systemization that witnessed a move towards more mathematical forms of Mendelism. These in turn disallowed other concepts of heredity—such as the notion of cytoplasmic inheritance⁷⁴ and Lamarckism⁷⁵—that scientists had previously found acceptable. From the 1920s onwards, some researchers, most notably R. A. Fisher, had been advocating the application of statistics rather than the simple reconstruction of pedigrees as the

Penrose, 1898-1972,” *Biographical Memoirs of Fellows of the Royal Society* 19 (December 1973): 523-535; Kevles, *Eugenics*, 162-163; Mazumdar, *Eugenics*, 226-231; Watt, “Part 2,” 343.

⁷³ Because of the importance of the study DNA in genetics since the 1950s, many histories of genetics concentrate their narrative on the discovery of the structure and function of DNA. For this reason, authors tend to concentrate on discoveries made during the 1930s and 1940s that would later contribute to the story of DNA, namely W. T. Astbury’s first x-ray crystallography pictures of DNA and the discovery by Avery, McCarty, and MacLeod that DNA could induce genetic change in bacteria. Elof Axel Carlson, *The Gene: A Critical History*, (Philadelphia: W. B. Saunders, 1966); Donald Chambers, ed., “DNA: The Double Helix: Perspective and Prospective at Forty Years,” *Annals of the New York Academy of Sciences* 758 (1995); Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, Expanded edition, (Planesview NY: Cold Spring Harbor Laboratory Press, 1996); Maxim Frank-Kamenetskii, *Unravelling DNA: The Most Important Molecule of Life*, (Reading, MA: Addison-Wesley, 1997); Lily Kay, *Who Wrote the Book of Life? A History of the Genetic Code*, (Stanford CA: Stanford University Press, 2000); Evelyn Fox Keller, *The Century of the Gene*, (Cambridge, MA: Harvard University Press, 2000); Robert Olby, *The Path to the Double Helix: The Discovery of DNA*, (New York: Dover Publications, Inc., 1994); Franklin Portugal and Jack S. Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*, (Cambridge MA: MIT Press, 1977); A. H. Sturtevant, *A History of Genetics*, introduction by Edward B. Lewis, (Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2001); N. A. Tiley, *Discovering DNA: Meditations of Genetics and a History of Science*, (New York: Van Nostrand Reinhold Company, 1983); Bruce Wallace, *The Search for the Gene*, (Ithaca: Cornell University Press, 1992). The subject of anticipation, either in this early period or after its “rediscovery” by the scientific community in 1991, is ignored in such texts. Moreover, as shall be seen in chapter six, even after its rediscovery in 1991, modern genetics textbooks only irregularly include mention of anticipation.

⁷⁴ Jan Sapp, “The Struggle for Authority in the Field of Heredity, 1900-1932: New Perspectives on the Rise of Genetics,” *Journal of the History of Biology* 16 no. 3 (Fall 1983): 311-342.; Jan Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, (New York: Oxford University Press, 1987); Jan Sapp, *Where the Truth Lies: Franz Moewus and the origins of molecular biology*, (Cambridge: Cambridge University Press, 1990). What was deemed an acceptable subject of study could be influenced by regional scientific styles. See for example: Jonathan Harwood, “National Styles in Science: Genetics in Germany and the United States between the World Wars,” *Isis* 78 no. 3 (September 1987): 390-414.

⁷⁵ In a 1932 *Nature* article, J. B. S. Haldane spoke out directly against those who still believed in Lamarckism. Richard Burkhardt Jr., “Lamarckism in Britain and the United States,” in *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, Ernst Mayr and William Provine eds., (Cambridge MA: Harvard University Press, 1980), 343-352.; J. B. S. Haldane, “The Hereditary Transmission of Acquired Characters,” *Nature* 129 (June 11, 1932): 856-858.

methodology of choice in the study of human heredity.⁷⁶ R. A. Fisher, J. B. S. Haldane, and the American Sewall Wright used mathematics and statistics to integrate the Darwinian theory of natural selection with biometry and Mendelism creating the field of quantitative genetics⁷⁷ and contributing to the “modern synthesis” of evolution.⁷⁸

The introduction of German mathematical genetics (*Vererbungsmathematik*) to Britain by the socialist Lancelot Hogben in 1930, and its development and popularization by other Left-leaning scientists including Haldane and Julian Huxley, began the process of revitalization and change.⁷⁹ These new mathematical-Mendelian methods promised to allow researchers to distinguish between the effects of heredity and environment on

⁷⁶ During his career, Fisher made several important contributions to this field, not the least of which was his 1918 paper which reconciled the Mendelians and the biometricians. During the 1930s, Fisher also contributed to the better understanding of ascertainment bias, a problem that plagued studies of human genetics. Because of small population sizes, the question of which individuals were counted and how became vitally important for performing accurate calculations on the data. R. A. Fisher, “The Correlation between Relatives on the Supposition of Mendelian Inheritance,” *Transactions of the Royal Society of Edinburgh* 52 (1918): 399-433; R. A. Fisher, “The Effect of Methods of Ascertainment Upon the Estimation of Frequencies,” *Annals of Eugenics* 6 (1934): 13-25; Kevles, *Eugenics*, 180-184; Mazumdar, *Eugenics*, 58-145; William Provine, *The Origins of Theoretical Population Genetics*, (Chicago: University of Chicago Press, 1971), 140-152.

⁷⁷ Papers written by Fisher, Haldane, and Wright during the 1920s and 1930s formed the basis for the fields of population genetics and quantitative genetics. W. G. Hill, ed., *Quantitative Genetics, Part I: Explanation and Analysis of Continuous Variation*, (New York: Van Nostrand Reinhold Company, 1984) 1-23, 58-92; W. G. Hill, ed., *Quantitative Genetics, Part II: Selection*, (New York: Van Nostrand Reinhold Company, 1984) 1-6, 128-148; Provine, *Origins*, 130-178.

⁷⁸ The term “evolutionary synthesis” was coined by Julian Huxley in 1942. Mayr dates the period of the modern synthesis as the time between 1936 and 1947. The biologist Robert Reid offers a more complicated and nuanced account of the modern synthesis in his *Biological Emergences*. Ernst Mayr, “Prologue: Some Thoughts on the History of the Evolutionary Synthesis,” in *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, Ernst Mayr and William Provine eds., (Cambridge MA: Harvard University Press, 1980), 1, 28-32, 39-44; William Provine, “England: Introduction,” in *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, Ernst Mayr and William Provine eds., (Cambridge MA: Harvard University Press, 1980), 329-334. Robert Reid, *Biological Emergences: Evolution by Natural Experiment* (Cambridge MA: MIT Press, 2007), 38-65. This aspect of developments in genetics is more often discussed in general histories of biology which tend to concentrate on issues like Mendelism and the development of evolutionary theory. See for example: Elof Axel Carlson, *Mendel’s Legacy: The Origin of Classical Genetics*, (New York: Cold Spring Harbor Press, 2004); Robert Olby, *Origins of Mendelism*, with an introduction by C. D. Darlington, (London: Constable and Company Ltd., 1966); Peter J. Bowler, *Evolution: The History of an Idea*, 3rd ed., revised and expanded, (Berkeley: University of California Press, 2003); Jan Sapp, *Genesis: The Evolution of Biology*, (Oxford: Oxford University Press, 2003).

⁷⁹ Mazumdar argues that Hogben, Haldane, and Huxley opposed eugenics on political grounds. Diane Paul suggests that it is important to remember that many of the Left-leaning geneticists of the 1930s, including Haldane among others, did believe and would continue to believe in certain aspects of eugenics even while arguing with proposed eugenic policies and contributing to the development of genetics and population biology. Mazumdar, *Eugenics*, 147-151; Diane Paul, “Eugenics and the Left,” *Journal of the History of Ideas* 45 no. 4 (1984): 567-590. For a more up to date version of the argument see: Diane Paul, *The Politics of Heredity: Essays on Eugenics, Biomedicine and the Nature-Nurture Debate*, (New York: State University of New York Press, 1998).

development.⁸⁰ Moreover, the discovery of the genetics of blood-grouping opened the way for the creation of a class-free form of genetics where traits could be properly assessed as being hereditary (or not) and then mapped in linkage studies to the blood groups. This would then open the way to what Haldane called a “sane eugenic policy” that would affect only those individuals suffering from or carrying genes for hereditary illnesses rather than being applied indiscriminately to their whole family, affected or not.⁸¹ The reformers were aided in the project by funding from the Rockefeller Foundation whose officers had been making a deliberate effort to foster what they felt was the best and most forward-looking scientific and medical research.⁸² Even

⁸⁰ Mazumadar, *Eugenics*, 5.

⁸¹ Mazumdar, *Eugenics*, 162-185; Mazumdar, “Two models,” 619-657.

⁸² Serology testing labs were set up with Rockefeller funding to attempt to find traits that could be linked to the ABO or MN blood loci. Unfortunately, most of this work was unsuccessful. The 46 (then believed to be 48) human chromosomes proved much more difficult to map than the 4 of the fruit fly. Success for this sort of research would need to wait until the development of new scientific methods in the last two decades of the twentieth century. Mazumdar, *Eugenics*, 162-185. The correspondence surrounding the research grants requested and given to the Galton Laboratory and allied researchers is quite interesting, but can unfortunately not be discussed in detail here. However, one comment made by William Teasdale to Warren Weaver is worthy of special note; it read: “There are but two geneticists with real possibilities in Europe today, and those are R.A.FISHER and J.B.S.HALDANE.” The same letter remarked that the Medical Sciences board should look into funding Penrose’s work on what I assume was the Colchester project. W. E. Tisdale to W. Weaver, 17 November 1934, folder 219, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, Rockefeller Archive Center, Sleepy Hollow, New York (hereafter designated RAC). For Rockefeller Foundation correspondence with and concerning the Galton Laboratory and its research programmes, see: Fisher to O’Brien, 18 July 1934, folder 219, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; O’Brien to Gregg, 13 November 1934, folder 219, box 16, series 401a, RC 1.1, Rockefeller Foundation Archives, RAC; Irwin to Weaver, 29 January 1935, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; O’Brien to Gregg, 1 March 1935, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Tisdale to Weaver, 1 March 1935, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Tisdale to Weaver, 5 March 1935, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; O’Brien to Gregg, 6 March 1935, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Mellanby to O’Brien, 13 March 1935, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Weaver to Tisdale, 27 March 1935, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; RF 35057, 17 April 1935, folder 218, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Active List, 9 November 1935, folder 221, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; O’Brien to Gregg, 17 October 1936, folder 221, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; RF 36132, 16 December 1936, folder 218, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Fisher to O’Brien, 11 May 1939, folder 221, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Galton Laboratory – Genetics, 30 June 1940, folder 221, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC. For the Foundation’s officers’ comments on the labs that they visited see: Warren Weaver officer’s diary, 16 May 1935, RG 12.1, Rockefeller Foundation Archives, RAC; Alan Gregg officer’s diary, 25 September 1945, folder 223, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC. The historian Pnina Abir-Am has spent much of her career examining the role of the Rockefeller Foundation’s funding policies on the direction of scientific research; see: Pnina Abir-Am, “The Discourse of Physical Power and Biological Knowledge in the 1930s: A Reappraisal of the Rockefeller Foundation’s ‘Policy’ in Molecular Biology,”

psychiatrists, such as Tredgold, had to come to terms with what these scientific changes meant in the context of their own profession. This period also saw a changing of the guard at the Galton Laboratory. In 1933, Pearson retired and two-thirds of his old position went to Fisher and Haldane with their different approaches and politics.⁸³ Old ideas such as the Lamarckian heredity of acquired characteristics might pop up from time to time for Haldane to shoot down, but the field of genetics was moving on to a more scientific, Mendelian, and mathematical footing.⁸⁴

(C) *The Origins of Human and Medical Genetics: 1930-1945*

The new fields of human and medical genetics had their origin in the intellectual tumult of the period before and after the Second World War.⁸⁵ From 1930-1945, the fledgling

Social Studies of Science 12 no. 3 (August 1982): 341-382; Pnina Abir-Am, "The Biotheoretical Gathering, Trans-Disciplinary Authority and the Incipient Legitimation of Molecular Biology in the 1930s: New Perspective on the Historical Sociology of Science," *History of Science* 25 (1987): 1-70; Pnina Abir-Am, "The Rockefeller Foundation and the rise of molecular biology," *Nature Reviews Molecular Cell Biology* 3 (January 2002): 65-70. Her 1982 paper sparked a debate on the importance of the Rockefeller's role in shaping molecular biology. Discussions of Abir-Am's thesis and her reply to her critics appeared in *Social Studies of Science* in 1984. See: John A. Fuerst, "The Definition of Molecular Biology and the Definition of Policy: The Role of the Rockefeller Foundation's Policy for Molecular Biology," *Social Studies of Science* 14 no. 2 (May, 1984): 22-237; Ditta Bartels, "The Rockefeller Foundation's Funding Policy for Molecular Biology: Success or Failure?" *Social Studies of Science* 14 no. 2 (May, 1984): 238-248; Robert Olby, "The Sheriff and the Cowboys: or Weaver's Support of Astbury and Pauling," *Social Studies of Science* 14 no. 2 (May, 1984): 244-247; Edward Yoxen, "Scepticism about the Centrality of Technology Transfer in the Rockefeller Foundation Programme in Molecular Biology," *Social Studies of Science* 14 no. 2 (May, 1984): 248-252; Pnina Abir-Am, "Beyond Deterministic Sociology and Apologetic History: Reassessing the Impact of Research Policy upon New Scientific Disciplines (Reply to Fuerst, Bartels, Olby and Yoxen)" *Social Studies of Science* 14 no. 2 (May, 1984): 252-263.

⁸³ After Pearson's retirement from University College, London, Fisher succeeded him as Galton professor of eugenics in 1933 and inherited the Galton Laboratory and the journal *Annals of Eugenics*. Haldane held the chair of genetics and then of biometry. Pearson's son Egon was appointed to head the department of statistics.

⁸⁴ Ironically, while British science was adopting mathematical Mendelism, Rüdin and his group in Germany were developing a new method they called *empirische Erbprognose* (empirical hereditary prognosis) to back their arguments for sterilization legislation which would be fully enacted by the Nazis. Mazumdar, *Eugenics*, 205.

⁸⁵ The terms "human genetics" and "medical genetics" are sometimes used interchangeably in the literature when discussing this period, depending upon the audience being addressed. In this study, the selection of the terminology "human genetics" and "medical genetics" is deliberate and will have an important role in later discussion. For the purposes of this study "human genetics" is designated as the more abstract, often lab-based, study of human genes; "medical genetics" involves the study of the inheritance of genetic diseases (and treatment where available); "clinical genetics," the third of the troika of terms commonly used to describe the field, is generally used to cover the work done in the process of genetic testing and counselling. There may be significant overlap in membership and research areas between these fields—as has been noted by its members. For example, Penrose might be seen as practicing both human and medical genetics. In 1948, the founding membership of the American Society of Human Genetics contained both geneticists and physicians. However, calls for the journal to be named the *American Journal of Medical*

ranks of human and medical geneticists were filled by an eclectic group of scientists, geneticists and physicians. Internal histories of the fields of human and medical genetics often look upon this period as one before the creation of the fields, as marked by the creation of the American Society of Human Genetics in 1948 or the technological developments of the field in the late 1950s.⁸⁶ However, recent scholarship in the history

Genetics were soundly defeated. This led the field of human genetics to achieve an accelerated rate of professionalization shortly after the end of the Second World War. The creation of the professional association, the American Society of Human Genetics in 1948 which launched its journal the *American Journal of Human Genetics* the following year are seen as important landmarks in this process. Conversely, the *American Journal of Medical Genetics* did not come into publication until 1977, even though departments of medical genetics were being formed in medical schools in the 1950s and 1960s.

The scientific and technological developments in the late 1950s that led to the development of clinical genetics also led some human geneticists, like A. G. Motulsky, to argue that it was at that point that the field of human genetics became increasingly “medicalized.” This interpretation downplays the research and findings of those specialists (ophthalmologists, neurologists, endocrinologists, etc.) who studied families with hereditary disease in the first half of the century and later and who contributed a great deal to the understanding of the inheritance of these diseases, even if their findings were not always recognized by human geneticists. I hold to the differentiation between human and medical genetics for a reason that will first become apparent later on in this chapter and will remain important for succeeding chapters. Those engaged in the more theoretical study of human genetics were more likely to hold strictly to an orthodox interpretation of Mendelian heredity and as such were less likely to believe in the existence of anticipation than were medical geneticists or specialists (neurologists etc.) who were actually examining families through time. In fact, as we shall see in chapter five, human geneticists essentially felt that they had to excuse findings of anticipation within their families, so it was difficult for them to admit that a physical factor might underlay anticipation. The issue of the points of origin of the fields of human, medical, and clinical genetics has been discussed by scientists from within these fields. See for example: E. A. Carlson, “H. J. Muller and human genetics,” in *The History & Development of Human Genetics: Progress in Different Countries*, Washington DC, 6 October 1991, Krishna Dronamraju ed., (Singapore: World Scientific, 1992) Krishna Dronamraju, *The Foundations of Human Genetics*, (Springfield IL: Charles C Thomas, 1989), 121-127.; Victor McKusick, “The Growth and Development of Human Genetics as a Clinical Discipline,” *American Journal of Human Genetics* 27 (1975): 261-273; A. G. Motulsky, “The William Allan Memorial Award Lecture. Human and Medical Genetics: A Scientific Discipline and an Expanding Horizon,” *American Journal of Human Genetics* 23 no. 2 (1971): 107-123; A. G. Motulsky, “Medical and Human Genetics 1977: Trends and Directions,” *American Journal of Human Genetics* 30 (1978): 123-131; J. M. Opitz, “The American Journal of Medical Genetics—Forward,” 1 no. 1 (1977): 1-2.

⁸⁶ Laurence Snyder believed that it was not until the 1940s, when scepticism against eugenics was on the rise, that interest in human genetics increased in America leading to “the formation of the American Society of Human Genetics in 1948, an event which holds promise of a true flowering of the subject on this side of the Atlantic.” Laurence Snyder, “Old and New Pathways in Human Genetics,” *American Journal of Human Genetics* 3 no. 1 (March 1951): 2. L. C. Dunn argued that “the eugenics movement cast a long shadow over the growth of sound knowledge of human genetics” delaying the proper development of the field (with the exception of a few dissenting voices, most notably Penrose) until after the Second World War. L. C. Dunn, “Cross Currents in the History of Human Genetics,” *American Journal of Human Genetics* 14 (1962): 1-4. Victor McKusick (creator of the genetic compendium *Mendelian Inheritance of Man* which has an important role in later chapters) dates the origin of the field of clinical genetics to the technical advances of 1959 “when a confluence took place of cytogenetics and biochemical genetics with the mere trickle of a stream, mainly formal genetics, which had been flowing even before 1900.” McKusick, “Growth and Development,” 261. James Neel speaks of the “recovery” of human genetics in the wake of the post-war lull “undoubtedly fostered by the realization of the extent of the Nazi atrocities on the basis of so-called eugenic considerations.” He argues that the field was bolstered by a series of technological developments and notes the creation of the American Society for Human Genetics (1948) and

of science and medicine has begun to push back the origins of the fields of human and medical genetics into the interwar period.⁸⁷

Despite approaching subjects such as eugenics and anticipation from opposite perspectives, two of the earliest advocates of medical genetics, Madge Macklin and Lionel Penrose, actively sought to educate physicians in the developing field of human heredity.⁸⁸ Madge Macklin, an American physician and pioneer genetic researcher who

the *American Journal of Human Genetics* (1949) as significant milestones for the field in America. James Neel, “The ‘Recovery’ of Human Genetics,” in *The History & Development of Human Genetics: Progress in Different Countries, Washington DC, 6 October 1991*, ed., Krishna Dronamraju, (Singapore: World Scientific, 1992), 6-10. While Elof Carlson discussed Muller’s genetic work in the 1920s and 1930s he dated “the founding of a new science” i.e. human genetics, to the foundation of the American Society of Human Genetics in 1948. E. A. Carlson, “H. J. Muller and human genetics,” in *The History & Development of Human Genetics: Progress in Different Countries, Washington DC, 6 October 1991*, Krishna Dronamraju, ed., (Singapore: World Scientific, 1992), 21-47; Hubert Soltan has taken an interest in describing the history of human and medical genetics in Canada (he uses both terms fairly interchangeably, although he describes medical genetics as the “strongest branch” of human genetics). He describes a small group of “pioneers” active in the field from the 1920s onwards—Madge Macklin, Norma Ford Walker, Bruce Chown, and Lionel Penrose, who began “to build both an academic and clinical base for human genetics in those two or three cities and universities able to support it in those distant times.” These pioneers introduced the teaching of human genetics to medical and other students and carried out important research but the teaching of genetics to medical students did not become widespread until the 1950s and 1960s and this culminated in the development of the Canadian College of Medical Genetics in 1975. H. C. Soltan, “The early history and development of human and medical genetics in Canada,” In *The History & Development of Human Genetics: Progress in Different Countries, Washington DC, 6 October 1991*, Krishna Dronamraju, ed., (Singapore: World Scientific, 1992), 57-82 and also H. C. Soltan, ed., *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*, (London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992). Another common approach, taken by Peter Harper, is to collect and examine a series of papers seen as important to the development of the field. Peter Harper, ed., *Landmarks in Medical Genetics: Classic Papers with Commentaries*, (Oxford: Oxford University Press, 2004).

⁸⁷ Daniel Kevles dates the origin of the field of human genetics to a group of individuals with varied academic and professional backgrounds working in England and America between 1930 and 1945. He identifies the majority of the most productive publishers as British. Nathaniel Comfort’s study concentrates on the nascent field of medical genetics in North America. Nathaniel Comfort, “‘Polyhybrid Heterogeneous Bastards’: Promoting Medical Genetics in America in the 1930s and 1940s,” *Journal of the History of Medicine and Allied Sciences* 61 no. 4 (2006): 415-455; Kevles, *Eugenics*, 193-211. Although he recognizes the contributions of earlier workers, William Leeming’s studies concentrate on the process of professionalization and the creation of a specialization in medical genetics in Canada and the UK which he dates to the post-1945 period. William Leeming, “Professionalization theory, medical specialists and the concept of ‘national patterns of specialization,’” *Studies of Science* 40 no. 3 (2001): 455-485; William Leeming, “The Early History of Medical Genetics in Canada,” *Social History of Medicine* 17 no. 3 (2004): 481-500.

⁸⁸ While Penrose argued against both eugenics and anticipation throughout his career, Macklin advocated both. Penrose’s lectures to medical students on these subjects will be dealt with as part of his contributions to theoretical approaches to anticipation. Strangely, even though both Macklin and Penrose were on staff at the University of Western Ontario between 1939 and 1945, and referenced each other’s work in their own writings, they did not collaborate. Macklin’s career reveals just how intertwined the study of eugenics, genetics, and medical genetics were during this period. While she blazed the trail for the study of heredity in cancer in general (breast cancer in particular), and pioneered the introduction of genetics into the medical school curriculum, she was also an active member of the Canadian and international eugenics movements

worked at the University of Western Ontario from 1921-1945, actually coined the term “medical genetics.”⁸⁹ Beginning in 1932, Macklin published a series of papers in which she called for the inclusion of medical genetics in the medical curriculum. Her advocacy is credited as a cause for the expansion of compulsory programmes in medical genetics in North America went from a single school in 1938, to 55 percent of schools in 1953.⁹⁰

and repeatedly expressed concern about the increase in the number of the feeble-minded, arguing for sterilization on eugenic grounds. One of the few physicians who joined the American Society of Human Genetics, Macklin became president of the society in 1958. See: M. T. Macklin, “The Hereditary Factor in Human Neoplasms,” *Quarterly Review of Biology* 7 (1932): 255-281; M. T. Macklin, “Genetical Aspects of the Sterilization of the Mentally Unfit,” *Canadian Medical Association Journal* 30 no. 2 (1934): 190-195; M. T. Macklin, “The Value of Accurate Statistics in the Study of Cancer,” *Canadian Journal of Public Health* 25 (1934): 369-373; M. T. Macklin, “Inheritance and Human Cancer,” *Ohio State Medical Journal* 43 (August 1947): 836-840; M. T. Macklin, “Comparison of the Number of Breast-Cancer Deaths Observed in Relatives of Breast-Cancer Patients, and the Number Expected on the Basis of Mortality Rates,” *Journal of the National Cancer Institute* 22 (1959): 927-951. For historical accounts of Macklin’s career, see: Comfort, “Polyhybrid,” 432-441; McLaren, *Master Race*, 128-145; H. C. Soltan, “Madge Macklin,” in *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*, ed., H. C. Soltan, (London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992), 11-26; H. Soltan, “Lionel Penrose,” in *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*, ed., H. C. Soltan, (London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992), 36-40.

⁸⁹ M. T. Macklin, “Medical Genetics”; a necessity in the up-to-date medical curriculum,” *Journal of Heredity* 23 no. 12 (1932): 485-486; M. T. Macklin, “The Need of a Course in Medical Genetics in the Medical Curriculum: A Pivotal Point in the Eugenic Program,” in *A Decade of Progress in Eugenics: Scientific Papers of the Third International Congress of Eugenics held at American Museum of Natural History, New York, August 21-23, 1932*, (Baltimore: The Williams & Wilkins Company, 1934), 157-158.

⁹⁰ M. T. Macklin, “Teaching human inheritance to medical students,” *Medical Journal and Record* 136 (September 1932): 215-217; M. T. Macklin, “Should the teaching of genetics as applied to medicine have a place in the medical curriculum,” *Journal of the Association of American Medical Colleges* 7 (November 1932): 368-373; M. T. Macklin, ““Medical Genetics’ A Necessity in the Up-to-date Medical Curriculum,” *Journal of Heredity* 23 no. 12 (1932): 485-486; M. T. Macklin, “Heredity as an Aid to Modern Therapy,” *The Canadian Medical Association Journal* 28 no. 4 (1933): 394-397; M. T. Macklin, “Medical Genetics,” *Journal of the Association of American Medical Colleges* 8 (September 1933): 291-304; M. T. Macklin, “The need of a course of medical genetics in the medical curriculum as the pivotal point in the eugenic program,” *Edinburgh Medical Journal* 40 (1933): 20-30; M. T. Macklin, “Education and Research in the Field of Inheritance of Disease,” *The Canadian Medical Association Journal* 32 no. 1 (1935): 80-82. Macklin published an outline of a proposed course of medical genetics in 1933 and in 1935 she published a 75 page article laying out how the study of heredity in disease could be taught and including a short bibliography. M. T. Macklin, “The Teaching of Inheritance of Disease to Medical Students. A Proposed Course in Medical Genetics,” *Annals of Internal Medicine* 6 (1933): 1335-1343; M. T. Macklin, “The Role of Heredity in Disease,” *Medicine* 14 (1935): 1-75. William Allan, Laurence Snyder, and Madge Macklin were all early advocates of the inclusion of medical genetics in medical school curricula. Allan became the first chair of the first American department of medical genetics at Bowman Grey Medical School, Snyder lectured on medical genetics in several institutions before becoming professor of medical genetics at the University of Oklahoma in 1947, Macklin took over Snyder’s courses at Ohio State when he moved on. For an internal history of genetics within medical schools ca. 1956 see: C. Nash Herndon, “Genetics in the Medical School Curriculum,” *American Journal of Human Genetics* 8 no. 1 (March 1956): 1-7. For historical overviews see: Comfort, “Polyhybrid,” 432-441; McLaren, *Master Race*, 128-145; Soltan, “Madge Macklin,” 11-26.

Between 1930 and 1945 some of the first textbooks on medical and human genetics were published in Britain and America. Their authors believed that the texts filled a real need and addressed a gap in medical education and practice.⁹¹ In his book, *Genetics and the Clinician*, Lindsey Ride reminded his readers that physicians who had been concerned with the constitutional diathesis of their patients had already been engaged in the study of genetics, even if they had not been using that terminology.⁹² A few of these texts, most notably those by Roberts and Ford, became standard texts for the new field appearing in multiple editions over a long period of time.⁹³ Although some of these texts discussed diseases with which anticipation had been associated, most notably Huntington's disease and myotonic dystrophy, none of the texts discussed anticipation.⁹⁴

THEORETICAL STUDIES OF ANTICIPATION

An analysis of theoretical approaches to anticipation between 1930 and 1945 reveals that a series of researchers from a wide variety of backgrounds and often conflicting agendas clinically or legislatively were calling anticipation into question. In the early 1930s three of these individuals, Karl Pearson, Arthur S. Paterson, and Lionel Penrose all wrote papers in which they argued against accepting the concept of anticipation, but their divergent agendas made them strange bedfellows indeed.

Pearson, a biometrician and head of the Galton Laboratory, had been leery of anticipation since he first heard Mott speak of it at the First International Eugenics Congress in 1912. In the early 1930s both he and Paterson, a young psychiatrist, physician and member of the Eugenics Society, rejected anticipation on mathematical and eugenic grounds. They and other eugenicists feared that "Mott's law" was being used

⁹¹ Lindsay Ride, *Genetics and the Clinician*, (Bristol: John Wright & Sons Ltd., 1938), vii; J. A. Fraser Roberts, *An Introduction to Medical Genetics*, (London: Oxford University Press, 1940), v; Laurence Snyder, *Medical Genetics: A Series of Lectures Presented to the Medical Schools of Duke University, Wake Forest College, and the University of North Carolina*, (Durham NC: Duke University Press, 1941), v; E. B. Ford, *Genetics for Medical Students*, (London: Methuen & Co. Ltd., 1942), 1.

⁹² Ride, *Genetics*, 4-5.

⁹³ The eighth edition of Roberts' text appeared in 1985, anticipation was not mentioned in that or any previous edition. The seventh edition of Ford's text appeared in 1973. Leeming references the texts by Roberts and Snyder as seminal for the field and often cited by authors during the period of expansion and growth of the field of medical genetics in the 1950s. Leeming, "Professionalization," 465.

⁹⁴ This is somewhat notable considering the complaints that Penrose levelled in his lectures to medical students against archaic practices, including the belief in anticipation. This will be discussed later in the section on theoretical studies of anticipation.

against the proposed sterilization legislation on the grounds that Nature itself would “end or mend” the afflicted stock without the need for governmental intervention. Likewise, they were worried by physicians who used Mott’s dictum—that an individual from a family affected by mental illness who reached the age of 25 without showing signs of disease could safely marry and conceive children—as part of their family planning practice.

Penrose, a psychiatrist, physician, human geneticist, and pacifist, rejected eugenics as a whole on moral and scientific grounds. Over time he played an important role in displacing eugenics from human and medical genetics. He treated anticipation as an example of woolly-headed thinking on the part of eugenicists. This view was consistent with most opinion within the new mathematically-based Mendelism to which he subscribed. The geneticist Richard Goldschmidt provided the sole dissenting voice when he attempted to explain anticipation as a complicated form of Mendelian inheritance. Although his ideas did not gain much credence within the genetics community they did help inspire Penrose to write his decisive attack on anticipation in 1948.

The “mainstream” view of eugenicists on anticipation ca. 1930

For the purposes of this investigation, we can take the anonymous editor of the *Eugenics Review* at his word when he claims that the opinions he offered in the “Notes of the Quarter” of the journal represented “the considered opinion of the bulk of responsible eugenicists.”⁹⁵ In January 1931, he laid out the arguments then in circulation concerning the Eugenics Society’s proposed voluntary sterilization legislation.⁹⁶ Opponents of sterilization argued that not all the children of defective parents were themselves defective and that these children would not be born if one sterilized all of the defective.⁹⁷ Mott himself had made similar arguments in his 1912 paper at the First International Eugenics Conference.⁹⁸ However, the editor argued, just because these children were not visibly defective did not mean that they were not hereditarily tainted: “The stream of

⁹⁵ Editor, “Notes of the Quarter,” *Eugenics Review* 22 (1931): 235-237. C. P. Blacker identifies Mr. Eldon Moore as the editor of the *Eugenics Review* from 1928-1933. Blacker, *Eugenics in Retrospect*, 25.

⁹⁶ Editor, “Notes,” 235.

⁹⁷ Editor, “Notes,” 235.

⁹⁸ Mott, “Heredity and Eugenics,” 427.

defective genes is always there, running sometimes above and sometimes below ground; and our job is to cut it short whenever it is accessible.”⁹⁹ To the argument that sterilization would not completely end the birth of more mentally defective individuals the editor replied: “We did not scrap the Navy during the War, just because it failed to sink the U-boats.”¹⁰⁰ The editor expressed concern over the use of Mott’s “law of anticipation” by opponents of the proposed sterilization law who declared that sterilization was unnecessary “on the ground that nature, by this “law of anticipation,” had provided an automatic means of eliminating the mentally unfit.”¹⁰¹ As the representative of “the considered opinions of the bulk of responsible eugenicists,” he argued that this misrepresented Mott’s work.¹⁰² He explained that Mott did not say that families afflicted by mental defect would be eliminated by anticipation. He held that “Sir Frederick’s ‘law’” was no more than a hypothesis founded upon a very few pedigrees; and that while anticipation might not have been seen outside the human race it was clear from later pedigree work that afflicted families suffered from considerable inbreeding which fed a tendency “to intensify or hasten the appearance of a character [that] is well established.”¹⁰³ Such comments make it quite clear that the attitude of anti-sterilization campaigners to anticipation disturbed him.

Karl Pearson: A Biometric Approach to Anticipation

The editor of *Eugenics Review* was not the only prominent author who was disturbed about the fact that Mott’s law was being used to argue against sterilization legislation—or even worse (in their opinion)—in favour of marriage and the conception of children of individuals from families afflicted with mental illness. Karl Pearson, head of the Galton Laboratory and an old critic of Mott’s law, was among a group of statistically inclined eugenicists who did not hesitate to fault Mott’s notion of anticipation, and in particular its application in the sterilization debate. As a biometrician, Pearson was more concerned with the hereditary health of the “stock” rather than that of the individual. This led him

⁹⁹ Editor, “Notes,” 235.

¹⁰⁰ Editor, “Notes,” 235.

¹⁰¹ Editor, “Notes,” 236.

¹⁰² Editor, “Notes,” 236-237.

¹⁰³ He offered a recent study by a Dr. Bray on asthma in succeeding generations as proof of this claim. Editor, “Notes,” 237.

to argue for a broad application of sterilization in cases where there was any question of a possibility of hereditary mental deficiency or disease. On 20 March 1930, he dusted off his old arguments for the new controversy in a lecture given at the Galton Laboratory and later published in *Annals of Eugenics*.¹⁰⁴

In this lecture Pearson framed himself as a layman addressing an audience of specialists well-versed in the questions of the day regarding the treatment of “the insane and mentally defective.”¹⁰⁵ He argued that while what he termed “mental inefficiency” was of grave concern to the nation, it was extremely difficult to accurately assess. His own view was “that a due apportionment of the source of insanity between environment and heredity will only be obtained when there is a possibility of starting from the public asylums, and working with a well-organized system of field-workers.”¹⁰⁶

As in his earlier papers, Pearson praised Nettleship as “one of the few men who understood what a pedigree means for scientific purposes,” and he called for “an Edward Nettleship who will study in the same thorough way the family histories of the insane.”¹⁰⁷ A sound and proper understanding of the role of heredity in mental illness, Pearson argued, was the only way basis on which physicians would be able to offer sound advice to their patients on marriage and sterilization.¹⁰⁸ While Pearson did not offer any single cause of insanity, he interpreted his own research as indicating that both physical and mental anomalies seemed to run within the same families. He inferred that this was either because these defects caused the families to become poor and then intermingle with one another, or because anomalies caused by a defect in some controlling factor led to a wide variety of manifestations in affected offspring.¹⁰⁹

In his analysis of the pedigrees of families showing insanity and mental deficiency he noted a common fallacy “into which no less an authority than Dr Mott fell”—that of using incomplete generations. By this he meant that researchers did not wait until the all of the members of a particular generation of a family had died before

¹⁰⁴ Karl Pearson, “On the Inheritance of Mental Disease,” *Annals of Eugenics* 4 (1931): 362-380.

¹⁰⁵ Pearson, “Inheritance,” 362.

¹⁰⁶ Pearson, “Inheritance,” 362.

¹⁰⁷ Pearson, “Inheritance,” 363.

¹⁰⁸ Pearson, “Inheritance,” 363.

¹⁰⁹ Pearson, “Inheritance,” 364.

beginning their calculations.¹¹⁰ Pearson argued that “much of the evidence for ‘antedating’ is solely this misreading of the facts” caused by the researcher seeing those who are afflicted at an early age (which gave the appearance of the disease dying out within a family) while missing those who do not develop the illness until middle or old age and who would go on to spread the disease to later generations.¹¹¹

From the 1910s, Pearson had been critical of attempts to apply the notion of Mendelian simple unit characteristics simplistically to the study of a condition as complex as feeble-mindedness and imbecility. He noted problems caused by difficulties in differentiating the sane from the insane and in distinguishing the intelligence of normal people from that of the feeble-minded.¹¹² Like most researchers of this period, Pearson had a tendency to conflate a wide variety of issues ranging from imbecility and feeblemindedness to depression and kleptomania under the banner of mental defect. He likewise argued “that mental and moral inefficiency—the insane and the wastrel—are closely linked together.”¹¹³

Like the editor of the *Eugenic Review*, Pearson was concerned about what he termed the “latency” of mental defect: “the familial disease can lie latent in particular cases for three or even more generations.”¹¹⁴ He held that “a clear bill of health in *direct* ancestry is only a very partial guide as to familial taint.”¹¹⁵ Pearson believed: that the effect of heredity was much more important than that of the environment in mental illness; that the taint could be latent for several generations and need not appear in direct descent to be present; that there were strong links between mental illness and moral deficiencies; that physical defects such as epilepsy, idiocy, imbecility, and deaf mutism can be caused by the lack of factors controlling mental efficiency.¹¹⁶ However, Pearson also cautioned against the belief that feeble-mindedness was caused by a single gene that was recessive to normal.¹¹⁷ He felt whole families were tainted by insanity or feeble-mindedness and that, while not all (or even most) of the members of the family might be

¹¹⁰ Pearson, “Inheritance,” 365.

¹¹¹ Pearson, “Inheritance,” 365.

¹¹² Pearson, “Inheritance,” 366.

¹¹³ Pearson, “Inheritance,” 368-70.

¹¹⁴ Pearson, “Inheritance,” 370.

¹¹⁵ Pearson, “Inheritance,” 370.

¹¹⁶ Pearson, “Inheritance,” 370.

¹¹⁷ Pearson, “Inheritance,” 374.

mentally deficient, that “the immorality of parenthood lies just as much with the apparently sane as with the obviously insane in such stocks.”¹¹⁸ Although never a member of the Eugenics Society, Pearson was a strong advocate for sterilization legislation, and he sat on many of the committees attempting to enact such laws. This commitment may offer some explanations for the vitriol with which Pearson, who was so favourably inclined towards the quality of Nettleship’s work, attacked both the “law” that Mott had fashioned out of Nettleship’s idea of anticipation and particularly the use to which that law was put by some counsellors advising the families of relatives of the insane. Pearson argued that uninformed physicians “cannot treat insanity, imbecility, feeble-mindedness and insanity,” and that they should look to eugenics for guidance.¹¹⁹

Arthur S. Paterson: A Eugenic, Statistical, and Psychiatric Approach to Anticipation

Arthur Paterson drew many of his arguments against anticipation from Pearson and his former student David Heron, but he was part of a new generation trained after the First World War. He would go on to a significant career in the field of psychiatry. Although Paterson and Lionel Penrose, whose views will be discussed in the next section, were both trained in medicine and psychiatry at much the same time, they took very different approaches to the question of sterilization and eugenics, with Paterson in favour and Penrose steadfastly against. Ironically, their opposing views led each of them to question the concept of anticipation and its application to human disease.

Paterson took his BA at Oxford in 1923 and then went to Edinburgh University where he received his medical degree in 1928. He served as an Assistant Physician at the Glasgow Royal Mental Hospital 1929-1930. After holding a Rockefeller Fellowship (1930-1931), he was appointed to the Pinsent-Darwin Research Studentship in Mental Pathology in Cambridge for three years (1931-33), after which he held further research posts in the US and Germany.¹²⁰ Before and during the Second World War he was the First Assistant in the Department of Psychiatry at Middlesex Hospital, and during the war he served as a Psychiatrist, in Sector V. EMS Metropolitan Area. From 1946 to 1966 he worked at the West London Hospital where he rose to the position of Physician in

¹¹⁸ Pearson, “Inheritance,” 376.

¹¹⁹ Pearson, “Inheritance,” 374-78.

¹²⁰ *Who’s Who*, 1984 ed., s. v. “PATERSON, Arthur Spencer.”

Charge, Department of Psychiatry and Director of the Psychiatric Laboratory.¹²¹

Paterson carried out most of his work on anticipation during his Cambridge years in the early 1930s. However, rather curiously, between 1937 and 1953 he co-authored several papers with Otto Maas, one of the strongest supporters of anticipation in the case of myotonic dystrophy.¹²²

Paterson's first paper on anticipation was derived from an address given to the Eugenics Society on 14 June 1932.¹²³ In the paper "'Anticipation' in Mental Disease," he offered an overview of the history of the concept of anticipation, "a 'law' which had been supposed by many writers to govern the heredity of mental disease."¹²⁴ He noted that the "phenomenon had been called *anticipation*, *ante-dating*, *ante-position*, and, in France, *précession*."¹²⁵ Paterson traced the development of the theory from Charles Darwin and B. A. Morel to the British psychiatrist Henry Maudsley, who believed "there was a silent tendency in Nature to restore an insane stock to a sound type, if regeneration was possible, or to end it, if the degeneration was too bad to end."¹²⁶ Paterson saw this view later recapitulated by Mott.¹²⁷ Paterson reported that Edward Nettleship's pedigree studies affirmed this tendency towards degeneration in certain diseases and that

¹²¹ *Who Was Who, 1981-1990*, 1991 ed., s. v. "PATERSON, Arthur Spencer."

¹²² Not all of the papers co-authored with Maas discussed anticipation. Paterson's role in these papers, as seen for example in the 1937 collaboration, was to carry out the psychiatric examinations of the individuals involved in Maas' studies. The 1937 paper examined the question of whether myotonic dystrophy could be said to cause mental changes and intellectual deterioration or whether low intelligence was simply a facet of the low social status of most of the affected individuals. Maas and Paterson found that mental deterioration in myotonic dystrophy was linked to the severity of muscular deterioration. Moreover, their study was not confined merely to members of the lowest levels of society. Some of their patients were drawn from the middle class and had been engaged as "brainworkers" prior to becoming ill. This particular study did not examine the question of anticipation in myotonic dystrophy. Those studies that did address the question of anticipation will be discussed later. Otto Maas and Arthur Paterson, "Mental Changes in Families Affected by Dystrophia Myotonica," *The Lancet* 1 (January 2, 1937): 21-23.

¹²³ Arthur Paterson, "'Anticipation' in Mental Disease," *Eugenics Review* 24 no. 3 (1932): 191. This paper was written in third person and leaves it uncertain as to whether Paterson gave the talk or was merely the person who reported on it. However, the Eugenics Society's *Annual Report 1932-33* confirms that Paterson was indeed the speaker on 14 June 1932. The Eugenics Society, *Annual Report 1932-33*, (London: The Eugenics Society, 1933), 3.

¹²⁴ Paterson was one of the few individuals involved in the study of anticipation in the 1930s who later attempted to trace the historical roots of the concept. The discussion of anticipation in most research papers, if it appeared at all, tended to concentrate on the use of the term within the history of the particular disease being studied. For example, papers on Huntington's disease might trace the concept to Heilbronner (1903) while papers on myotonic dystrophy would likely reference Fleischer's studies. Paterson, "Anticipation," 191.

¹²⁵ Paterson, "Anticipation," 191.

¹²⁶ Paterson, "Anticipation," 191.

¹²⁷ Paterson, "Anticipation," 191.

Nettleship “believed anticipation in these cases to be the rule.”¹²⁸ Paterson also realized that Nettleship had interested Mott in the study of anticipation.¹²⁹

Paterson then turned to analyzing Mott’s work “because Mott was the most distinguished writer who had upheld the so-called law of anticipation” and because “this law has been repeatedly quoted as an argument against the utility of eugenics measures, since it was argued that Nature caused insane stocks to die out, or else, less frequently, allowed a spontaneous recovery.”¹³⁰ Paterson argued that Mott’s observations were based on statistical fallacies rather than any real “Law of Anticipation.”¹³¹ He felt that the population sample under examination was biased due to the selection of parents who had offspring before becoming insane.¹³² Moreover, the length of time of the study was such that it noticed children who became insane at an earlier age than their parents and missed any who became insane at a later age than their parents.¹³³ Like Pearson, Paterson also criticized Mott’s study for not using complete generations (i.e. generations in which all of the individuals had died or reached such an advanced age that the presence or absence of disease could be confidently ascertained), and so he suggested that Mott’s conclusions were drawn from incomplete data.¹³⁴ Paterson believed that “the real truth, however, was that if Mott had waited till the propositus’ generation was extinct, he would have found the amount of insanity the same.”¹³⁵ In his own study of the Colney Hatch Mental Hospital Records which compared Mott’s 1911 study to currently available records, Paterson claimed to show “that if one considered as the youngest generation the second youngest generation in the pedigree—that is, the youngest completed

¹²⁸ Although Paterson lists Nettleship among those who had contributed to work on the concept, and states that he was the first to believe that it was a rule of heredity, Paterson did not seem to know that Nettleship first coined the term “anticipation” to describe this form of degenerate heredity. Paterson, “Anticipation,” 191.

¹²⁹ Paterson, “Anticipation,” 191.

¹³⁰ Paterson, “Anticipation,” 191.

¹³¹ Many of these statistical fallacies were among those identified earlier by Pearson and Heron and were later be picked up by Penrose in his own arguments about anticipation. (See chapter two) Paterson, “Anticipation,” 192.

¹³² That is, Mott was selecting for a later onset of mental illness in the parental generation. Paterson, “Anticipation,” 192.

¹³³ This then is a double source of bias towards anticipation—selecting for parents with a relatively late age of onset and children with an early age of onset—something bound to show anticipation (whether or not it was a real biological phenomenon). Paterson, “Anticipation,” 192.

¹³⁴ Paterson, “Anticipation,” 192.

¹³⁵ Paterson, “Anticipation,” 192.

generation—there was no anticipation with the older generations.”¹³⁶ Other factors that Paterson thought contributed to the “appearance” of anticipation included the fact that the expansion of the number of beds in London asylums between 1890-1910 meant that those in the parental generation were committed only in dire circumstances, often after several bouts of insanity, while those in the children’s generation were committed more readily and at an earlier age.¹³⁷

Paterson felt that “these facts taken from Mott’s own material showed that the apparent anticipation merely resulted from the way in which the material was collected.”¹³⁸ Moreover, “there was no evidence that Nature ended a stock by the gruesome method of causing anticipation to appear at a progressively earlier age in each succeeding generation.”¹³⁹ Additionally, Paterson disagreed with Mott’s assertion that the child of an insane parent should be allowed to marry if they reached the age of 25 without showing signs of insanity. He referred to German research showing that children with an insane parent were “from 3 times to 83 times more likely to suffer from a given type of insanity than the child of healthy parents. The degree of probability depended on the type of psychosis.”¹⁴⁰ In response to Mott’s argument that by the time the first attack of insanity occurred in the parent most of the children would have been born, rendering eugenic measures useless, Paterson argued that the most strongly inherited form of insanity was intermittent, and the parents therefore would be able to have children during their sane periods.¹⁴¹

Paterson concluded by saying that the so-called law of anticipation had never been *proven* statistically true in the case of mental illness although it had been given “great prominence in psychiatric text-books.”¹⁴² He argued that it was important for researchers to better ascertain “the hereditary prognosis in different forms of mental

¹³⁶ Paterson, “Anticipation,” 191-192.

¹³⁷ Paterson, “Anticipation,” 192.

¹³⁸ Paterson, “Anticipation,” 193.

¹³⁹ Paterson, “Anticipation,” 193.

¹⁴⁰ Paterson, “Anticipation,” 193.

¹⁴¹ Paterson, “Anticipation,” 193.

¹⁴² Paterson, “Anticipation,” 193.

disease” in order to better advise their patients.¹⁴³ While Mott had recognized the importance of this issue, he had not investigated the problem before his death.¹⁴⁴

In 1933, Paterson published a longer and more detailed discussion of his argument against anticipation in *The Journal of Neurology and Psychopathology* in order “to examine and criticize a supposed law which has been given great prominence by some writers on the heredity of mental disease.”¹⁴⁵ He traced the lineage of the idea through Darwin’s *Animals and Plants under Domestication*, Morel’s *Traité des dégénérescences de l’espèce humaine*, Henry Maudsley’s works, and then to Nettleship.¹⁴⁶ Noting that Nettleship introduced Mott to the concept of anticipation, Paterson turned to a closer examination of Mott’s conception of the idea “because he was the most eminent English writer to support this theory, and was the first to give statistical backing to Morel’s theory.”¹⁴⁷ After discussing Mott’s first published works on anticipation, he made an extended examination of the material collected at Mott’s instigation for 20 years at Colney Hatch, London county’s largest mental hospital.¹⁴⁸ He reiterated Pearson’s and Heron’s opinions that many of the findings that appeared to show anticipation were due to statistical fallacies, mainly selection and ascertainment bias.¹⁴⁹ Paterson maintained that because the study took place over a short period of time and was looking for parents and children who had been committed to insane asylums, Mott was selecting for a later age-of-onset form of mental illness in the parental generation (because they would have had their children before becoming ill) and at an earlier age-of-onset in the children’s generation (since if they became ill at a later age they would be missed by the study).¹⁵⁰ This selection would then give the appearance of

¹⁴³ Paterson, “Anticipation,” 193.

¹⁴⁴ Paterson, “Anticipation,” 193.

¹⁴⁵ Arthur Paterson, “The So-called Law of Anticipation in Mental Disease,” *The Journal of Neurology and Psychopathology* 13 no. 51 (January 1933): 193.

¹⁴⁶ Paterson discussed Nettleship’s contribution to the development of the concept of anticipation mainly in association with the 1913 paper that he co-authored with Lidbetter in *Brain*. Paterson, “So-called law,” 193-4.

¹⁴⁷ Paterson, “So-called law,” 195.

¹⁴⁸ He mentioned articles by Mott in *Brain* and the *British Medical Journal*, but did not specify which ones. Paterson, “So-called law,” 195.

¹⁴⁹ For a fuller discussion of Pearson’s (1912) and Heron’s (1914) arguments against anticipation see chapter two. Paterson, “So-called law,” 195.

¹⁵⁰ The selection of late age of onset parents was exacerbated because Mott calculated the age of onset of disease from the date of first admission to the mental hospital. However, when these individuals were young only the most dire cases were actually hospitalized and Paterson found records stating that many of

anticipation of a disease's age of onset over succeeding generations.¹⁵¹ Paterson also criticised Mott for looking at cases where the inheritance of insanity was not direct but rather appeared in aunts or uncles and their nephews or nieces, and even in some cases in unrelated individuals who had merely married in to the family.¹⁵²

Paterson was particularly critical of Mott's assertion that anticipation "was one of nature's methods for ending or mending a degenerate stock."¹⁵³ He denied that there was evidence of anticipation of a disease's age of onset over succeeding generations and stated that there was no evidence of a link between sterility and insanity. He argued rather than showing degeneration through succeeding generations until sterility ensued, that "the literature contains numerous pedigrees which show that tainted stocks can be exceedingly prolific."¹⁵⁴ Paterson again countered Mott's assertion that if a child from an affected family reached the age of twenty-five without showing signs of insanity that they might safely marry. Citing recent research which classified insanity into various types, he argued that some forms of insanity—such as schizophrenia and manic-depressive disorder—seemed more liable to be inherited than others.¹⁵⁵ Having rejected Mott's evidence, Paterson turned to the question of "social surgery of the insane" and focused on the fact that counsellors following Mott's teaching would not discourage "a patient suffering from, say, attacks of recurrent mania from becoming a parent."¹⁵⁶ This, then, was the crux of Paterson's argument: he wanted those using Mott's law as the basis for a policy of not sterilizing the insane to realize that such a policy was incorrect because it was based on false assumptions.¹⁵⁷

the parents had suffered from previous bouts of insanity but had not been admitted at the time. Paterson, "Socalled law," 195-197, 203-206.

¹⁵¹ Paterson, "Socalled law," 197-200.

¹⁵² Paterson, "Socalled law," 201-202.

¹⁵³ Paterson, "Socalled law," 208.

¹⁵⁴ Paterson, "Socalled law," 208.

¹⁵⁵ Paterson also classed epilepsy among those sorts of mental disease that were more likely to appear in the children of affected parents. According to the research he cited, the children of affected parents were 12.3 times more likely to suffer from schizophrenia, 82.6 times more likely to suffer from manic-depressive psychosis, and 3.1 times more likely to suffer from epilepsy. Paterson, "Socalled law," 208-209.

¹⁵⁶ Paterson, "Socalled law," 209.

¹⁵⁷ Paterson, "Socalled law," 210.

Lionel S. Penrose: An anti-Eugenic, Medical, and Mathematical-Mendelian Approach

Lionel Penrose was a human geneticist who was singularly influential in shaping scientific opinion about anticipation from the late 1930s through the early 1970s. A Quaker by upbringing and choice, Penrose was a pacifist of left-wing political persuasion who spent his career arguing against those who would confuse socio-economic influences with genetic causes of mental disorders. He advocated the humane treatment of the insane and mentally defective and opposed those who proposed sterilization as a solution to the problem posed by these individuals.¹⁵⁸ At Cambridge he studied first for the moral science tripos (mathematics, philosophy, and psychology) before developing an interest in psychiatry and psychoanalysis. He then travelled to Vienna to study Freudian analysis before finally taking up medicine and graduating in 1930.¹⁵⁹ In 1930 Penrose began his research project into the causes of mental deficiency at Colchester.¹⁶⁰ This study “provided a framework for progress in understanding mental deficiency, which remained a dominant interest for the rest of his life.”¹⁶¹ Penrose’s influential book, *The Biology of Mental Defect*, based in part on the Colchester study, was published in 1949 and went through four editions before his death in 1972.¹⁶² While Penrose was in Canada from 1939 to 1945, he published papers that were critical of some of the new “scientific” treatments of insanity, including electroshock and drug treatments.¹⁶³ In 1945 he was

¹⁵⁸ Penrose spent the First World War with a Friends (Quaker) Ambulance Unit. Between 1935 and 1939 he worked with a number of movements advocating the better treatments of criminals and the mentally ill as well as being active in the peace movement. The Penrose family left Britain in 1939 on the advice of J. B. S. Haldane. Absent without leave from his position at Colchester during this period, Penrose accepted a position with the Ontario (Psychiatric) Hospital in London, Ontario and held additional appointments as director of psychiatric research for the Ontario Ministry of Health and as part-time faculty in the Medical School at the University of Western Ontario. The family returned to Britain, again at the invitation of Haldane, in 1945. MSS, offprints, pamphlets and reports collected under the heading “The Study of mental disease and crime,” 1935-1939, Penrose Papers, 40/1-3; Papers and correspondence regarding Penrose’s appointment to the Galton Chair, 1943-1945, Penrose Papers, 49/1; Kevles, *Eugenics*, 152-155; Renata Laxova, “Lionel Sharples Penrose, 1898-1972: A Personal Memoir in Celebration of the Centenary of His Birth,” *Genetics* 150 (December 1998): 1334; Soltan, “Penrose,” 37-38; Watt, “Part 1,” 137, 145.

¹⁵⁹ Kevles, *Eugenics*, 152-154; Laxova, “Penrose,” 1334; Watt, “Part 1,” 137.

¹⁶⁰ Watt, “Part 1,” 137.

¹⁶¹ Watt, “Part 1,” 138.

¹⁶² Watt, “Part 1,” 138.

¹⁶³ Penrose argued that the use of one drug, metrazol, should be discontinued and that electroshock treatment had no value for cases of schizophrenia and only limited value in cases of depression, making those who were likely to get better anyway recover somewhat faster. By five years out of treatment, however, he found no difference in outcome between patients who had and who had not received electroshock. Moreover, he said that discharge rates were no true measure of the successful treatment of mental illness as they did not take into account cases where the patients were later readmitted. The

appointed to the prestigious Galton Chair of Eugenics at University College, London. He held this chair until 1965 and acted as a consultant on human genetics at University College Hospital.¹⁶⁴ From this position Penrose played an important role in advocating the application of Mendelian principles to human genetics.

Penrose was an anti-eugenicist who began his working life within an environment dominated by eugenics. His early work at Colchester was funded by the Medical Research Council and by the Darwin Trust, which was interested in funding research with a social Darwinist bent.¹⁶⁵ Although Penrose himself never joined the Eugenics Society, his wife, Margaret, did, and his opinion and advice was often sought by the group even though his ideas were often at odds with those of the eugenicists.¹⁶⁶ Unlike many of those who studied human heredity in the first half of the twentieth century, Penrose thoroughly integrated the new ideas of mathematical Mendelian genetics into his scientific world-view. Many members of the Eugenics Society continued to labour under the older paradigm which included ideas of the heritability of acquired characteristics.¹⁶⁷ In his own work Penrose used Mendelian ideas of inheritance and statistical analysis to formulate his findings.¹⁶⁸ Since the incidence of criminality in sample families, such as the notorious Jukes, was far above that predicted by Mendelian analysis of inheritance, Penrose ridiculed those who believed that anti-social behaviour was genetic.¹⁶⁹ The methodological inadequacies and biases of most work carried out in human genetics in the 1930s gravely concerned him.¹⁷⁰ His work at Colchester had taught him just how

superintendents of the mental hospitals in Ontario seem to have been unwilling to take Penrose's advice on these issues. Biographical Material, 1 February 1944, Penrose Papers, 49/1; Harvey Simmons, *Unbalanced: Mental Health Policy in Ontario, 1939-1989*, (Toronto: Wall & Thompson, 1990), 19-23. He was also elected a fellow of the American Association of Mental Deficiency "in recognition of meritorious contributions to the field of Mental Deficiency." Certificate electing Penrose a fellow of the American Association of Mental Deficiency, 12 May 1944, Penrose Papers, 17/5.

¹⁶⁴ Kevles, *Eugenics*, 155; Watt, "Part 1," 137.

¹⁶⁵ Kevles, *Eugenics*, 150-151.

¹⁶⁶ At least two of Penrose's children (Sir Roger Penrose FRS and Dr Shirley Hodgson FRCP) were originally unaware of their mother's membership in the Eugenics Society but, when informed of it, suggested that she had likely joined to keep Penrose informed of the society's policies. Watt, "Part 1," 138.

¹⁶⁷ Watt, "Part 1," 145.

¹⁶⁸ Watt, "Part 1," 145.

¹⁶⁹ Kevles, *Eugenics*, 155.

¹⁷⁰ Penrose published papers discussing the complicated genetic nature of mental deficiency and on the "multi-factorial nature of the genetic determinants of intelligence" long before the Colchester Survey appeared in print. See for example: Lionel Penrose, "Mental Deficiency—II: The Sub-Cultural Group," *Eugenics Review* 24 no. 4 (January 1933): 289-291; Lionel Penrose, "The Complex Determinants of Amentia," *Eugenics Review* 26 no. 2 (July 1934): 121-126; Kevles, *Eugenics*, 158, 193.

complex the study of mental defect was and underlined the fact that a simple means of correcting such varied illnesses (such as sterilization) was unlikely.¹⁷¹ Penrose criticised proponents of positive eugenics, arguing that scientists did not know how to identify ‘good’ genes and that selective breeding, if promoted broadly, would lead to homozygosity and a consequent loss of variability and resilience.¹⁷² He was also critical of those who advocated negative eugenics approaches to the treatment of the poor and feeble-minded.¹⁷³ He found that many diseases suffered by these individuals were caused by genetically recessive disorders; and since there was no way to detect these genes beforehand, sterilization was obviously not an effective solution.¹⁷⁴ He also ridiculed those who believed that the national population was degenerating because of the unrestricted breeding of “undesirables” since, if this was possible, “by now there would be nothing but defectives left in the population.”¹⁷⁵ Penrose was one of a growing number of geneticists who advocated the adoption of Mendelian genetics and the use of more scientific and statistical research techniques. Under his editorship the subtitle of the *Annals of Eugenics*, previously ‘a journal devoted to the genetic study of human

¹⁷¹ Watt, “Part 2,” 343.

¹⁷² Many of these arguments appeared in Penrose’s first textbook, *Mental Defect*, which was first published in Britain in 1933 and in which he stated that “mental defect is fundamentally a social, and not simply a biological or psychological, problem” He argued that social and economic factors were “liable to obscure all others and public opinion varies in its attitude towards mental defect precisely in accordance with its attitude towards other social and economic problems.” Penrose called upon those who were examining the issue to “throw aside all social and moral prejudices” and to “take into full consideration the effects of the present economic conditions and the complex nature of modern civilization.” An American edition appeared the following year. Many of the reviewers of *Mental Defect* liked Penrose’s assertion that sterilization would not solve the problem of mental defect and found his work a valuable contribution to the ongoing discussion of the proposed British sterilization legislation. C. P. Blacker’s response to Penrose’s *Mental Defect* is dealt with above. Penrose, *Mental Defect*, (1933), 13; Lionel Penrose, *Mental Defect*, (New York: Farrar & Rinehart, 1934); Reviews of *Mental Defect*, 1933-1934, Penrose Papers, 57/3; Watt, “Part 2,” 139-340.

¹⁷³ Watt, “Part 2,” 342.

¹⁷⁴ Penrose seemed to have been more open to possible environmental as well as genetic factors in his earlier work. See for example, Penrose, *Mental Defect*, (1933), 53-65. In his Buckson Browne Prize essay Penrose would be particularly scathing: “There would be few, if any, individuals in the community who were not susceptible in some degree to the influences of such diseases, and, clearly, to eliminate, by sterilization, all genes responsible for the susceptibilities to the important diseases affecting man would be to annihilate the race.” Lionel Penrose, *The Influence of Heredity on Disease: Buckston Browne Prize Essay, 1933*, (London: H. K. Lewis & Co. Ltd., 1934), 73. Watt, “Part 2,” 344.

¹⁷⁵ As quoted in Kevles, *Eugenics*, 156. After the Second World War, Penrose postulated that the large families born to the so-called “morons” that made up for the smaller families of the “normals” and helped to maintain the size and composition of the population in a state of stable equilibrium (rather than leading to the downfall of civilization as had been argued by some eugenicists during the interwar period). Lionel Penrose, *Outline of Human Genetics*, (London: Heinemann, 1959), 115-118.

populations’, was changed to ‘a journal of human genetics’ and the title itself was eventually changed to *Annals of Human Genetics* in 1954.¹⁷⁶ In 1963, and after much effort, Penrose finally succeeded in having the very name of the Galton Chair itself changed from the Chair of Eugenics to the Chair of Human Genetics.¹⁷⁷

Penrose’s 1933 Buckston Browne Prize winning essay “The Influence of Heredity on Disease” contains what appears to be his first published discussion of anticipation.¹⁷⁸ In this essay, Penrose set out “to examine carefully the methods available for the study of human heredity” with special reference “to the application of these methods in medical study.”¹⁷⁹ The discussion of anticipation took place in his section on “Non-Mendelian Genetics” where Penrose dismissed such ideas as hereditary syphilis, cytoplasmic inheritance, the poisoning of the germ-plasm by environmental and other toxic substances, and the inheritance of acquired characteristics (as posited by various forms of Lamarckism).¹⁸⁰ Penrose called the “law of anticipation” as “propounded by Mott” a “popular concept” which he could not accept.¹⁸¹ He stated: “The belief in the operation of this natural law has been held rather widely, but it is almost certainly erroneous.”¹⁸² The anti-eugenicist Penrose thus agreed with the eugenicist Paterson that selection bias—i.e. the selection of patients who remained healthy long enough to have children in the parental generation—“is sufficient to account for the phenomenon of antedating.”¹⁸³ Penrose, then, considered anticipation to be one among many incorrect ideas concerning human heredity that required correction.

Between 1936 and 1938, in a series of lectures to physicians and medical students Penrose set out to correct those mistaken beliefs. His lecture delivered at the Maudsley hospital in 1936 argued that the importance of heredity in human disease had been long

¹⁷⁶ Penrose’s career at the Galton Laboratory will be dealt with more fully in chapter four. Watt, “Part 1,” 145.

¹⁷⁷ Watt, “Part 1,” 145.

¹⁷⁸ *Influence of Heredity on Disease* seems to have been fairly well received but many reviewers were concerned that the book would not serve as an aid to the average physician who wanted more information on genetics or hereditary disease. Some reviewers disagreed with Penrose’s anti-eugenic arguments e.g. questioning against the efficacy sterilization as a eugenic measure. Reviews of *The Influence of Heredity on Disease*, 1933-1935, Penrose Papers, 58.

¹⁷⁹ Penrose, *Influence*, 3.

¹⁸⁰ Penrose, *Influence*, 15-18.

¹⁸¹ Penrose, *Influence*, 17.

¹⁸² Penrose, *Influence*, 17.

¹⁸³ Penrose, *Influence*, 17.

been stressed by physicians, who understood the importance of the family history in diagnosis and treatment. Moreover, physicians had constructed the notion of the hereditary diathesis examined its role in familial illness long before biologists became interested in the subject. He argued, however, that medicine had not kept up with the recent advances in biology, and to bring it up to date, he discussed four “erroneous notions which are widespread.”¹⁸⁴ One of these was Mott’s “Law of Anticipation,” which, Penrose argued, “appears to be a statistical artefact.”¹⁸⁵ In his notes for the lecture Penrose devotes one page to Mott. He specifically referenced Mott’s 1910 Huxley Lecture, and, notably, Mott’s notion that insanity did not usually proceed beyond three generations, and that “rotten twigs are continually breaking off the tree of life.”¹⁸⁶ In a course of lectures on human genetics that Penrose gave in 1936 at an unknown location he stressed the “essentially arithmetical nature of mendelism [*sic*].”¹⁸⁷ During a lecture at Birmingham on “The inheritance of mental characters” in 1937 he similarly argued that Mendelian genetics could and should be applied to the study of human diseases but that only a few types of mental diseases, such as the insanity in Huntington’s disease and amaurotic family idiocy (Tay-Sachs), could be said to be caused by the inheritance of a single gene, either dominant or recessive.¹⁸⁸ Similar arguments surfaced in his 1938 address to the British Association for the Advancement of Science meeting in Cambridge and in later lectures.¹⁸⁹

¹⁸⁴ These notions were: 1. that hereditary influence could be judged to be either “positive” or “negative”; 2. that the theory of germ-plasm degeneration was false (any injury to the germ-plasm would be short-lived at best) and that Mott’s Law of Anticipation “appears to be a statistical artefact”; 3. that the term “linked characters” connecting diseases like tuberculosis and dementia praecox was “a complete misnomer”; and 4. that if heredity was being examined that environment had no effect. Penrose, “Heredity and Medicine” Lecture at Maudsley in Postgraduate Course, 1936, Penrose Papers, 53/2.

¹⁸⁵ Penrose, “Heredity and Medicine” Lecture at Maudsley in Postgraduate Course, 1936, Penrose Papers, 53/2.

¹⁸⁶ As quoted by Penrose in: Penrose, “Heredity and Medicine” Lecture at Maudsley in Postgraduate Course, 1936, Penrose Papers, 53/2. Mott’s 1910 Huxley Lecture actually preceded his use of the term anticipation but it did contain some of his most memorable prose as the quotations selected by Penrose prove.

¹⁸⁷ Penrose, “Syllabus of proposed course of lectures on Human Genetics”, 1936, Penrose Papers, 53/3.

¹⁸⁸ Penrose, “The inheritance of mental characters”, c. 1937, Penrose Papers, 53/4.

¹⁸⁹ Penrose, “Heredity and mental hygiene”, 1938, Penrose Papers, 53/6. These lectures in fact continued after Penrose published his 1948 paper that argued that anticipation was the result of experimental error and statistical miscalculations rather than any sort of real mode of heredity. This will be discussed further in chapter four. Penrose, “Methods of research in genetics useful in psychiatry”, 9 October 1956, Penrose Papers, 53/19.

The question of why certain diseases, such as Huntington's, had such great variability in symptoms and in age of onset perplexed Penrose. In 1936, he published a paper in which he attempted to apply mathematical Mendelian methods to address this conundrum.¹⁹⁰ He posited that for certain disease genes (**M**) there existed allelomorphs that might be either neutral (**A'**) or have a modifying effect (**A**).¹⁹¹ He then postulated what effects these allelomorphs might have according to the distribution of these different kinds of modifiers within a population.¹⁹² The calculations required in the case where the modification was caused by an independent gene were more complex.¹⁹³ Penrose then applied this calculus to the variety of hereditary effects seen in epiloia and in mental defect, and he argued that one could explain the degrees of disease and defect seen in these populations with the existence of a modifiers.¹⁹⁴ He continued to refine this type of analysis using posited allelomorphs over the next decade.

Richard Goldschmidt: A Genetical Approach to Anticipation

Richard Goldschmidt was a German-born Jewish geneticist who emigrated to the United States after being dismissed from his position at the Kaiser Wilhelm Institute of Biology due to Nazi policies and who then took up a position at the University of California, Berkeley. He was the only professional experimental geneticist to publish on the question of anticipation during the first half of the twentieth century.¹⁹⁵ One of the

¹⁹⁰ In this paper Penrose did not discuss the question of anticipation, nor, with the exception of Huntington's disease, any disease associated with it. This is, however, where Penrose began working out how the presence of modifying factor(s) might affect the expression of a disease gene and how the distribution of those factors in a population might affect the variety of phenotypic expressions of particular diseases or conditions, including mental defect (which was still considered by some to be the result of a simple Mendelian recessive). Lionel Penrose, "Autosomal Mutation and Modification in Man with Special Reference to Mental Defect," *Annals of Eugenics* 7 (1936): 1-16.

¹⁹¹ That is that the possible genotypes for these circumstances would be: normal – **AA**, **AA'**, **A'A'**, modified disease (possibly appearing normal) – **AM**, normal disease – **A'M**, and a probably lethal form – **MM**. Penrose, "Autosomal," 2.

¹⁹² Penrose, "Autosomal," 3-4.

¹⁹³ Penrose, "Autosomal," 4-6.

¹⁹⁴ Penrose, "Autosomal," 6-15.

¹⁹⁵ Goldschmidt was the director of the Genetics Department at the Kaiser Wilhelm Institute for Biology in Berlin from 1913 to 1935. Caught travelling in the U.S. at the outbreak of the First World War, Goldschmidt spent the war first at the University of California and then at Yale where he was joined by his family in 1915. In 1917, after the U.S. entered the war he was placed in an internment camp until repatriation after the war. Goldschmidt's autobiography contains a riveting account of his escape from Germany in 1935. He credited the Rockefeller Foundations' actions on his behalf with helping to secure the position at the University of California, Berkeley. His status among geneticists was and is rather

criticisms of anticipation was that it had not been seen in any biological system other than man. Surely, the Editor of *Eugenics Review* argued in 1930, if anticipation was a real biological phenomenon there should be examples in plants or animals.¹⁹⁶ Goldschmidt was the first geneticist who claimed to have seen similar patterns of heredity in non-human experimental subjects—his fruit flies—and he sought to use his findings to explain the appearance of anticipation within human diseases.¹⁹⁷

Previous studies of myotonic dystrophy had generally agreed that the disease was caused by a single dominant gene whose penetrance and expressivity increased over the course of several generations.¹⁹⁸ Goldschmidt believed that this theory was incorrect. He argued that the genetics of myotonic dystrophy could be explained by mechanisms used to explain certain genetic events in fruit flies.¹⁹⁹ His conclusion was at odds with all previous analyses of myotonic dystrophy: he believed that the gene was recessive, not dominant.²⁰⁰ When the gene appeared in heterozygous form it had little or no effect, he argued. However, when two copies of the defective gene were present the effect was lethal or sub-lethal.²⁰¹ The key to Goldschmidt's theory was that he posited the existence of "dominigenes" whose actions "shift the heterozygote towards an intermediate condition, which is [expressed as] the visible disease."²⁰² Goldschmidt argued that a

controversial due to his sometimes unorthodox theories. For example, his *The Material Basis of Evolution* (1940) advocated the "hopeful monsters" theory of evolution rather than one of slow, incremental change. Richard Goldschmidt, *The Material Basis of Evolution*, (Yale University Press, 1940. Reprinted. New Jersey: Pageant Books, Inc., 1960). See also: Richard Goldschmidt, *In and Out of the Ivory Tower: The Autobiography of Richard B. Goldschmidt*, (Seattle: University of Washington Press, 1960), 290-303; Brigham Narins Ed., *Notable Scientists from 1900 to the Present*. Vol. 2, Farmington Hills, MI: The Gale Group, 2001, 876-877; Michael Dietrich, "Richard Goldschmidt: hopeful monsters and other 'heresies'," *Nature Reviews Genetics* 4 (January 2003): 68-74.

¹⁹⁶ See for example, Editor, "Notes," 237.

¹⁹⁷ Richard Goldschmidt, "'Progressive Heredity' and 'Anticipation': The Possibility of a Genetic Explanation of Certain Odd Hereditary Phenomena Observed in Man," *Journal of Heredity* 29 (1938): 140.

¹⁹⁸ Goldschmidt, "Progressive," 140-141.

¹⁹⁹ Goldschmidt's animal model was the *vg* mutation in *Drosophila*. In the case of this mutation "there exists a series of multiple alleles of this gene, which produce a different amount of destruction of wing area, beginning with a minute nick at the tip of the wing and leading through all intermediate stages up to almost complete destruction (No-wing-allele)." Goldschmidt, "Progressive," 141-142.

²⁰⁰ The notion that myotonic dystrophy was caused by a recessive rather than a dominant gene would be explored by other researchers. See the discussion of research in myotonic dystrophy below. Goldschmidt, "Progressive," 142.

²⁰¹ Goldschmidt, "Progressive," 142.

²⁰² The term "dominigenes" was Goldschmidt's invention and it would perplex later researchers, including Penrose (1948), who called the notion "obscure." Goldschmidt coined the term in 1935 when he argued that modifying genes should be given the name. Despite his efforts and reputation, this terminology did not catch on in the literature. It is uncertain exactly what Goldschmidt meant by the term in the context of his

number of these dominigenes exists within a population and that they can act in cumulative fashion causing the wide variety of symptoms seen epidemiologically.²⁰³ Anticipation in human diseases, then, would be caused by an accumulation of dominigenes over successive generations. A lessening of the effect—the seldom seen phenomenon of regeneration—could be caused by decreasing the number of dominigenes.²⁰⁴ However, this theory was not well received: as Goldschmidt himself had noted earlier in his paper, “Geneticists, as a rule, are rather skeptical towards such reports [of progressive heredity], which seem to contradict the elementary notions of Mendelian heredity” and it appears that the genetics community was not willing to accept Goldschmidt’s hypothesised dominigenes.²⁰⁵ Despite his contributions, therefore, before 1948 no generally accepted theory explained the phenomenon of anticipation sufficiently to convince members of the genetics, human genetics, and medical genetics communities of the concept’s validity.

Goldschmidt’s 1938 paper was also the first to mention the rift then beginning to open, on the one hand, between geneticists and human geneticists trained in ideas of Mendelian heredity and, on the other hand, physicians and others who still subscribed to

1938 discussion of anticipation. He may have been suggesting that a variety of allelic forms existed that caused the phenotypic variability in the disease or he could have been referring to the presence of a series of unrelated genes which had some modifying action on the defective gene. The latter explanation seems somewhat more likely given Goldschmidt’s assertion that “a series of dominigenes exist with additive effect.” Although Penrose had already discussed the possible action of allelic modification or modification by unrelated genes in his 1936 article, he seemed to be unaware of this discussion, and cited only the German literature on myotonic dystrophy and his own work on genetics in the references. His rather strange approach to anticipation is somewhat more understandable when placed within the context of his broader work on physiological genetics rather than in the context of studies of myotonic dystrophy, eugenics, or even human genetics. However, he was clearly aware of earlier human studies on anticipation and progressive heredity. Goldschmidt was interested in situations where the actions of a gene were modified by the presence or absence of other genes. While his own work research focused on a recessive gene in *Drosophila* that produced vestigial wings, he noted in *Physiological Genetics* (1938) that a similar effect was seen in the case of dominant genes (conditioned dominance). Goldschmidt would later drop his unique terminology referring simply to “genetic modifiers” (1952) and “the so-called vestigial dominigenes of Goldschmidt” which actually “act as enhancers of suppressors of other mutant actions” (1955). Goldschmidt, “Progressive,” 142; Richard Goldschmidt, *Physiological Genetics* (New York: McGraw-Hill Book Company, 1938), 107-112; Richard Goldschmidt, *Understanding Heredity: An Introduction to Genetics*, (New York: John Wiley & Sons, Inc., 1952), 172-178; Richard Goldschmidt, *Theoretical Genetics* (Berkeley: University of California Press, 1955. Reprint 1958), 132-133; Penrose, “Autosomal,” 1-16; Lionel Penrose, “The Problem of Anticipation in Pedigrees of Dystrophia Myotonica,” *Annals of Eugenics* 14 (1948): 130.

²⁰³ Goldschmidt, “Progressive,” 142.

²⁰⁴ Goldschmidt. “Progressive,” 142.

²⁰⁵ Goldschmidt, “Progressive,” 140.

older ideas such as progressive heredity and anticipation.²⁰⁶ Goldschmidt argued that the distrust of these latter ideas was such that:

It is therefore silently or openly assumed by non-medical geneticists that the numerous cases of progressive heredity and anticipation found in medical literature are the products of statistically inadequate data, of erroneous diagnosis, of the presence of a combination of different diseases or of similar errors of recording.²⁰⁷

The divide between theoretically inclined scientists and researchers involved mainly in the clinical assessment and treatment of people with hereditary diseases is apparent when one contrasts the (mostly negative) theoretical views towards the concept of anticipation discussed above and the (mainly positive but not wholly so) views that will be examined in the following section devoted to studies of particular diseases.

APPLIED STUDIES OF ANTICIPATION

While between 1930 and 1945 a few researchers sought ways to explain, or explain away, findings of anticipation, many physicians continued to use the notion of anticipation to understand the patterns of heredity at work in specific disorders—Huntington’s disease, myotonic dystrophy, diabetes, and ophthalmologic disorders, to name the most important. Most of the physicians whose work will be discussed below were medical specialists (neurologists, ophthalmologists etc.) whose work concerned a specific hereditary disease. A few of them attempted to offer explanations, Mendelian and otherwise, for their findings of anticipation, but most were content to report what they took to be its presence or absence in disorders with which anticipation had traditionally been associated.

(A) Three Key Researchers: Madge Macklin, Julia Bell, and Fritz Lenz

This section begins with a discussion of the work of three individuals who discussed the concept anticipation in a broader context—one believed that it existed and two did not. Dr. Madge Macklin, one of the founders of medical genetics and a strong advocate of introducing the teaching of genetics to medical students, employed

²⁰⁶ Many of Penrose’s lectures (discussed above) were an attempt to correct these ‘old-fashioned’ beliefs that he argued were held by physicians.

²⁰⁷ Goldschmidt, “Progressive,” 140.

anticipation to explain the pattern of inheritance in a variety of disorders, most notably diabetes and Huntington's disease. Dr. Julia Bell, who worked at the Galton Laboratory from 1908 to 1965 (with a break between 1914 and 1920 when she pursued her medical education), examined reports of anticipation as part of her meta-analyses of a variety of diseases in *The Treasury of Human Inheritance*.²⁰⁸ Her view of anticipation became increasingly negative during these years. The German eugenicist Fritz Lenz was also critical of the theory of anticipation. In 1931, his views spread to the English-speaking world with the simultaneous publication of *Human Heredity* in London and New York.²⁰⁹

Because of the complexities involved, the application of the concept of anticipation to mental illness and mental defect requires some preliminary discussion. Chapter two discussed how, from the 1910s onwards, anticipation was used to explain patterns of inheritance in a variety of mental disorders from the specific (most notably schizophrenia) to the diffuse (mental defect). This trend continued between 1930 and 1945. As shown in the earlier discussion, in this period the study of the so-called mentally defective was inextricably tied up with the question of the campaign for legalizing sterilization. The final section of this chapter considers how the opinion of A. F. Tredgold (pro-eugenics but opposed to sterilization legislation) on the concept of anticipation changed in response to developments in the fields of medicine, psychiatry, and genetics. While Tredgold's views on anticipation changed with time, however, the views of Ernest Lidbetter, who had been introduced to the concept of anticipation by Nettleship himself in the 1910s, did not. Lidbetter continued to use anticipation as part of his analysis of so-called "problem families" in his attempt to prove that physical and economic unfitness were linked and would respond to a eugenic solution—namely sterilization. Thus, some eugenicists used anticipation to argue *for* the creation of

²⁰⁸ Sarah Budney, "Julia Bell, MRCS LRCP FRCP (1879-1979). Steamboat lady, statistician and geneticist," *Journal of Medical Biography* 4 (1996): 12.

²⁰⁹ *Human Heredity* was co-authored by Erwin Baur, Eugen Fischer, and Fritz Lenz but Lenz was responsible for the entire discussion of anticipation which was included in his discussion of "morbid hereditary factors." Baur, Fischer, and Lenz, *Human Heredity*. Baur was a well-esteemed plant geneticist, so it is a bit of a surprise that he would enter into such a long term collaboration with Fischer and Lenz who would become among the most notorious Nazi race scientists. The geneticist Bentley Glass suggests that a mixture of bitterness and nationalism drove this otherwise ethical individual into such company. Bentley Glass, "A Hidden Chapter of German Eugenics between the Two World Wars," *Proceedings of the American Philosophical Society* 125 no. 5 (October 1981): 357-367.

legislation to sterilize the unfit while others used the concept to argue *against* the same legislation.

Madge Macklin: Founder of Medical Genetics

The importance of Dr. Madge Macklin's contributions to the study of medical genetics and to its widespread adoption within medical education programmes has already been discussed. Let us turn now to her observations concerning anticipation.²¹⁰ In her 1932 paper "The Relation of the Mode of Inheritance to the Severity of an Inherited Disease," Macklin discussed anticipation in a general context.²¹¹ She noted that the origin of the concept of anticipation was obscure but that she "first found it referred to in the writings of that great student of human inheritance in eye defects, Edward Nettleship" who "designated it as the law of anticipation, meaning that a disease which was inherited in the direct line of descent tended to appear at an earlier age in the children than it did in the parents."²¹² In her own studies of hereditary diseases, Macklin had noted anticipation in diseases with severe effects including muscular atrophy, muscular dystrophy, and polycystic kidney disease.²¹³ She noted that the presence of anticipation in these disorders might cause some observers to draw incorrect conclusions:

It would be assumed then that one need not worry about these diseases, that they tended to wipe themselves out by occurring at progressively earlier ages. This unfortunately is not true. If it were, we would have dispensed with these inherited defects long ere this, but we find them constantly increasing, partly because surgical skill has tended to correct those which can be modified, and modern philosophy protects and cares for those who cannot be rehabilitated. How to reconcile the law of anticipation and the increasing amount of inherited disease?²¹⁴

This problem, she answered, was due to the fact that while the *average* age of onset might be lower from one generation to the next, some among the children's generation

²¹⁰ Macklin's use of anticipation to explain heredity in specific disorders, like diabetes, will be discussed below.

²¹¹ M. T. Macklin, "The Relation of the Mode of Inheritance to the Severity of an Inherited Disease," *Human Biology* 4 (1932): 69-79

²¹² Macklin, "Relation," 77.

²¹³ Macklin, "Relation," 77.

²¹⁴ Macklin, "Relation," 78.

would be affected at a later age than their parents and serve to begin the cycle all over again.²¹⁵ Macklin also disagreed with the notion that anticipation might be a means by which Nature could “end or mend” an affected stock. She argued rather that a disease displaying anticipation “does not thereby tend to eradicate itself, there usually being several members of a generation in whom the disease starts sufficiently near the age at which the parent was affected or even beyond that, to ensure his being the starting point of a new cycle.”²¹⁶ Macklin, then, believed in the existence of anticipation but considered it a complicating factor in hereditary illness, rather than a mechanism by which the disease might be eradicated.

Julia Bell: Mathematician, Biometrician, Physician, and Human Geneticist

Julia Bell’s career is noteworthy not merely because of its enviable length and her considerable accomplishments but because of the breadth and depth of her training. The tenth of fourteen children, she passed the entrance examination to Cambridge in 1898 and began studies in Girton College.²¹⁷ Because of an 1897 Cambridge University vote against the granting of degrees to women, Bell and her contemporaries were unable to receive degrees. However, between 1904 and 1907 Trinity College, Dublin agreed to grant degrees to women from Cambridge and Oxford who had passed their examinations and could pay the fee for their BA (£10.3s.0d.) and/or MA (£9.16s.0d.). In 1907, with the encouragement of her father, Bell joined the ladies travelling by steamboat across the Irish sea and received her BA and MA.²¹⁸ Bell’s early training in mathematics brought her to the attention of Karl Pearson, who had a habit of hiring Girton graduates, and she worked for him as a statistical assistant from 1908. Bell was seconded as an assistant, and later primary, author for the Galton Laboratory’s masterwork—*The Treasury of Human Inheritance*.²¹⁹ Her work on *The Treasury of Human Inheritance* covered half a

²¹⁵ Macklin, “Relation,” 78.

²¹⁶ Macklin, “Relation,” 79.

²¹⁷ At that time Cambridge’s colleges were segregated. Girton was the first woman’s college (founded in 1869), and the code of conduct for female students in the university was a strict one. Sarah Budney, “Julia Bell MRCS LRCP FRCP (1879-1979). Steamboat lady, statistician and geneticist.” *Journal of Medical Biography* 4 (1996): 8-9.

²¹⁸ Budney, “Julia Bell,” 9.

²¹⁹ Budney calls the *Treasury* “an unparalleled collection of pedigrees of human diseases.” The geneticist Peter Harper holds that the *Treasury* “represents the most extensive, and one of the earliest series of documentations and analyses of human genetic disorders” and that it “remains a valuable scientific as well

century between 1909 and 1958—she worked as a contributor to the first volume and was the major author of volumes two, four, and five. Although she left the Galton Laboratory in 1914 to train as a physician (qualifying in 1920 at the age of 41) she continued to work on *The Treasury of Human Inheritance* and returned as a Galton research fellow in 1926.²²⁰ Much of Bell's work was essentially statistical in nature and involved correlating and analysing newly collected and previously published pedigrees for *The Treasury of Human Inheritance*.²²¹ It was by doing analyses of this type that she found evidence of a genetic linkage between haemophilia and red-green colour blindness in males, a rare discovery during a period when many were looking for linkage and not finding it.²²² Her time at the Galton Laboratory reflects the changes during this period. She trained under Pearson and mastered his biometrical methodology, shifted to the adoption of mathematical Mendelism that Fisher then came to advocate, and, after her retirement in 1944, worked as an honorary research associate under the human geneticist Lionel Penrose.

As part of her statistical analyses, Bell often calculated whether there were differences in the ages of onset of disease in parents and offspring. A substantial decrease in the age of onset between one generation and the next was considered one of the hallmark signs of anticipation. Bell, however, was generally doubtful about anticipation, and her comments about it became increasingly critical over time.²²³ As a

as an historical record of the genetics of a range of important inherited disorders.” The five volume *Treasury* published in installments between 1909 and 1958 remained unparalleled as a collection of genetic information until Victor McKusick began publishing his collection *Mendelian Inheritance in Man* in 1966. Budney, “Julia Bell,” 10-11; Peter Harper, “Julia Bell and the *Treasury of Human Inheritance*,” 116 (2005): 422-432; Victor McKusick, *Mendelian Inheritance in Man: Catalogues of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, (Baltimore MD: The Johns Hopkins Press, 1966).

²²⁰ Budney, “Julia Bell,” 9.

²²¹ For an extended discussion of the *Treasury* and its importance as a genetic and historical record see: Harper, “Julia Bell,” 422-432.

²²² In 1943 Bell and Dr J. Purdon Martin published a paper on X-linked mental retardation (later known as Martin-Bell syndrome) that would be shown in 1981 to have the classic fragile chromosomal site of a form of genetic mental retardation known as Fragile-X. The importance of Fragile-X disease to the history of anticipation will become apparent in chapter five and six but it is interesting to note here that of the early workers Bell alone examined multiple disorders that would later be proven to have the expanding trinucleotide repeats that cause anticipation. Budney, “Julia Bell,” 11-12; J. Purdon Martin and Julia Bell, “A Pedigree of Mental Defect Showing Sex-Linkage,” *Journal of Neurology and Psychiatry* 6 (1943): 154-157.

²²³ Bell's discussions of anticipation took place within her analyses of heredity in a variety of disorders. Those disorders will be discussed individually below. Only Bell's outlook on anticipation is discussed here.

statistician working under Pearson, she was well aware of arguments against anticipation and of the sorts of statistical and methodological errors that might lead to mistaken findings of anticipation. Her comments reflect this awareness. By 1943, she was clearly attributing the “appearance” of anticipation to the usual culprits of incomplete collection and analysis of data.²²⁴ Not a theoretician herself, Bell offered little in the way of a genetic explanation for these findings beyond discussing basic dominant or recessive inheritance but she did discuss problems of selection and ascertainment bias which could skew statistical analyses. Her published work and her discussions with more theoretically minded colleagues at the Galton Laboratory and University College London did, however, spark attempts to explain variations in age of onset and anticipation. In 1941, J. B. S. Haldane suggested that modifying genes might cause the variation in age of onset seen in Bell’s work in the *Treasury of Human Inheritance*, including Huntington’s disease.²²⁵ Moreover, one of her discussions with Penrose (by then newly appointed Chair at the Galton Laboratory) concerning anticipation and patterns of heredity in myotonic dystrophy led him to write his landmark paper on the subject in 1948.²²⁶

Fritz Lenz: German Physician and Eugenicist

Fritz Lenz, a German eugenicist and geneticist, has been described as “the one person who did more than any other to spell out the importance of eugenics during the Weimar years.”²²⁷ He and the co-authors of *Human Heredity*, the botanist Erwin Baur and the anthropologist Eugen Fisher were all part of what historian Paul Weindling refers to as the “Freiburg phalanx” of German eugenics theory that “fused French degenerationist theories, British Social Darwinism and distinctive German biological and social

²²⁴ Julia Bell, *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 4: On Pseudohypertrophic and Allied Types of Progressive Muscular Dystrophy*, ed., R. A. Fisher, (Cambridge: Cambridge University Press, 1943), 294.

²²⁵ J. B. S. Haldane, “The Relative Importance of Principal and Modifying Genes in Determining Some Human Diseases,” *Journal of Genetics* 41 (1941): 149-157.

²²⁶ See Penrose, “Problem,” 125-126.

²²⁷ Sheila Weiss, “The Race Hygiene Movement in Germany 1904-1945,” in “*The Wellborn Science*” *Eugenics in Germany, France, Brazil, and Russia*, ed., Mark Adams, (New York: Oxford University Press, 1990), 30. See also Peter Weingart, “German Eugenics between Science and Politics,” *Osiris* 5 (1989): 267-269.

concerns.”²²⁸ Lenz had argued against anticipation since at least the second edition of *Menschliche Auslese und Rassenhygiene* (1923) where he described it as apparent rather than real and therefore not a valid object of scientific analysis.²²⁹ The 1927 edition, *Menschliche Erblichkeitslehre*, was translated into English as *Human Heredity*, published in London and New York in 1931.²³⁰ In this edition, Lenz continued “to express my doubts concerning this doctrine of ‘anticipation’” which he believed was caused by a “statistical illusion.”²³¹ Lenz discussed and dismissed the possibility of anticipation occurring in the several conditions with which it had traditionally been associated, including cataract, hereditary ataxia, glaucoma, diabetes, Huntington’s chorea, and myotonic dystrophy.²³² Almost identical arguments appeared in the 1936 edition of

²²⁸ Weindling calls the Freiburg group “of outstanding importance” to the development of eugenics in Germany. Weismann was also an important founding member of this group, although he would fall out of favour after 1933. The three authors met while Lenz was still a medical student at Freiburg and the book was in the planning stages by 1914. Paul Weindling, *Health, race and German politics between national unification and Nazism, 1870-1945*, (Cambridge: Cambridge University Press, 1989), 96-98, 144-145.

²²⁹ Fritz Lenz, *Menschliche Erblere und Rassenhygiene*. Band 2, *Grundriß der menschlichen Erblichkeitslehre und Rassenhygiene*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz, (Munich: J. F. Lehmanns Verlag, 1923), 339.

²³⁰ Baur, Fisher, and Lenz, *Human Heredity*. *Human Heredity* was reviewed by Lancelot Hogben in 1931. He bemoaned the delay in translation as the field was rapidly advancing, but was far more critical of the fact that recent advances in genetic methodologies (including those made by Lenz himself) were not included in the book as the methodology section remained essentially unchanged from the 1923 edition: “Of late human geneticists in Scandinavia and Germany have been developing statistical methods by which it is possible to test the applicability of Mendelian laws to recorded pedigrees of diseases extant in medical literature, such as those which Pearson and his colleagues have collected with immense care and industry in the Treasury of Human Inheritance. Of the existence of these methods the reader will glean no information in this book.” Hogben called the third section of the book, written by Lenz, “the most useful part of the book” in relation to its encyclopaedic discussion of heredity in human diseases. However, he expressed considerable disappointment that this section did not use the more modern methodologies of human genetics with which Lenz was clearly familiar, and expressed incredulity that the last section “The Inheritance of Intellectual Gifts” was also written by Lenz, describing it as “a sprightly exposition of the Hitlerite *Weltanschauung*.” Lancelot Hogben, “Human Heredity,” *Economica* 34 (November 1931): 464-466. On the relations in the 1920s between the American eugenicist Charles Davenport and the co-authors Baur and Lenz, see: Stefan Kühl, *The Nazi Connection. Eugenics, American Racism, and German National Socialism*, (Oxford: Oxford University Press, 1994), 18-20. Laurence Snyder, the American advocate of medical genetics, used *Human Heredity* as the text for his course in medical genetics. Comfort, “Polyhybrid,”

²³¹ Lenz argued that this ‘illusion’ was caused by selective reproductive pressure. In the older generations, late-onset cataract was selected for, since individuals with early vision difficulties tended not to marry. The reverse was true in the younger generations where the discovery of early cataract was deemed important and where those siblings who might yet develop cataract in old age would be incorrectly identified as healthy. In a footnote Lenz credited Weinberg with being the first to note this statistical pitfall in 1914. These arguments are of course very similar to the ones outlined in 1912 and 1914 by Pearson and Heron respectively, but Pearson, Heron, and Weinberg seem to have been unaware of each others’ work. Baur, Fischer, and Lenz, *Human Heredity*, 244.

²³² Baur, Fischer, Lenz, *Human Heredity*, 243-244, 354-356, 418-421.

Menschliche Erblehre concerning the “apparent” rather than “real” appearance of anticipation in cataract, diabetes, and myotonic dystrophy²³³ and again in the 1940 edition of *Erbpathologie* concerning cataract, glaucoma, and myotonic dystrophy.²³⁴

(B) Anticipation in Various Disorders

Between 1930 and 1945 a number of researchers continued to study diseases with which anticipation had come to be associated. Some of these researchers were content to observe the presence or absence of anticipation in their family studies. Other researchers, however, began to offer explanations for their findings of anticipation seeking to explain, or explain away, their observations with a variety of methodological, statistical, and genetic reasons.

Huntington’s Disease

Between 1930 and 1945, researchers examining Huntington’s disease over several generations within affected families continued to report anticipation in age of onset over succeeding generations. However, due to the influence of the work of Charles Davenport and his argument that anticipation was not found in Huntington’s disease, findings of anticipation remained somewhat controversial.²³⁵ In 1932, Madge Macklin discussed this issue in her article “The relation of the mode of inheritance to the severity of an inherited mental disease.”²³⁶ She argued that Davenport’s objection that the perception of anticipation in Huntington’s disease was caused by selection bias—that studying the disease over several generations favoured the selection of families in which the grandparents had the late onset form of the disease—could be countered by using an

²³³ In this edition, Weinberg was not given credit for establishing the statistical criticisms of anticipation. Erwin Baur, Eugen Fisher, and Fritz Lenz, *Menschliche Erblehre und Rassenhygiene*. Band 1, *Menschliche Erblehre*, (Munich: J. F. Lehmanns Verlag, 1936), 336-340, 454-457, 519-521.

²³⁴ Weinberg’s contributions were once more recognized in this edition. In *Erbpathologie* the discussion of myotonic dystrophy was taken over by Wilhelm Weitz. Johannes Lange, Fritz Lenz, Otmar von Verschuer, and Wilhelm Weitz, *Menschliche Erblehre und Rassenhygiene*, Band 1: 2. Hälfte, *Erbpathologie*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz, (Munich-Berlin: J. F. Lehmanns Verlag, 1940), 16-18, 34-35, 341, 350-354.

²³⁵ Davenport’s work was discussed more fully in chapter two. Charles Davenport, “Huntington’s Chorea in Relation to Heredity and Eugenics,” *Proceedings of the National Academy of Sciences of the United States of America* 1 no. 5 (15 May 1915): 283-285; Charles Davenport and Elizabeth Muncey, “Huntington’s Chorea in Relation to Heredity and Eugenics,” *Eugenics Record Office Bulletin* 17 (October 1916): 207-209.

²³⁶ Macklin, “Relation,” 78-79.

experimental design covering complete generations. By examining the ages of onset of all affected parties in succeeding generations the researcher would be able, she thought, to state with certainty whether or not anticipation was occurring in Huntington's disease.²³⁷ After carrying out such an examination, Macklin concluded that "the law of anticipation seems to be a real fact in hereditary diseases."²³⁸

A 1932 study by the Swiss researcher Alice Gaule examined a family with Huntington's disease over six generations.²³⁹ In one branch of the family she found anticipation of the age of onset and the progressive worsening of symptoms over succeeding generations.²⁴⁰ In the first and second generations, Gaule noted that the illness began most often over the age of 60 years and that no-one in the first four generations became ill under the age of forty. By the fifth generation, however, more individuals became ill under the age of forty and the only individual in the sixth generation that was diagnosed with Huntington's was already showing symptoms at 19 years of age.²⁴¹ A similar study, carried out in 1935 by Kurt Wasum examined five generations of a German family with Huntington's disease. He too reported that the pattern of heredity of the disease within the family showed anticipation.²⁴²

In 1934, as part of the series *The Treasury of Human Inheritance*, Julia Bell carried out an examination of Huntington's disease. She noted difficulties with defining the exact age of onset, due to the variable nature of the symptoms and the wide range of ages of onset of the disease, the latter pattern being further complicated by the fact that individuals from families with the disease might either seek medical attention at the smallest signs of the disease or, conversely, ignore the symptoms until they became debilitating.²⁴³ Bell made calculations for age of onset in parents and children and age of onset in siblings but noted that:

²³⁷ Macklin, "Relation," 78.

²³⁸ Macklin, "Relation," 79.

²³⁹ Alice Gaule, "Das Auftreten der Chorea Huntington in einer Familie der Nordostschweiz," *Schweizer Archiv für Neurologie und Psychiatrie* 29 (1932): 90-112.

²⁴⁰ Gaule, "Nordostschweiz," 90.

²⁴¹ Gaule, "Nordostschweiz," 111.

²⁴² Kurt Wasum, "Chorea Huntington-Sippe (Beschreibung einer an reiner Chorea Huntington erkrankten Sippe, mit Stammbaum)," *Archiv für Psychiatrie und Nervenkrankheiten* 103 (1935): 98-99.

²⁴³ Julia Bell, *The Treasury of Human Inheritance*, Vol. 4, *Nervous Diseases and Muscular Disorders, Part I: Huntington's Chorea*, ed. R. A. Fisher, (Cambridge: Cambridge University Press, 1934), 9-11.

Particularly is the table for age of onset on parent and offspring subject to selection, in that parenthood is improbable before the age of 20-24 years and is unlikely to occur if the onset has been at an earlier age; moreover, children born to parents who have Huntington's chorea at the age of 20-24 must start life in a peculiarly unfavourable environment, particularly if the mother is affected. I can give no assurance that some of the parents of the above Table 1, who were aged say 20-29 years at the onset of the disease, may not have children who subsequently became affected at an age later than 34.²⁴⁴

Although Bell did not directly discuss anticipation in her study of Huntington's disease, she expressed caution about selection and environmental effects, and she was concerned that late-onset cases might lurk in the last generation. Nevertheless, her tables did show a drop in the age of onset of disease between parents and children.²⁴⁵

In the late 1930s two studies were published that discussed the differing views of anticipation in Huntington's disease. As discussed in chapter two, the American eugenicist Charles Davenport argued against the existence of anticipation in Huntington's disease.²⁴⁶ Both Spillane and Phillips (1937) and Stone and Falstein (1939) agreed with Davenport to the extent that, for the most part, anticipation could not *generally* be a feature of Huntington's disease, since otherwise the disease would no longer be in existence.²⁴⁷ Both these studies, however, reported that anticipation *did* occur in *certain* families they examined, though they found it to be the exception rather than the rule.²⁴⁸

Most of the discussion of anticipation in relation to eugenics in this chapter has been restricted to the proposed British voluntary sterilization legislation aimed mainly at the "mentally defective." That other conditions would likely be brought within the scope of future legislation was noted by John Spillane and Robert Phillips in their study of

²⁴⁴ Bell, *Huntington's Chorea*, 13-14.

²⁴⁵ Bell, *Huntington's Chorea*, 13.

²⁴⁶ Davenport, "Huntington's," 283-285; Davenport and Muncey, "Huntington's," 207-209.

²⁴⁷ The American doctors Stone and Falstein surveyed the literature on anticipation and Huntington's since Nettleship (1910) and ranged from the work of Heilbronner (1903) to Wasum (1935). John Spillane and Robert Phillips, "Huntington's Chorea in South Wales," *Quarterly Journal of Medicine* 6 (1937): 408; Theodore Stone and Eugene Falstein, "Genealogical Studies in Huntington's Chorea," *The Journal of Nervous and Mental Disease* 89 (1939): 805-809.

²⁴⁸ Spillane and Phillips, "Wales," 408; Stone and Falstein, "Genealogical," 806-808.

Huntington's disease in south Wales.²⁴⁹ They remarked in their opening comments that “the chronic hereditary choreas will always serve to attract attention, not only because of the pitiable state of the sufferers, but also because a knowledge of such weakness in certain family strains may eventually prove the basis of eugenic legislation.”²⁵⁰ Stone and Falstein also called for legislation in the form of legalized sterilization as the only possible way to eradicate Huntington's disease.²⁵¹

Myotonic Dystrophy

Between 1930 and 1945 ophthalmologists, neurologists, and others continued to seek explanations for evidence of anticipation in myotonic dystrophy a condition in which cataract might be the only sign of disease in earlier generations, while in later generations the neuromuscular system would be severely affected. The acceptance of the Mendelian model of heredity would bring about an increasing need to find reasons behind the disease's peculiar pattern of inheritance and variability of symptoms. The groundbreaking British physician Dr. Archibald Garrod discussed myotonic dystrophy in his 1931 book *The Inborn Factors in Disease*.²⁵² As one of the “abiotrophies” (hereditary diseases of the neuromuscular system), myotonic dystrophy distinguished itself, he maintained, by affecting a wide variety of bodily systems.²⁵³ In his opinion, the disease was clearly caused by an inborn factor or factors:

The development of a characteristic syndrome in member after member of a family, and often in members of successive generations; its appearance at about the same period of life in the members of a generation, and its

²⁴⁹ Mental symptoms are not uncommon in patients suffering from Huntington's disease. However, in order to be eugenically effective, sterilization would need to be carried out before childbearing age, which would also pre-date the symptoms of all but the earliest-onset cases of Huntington's disease. With no way to distinguish carriers of the defective gene, this could lead, in effect, to the sterilization of all children of Huntington's sufferers although, statistically, only half of them would develop the disease later in life.

²⁵⁰ Spillane and Phillips, “Wales,” 403.

²⁵¹ Stone and Falstein, “Genealogical,” 808-809.

²⁵² Garrod was the first British physician to apply Mendelian inheritance to the study of inherited disease. His study of alkaptonuria noted that it followed autosomal recessive inheritance and he hypothesized that the disorder was caused by the mutation of a gene responsible for an enzyme required for the correct metabolism of alkaptans. His *Inborn Errors in Metabolism* (1909 2nd ed. 1923) is considered a landmark work. J. B. S. Haldane was influenced by Garrod's work in his study of phenylketonuria. Kevles, *Eugenics*, 215-217.

²⁵³ The book had its origin in Garrod's 1927 Huxley Lecture “Diathesis.” Archibald Garrod, *The Inborn Factors In Disease* (Oxford: The Clarendon Press, 1931), 82, 94-95.

tendency, in most instances, to anticipate from generation to generation, suffice in themselves to prove the importance of the constitutional element.²⁵⁴

Garrod's summary of the pattern of inheritance in myotonic dystrophy provides a good example of what many physicians who were amenable to the idea believed of anticipation.

In 1932, the Dutch ophthalmologist and geneticist Petrus Johannes Waardenburg discussed anticipation in myotonic dystrophy in the seventh volume of the *Bibliographia Genetica*.²⁵⁵ Waardenburg believed that several non-ophthalmologic diseases had been identified as progressively degenerative, including Huntington's disease.²⁵⁶ In the case of myotonic dystrophy, it had been recognized since the work of Fleischer (1916-1922) that the disease seemed to progress from cataract alone in one generation to cataract with myotonic dystrophy in following generations. Waardenburg proposed that myotonic dystrophy was caused by a single gene, but that the gene could express in a variety of ways, depending upon other factors.²⁵⁷

The 1933 paper, "Cataract in dystrophia myotonica," by New Zealand-born neurologist J. E. Caughey, is notable in retrospect because in 1963 this author was one of the last physicians to defend the existence of anticipation in myotonic dystrophy, in the face of opposition from human geneticists.²⁵⁸ Caughey's 1933 article examined cataract in the so-called "dystrophic generation" in which "the fully-developed disease appears with myotonia, muscle wasting and general dystrophic signs."²⁵⁹ Although Caughey agreed that "the phenomenon of anticipation as seen in other heredo-familial diseases is well seen in dystrophia myotonica in the occurrence of cataract," he was unable to

²⁵⁴ Garrod, *Inborn Factors*, 94.

²⁵⁵ P. J. Waardenburg, *Bibliographia Genetica*, Vol. 7, *Das Menschliche Auge und seine Erblangen*, ed., J. P. Lotsy and W. A. Goddijn, (The Hague: Martinus Nijhoff, 1932), 298-304.

²⁵⁶ Waardenburg cites Heilbronner for being the first to recognize this sort of progression in hereditary degenerative disorders. I assume he is referring to Heilbronner's 1903 finding of progressive heredity in Huntington's disease. Waardenburg, *Bibliographia*, 299.

²⁵⁷ Waardenburg, *Bibliographia*, 299-304.

²⁵⁸ The importance of Caughey's discussion in the textbook the later co-authored with the human geneticist N. C. Myroanthopolous will be discussed in chapters four and five. J. E. Caughey, "Cataract in dystrophia myotonica," *Transactions of the Ophthalmological Society of the United Kingdom* 53 (1933): 60-72.

²⁵⁹ Caughey, "Cataract," 60.

examine cataracts from earlier generations in order to ascertain if the nature of the cataract remained the same from generation to generation.²⁶⁰

During the early 1930s, two Russian researchers, N. Kryschowa and H. Bajevskaja, joined in the hunt for an explanation for the odd pattern of heredity in myotonic dystrophy. They argued that myotonic dystrophy was caused by a dominant gene. Nevertheless, they believed that the expression of the gene was obviously pleiotropic—i.e. a single gene was causing a variety of phenotypes or physical effects. In their view, the addition of modifying genes or some environmental effect would help to explain why the expression of the disease varied from case to case.²⁶¹

The German neurologist Otto Maas had a long-standing interest in the study of myotonic dystrophy. Named the first director of a specialized neurological unit in a Berlin hospital in 1911, Maas held that position until 1933 when he and his Jewish colleagues were forced to emigrate from Germany.²⁶² In 1937, Maas was working at the National Hospital for Nervous Diseases in London, when he published a large study on myotonic dystrophy.²⁶³ In it, he classified his subjects as “severe cases,” “milder cases,” “suspicious cases,” “slightly suspicious cases,” and, rarely, “healthy cases.”²⁶⁴ He claimed to be able to see signs of disease in almost all of the members of the families that he studied, well beyond the 50% predicted by Mendelian heredity of a dominant gene.²⁶⁵ Like most previous researchers, Maas reported the variable nature of the disease; he also felt that “a sharp differentiation between severe and milder cases cannot be made.”²⁶⁶

One of the most interesting features of Maas’ paper was that he had Lionel Penrose analyze the results of his observations and his use of Penrose’s report and tables

²⁶⁰ Caughey, “Cataract,” 60, 71.

²⁶¹ N. Kryschowa and H. Bajevskaja, “Ein familiärer Fall der atrophischen Myotonie,” *Zeitschrift für die gesamte Neurologie und Psychiatrie* 150 (1934): 504-514.

²⁶² B. Holdroff, “Founding Years of Clinical Neurology in Berlin Until 1933,” *Journal of the History of the Neurosciences* 13 no. 3 (September 2004): 223-238.

²⁶³ Otto Maas, “Observations on Dystrophia Myotonica,” *Brain* 60 (1937): 498-524.

²⁶⁴ Maas, “Observations,” 498, 510.

²⁶⁵ Part of this was due to the fact that Maas advocated the use of mechanical excitation as a more accurate way to test for myotonia on the grounds that since it could detect signs of the disease in otherwise apparently healthy individuals. Additionally, he believed that polychromatic cataracts of the form seen in myotonic dystrophy should be considered diagnostic. Maas, “Observations,” 499, 502-503, 523. Lionel Penrose found the lack of normal individuals striking. In his commissioned report (quoted by Maas in the paper) Penrose noted: “I do not think that the hypothesis of cytoplasmic inheritance which I suggested as a possible explanation of the great variety of forms is very probable, but I think that it might be the only way of explaining the extreme rarity of normal individuals.” Maas, “Observations,” 516.

²⁶⁶ Maas, “Observations,” 499-501.

to support his points.²⁶⁷ Penrose noted here that, although fraternal anticipation (younger siblings getting the disease before their older siblings) seemed to be common, that “the number of cases so far available is too small to establish a definite rule,” and that many factors were likely to be involved in creating this effect.²⁶⁸ He concluded that nonetheless “there may be a main gene responsible for dystrophia myotonica and numerous modifying influences, one of which may be associated with birth order.”²⁶⁹ In his examination of the transmission of the disease from parent to child Penrose noted that the findings “would be in keeping with the hypothesis of dominant inheritance, but in which more than one factor is involved.”²⁷⁰ In his own analysis, Maas agreed with earlier researchers that myotonic dystrophy was likely caused by a dominant mutation that could be transmitted through apparently healthy persons who must, therefore, be affected by the disease, if only slightly.²⁷¹ Maas saw signs of anticipation in several families studied by himself and other researchers.²⁷² On the question of mental deterioration in later generations, Maas’ observations indicated “that mental illness is at least more common in the later generations of affected families.”²⁷³ He noted that almost every patient who was badly enough afflicted with psychiatric effects from myotonic dystrophy that they had to be hospitalised, had a parent suffering with a more moderate form of the disease.²⁷⁴ Though anticipation occurred in many families suffering from myotonic dystrophy, Maas reported that “while progressive deterioration may occur in some families, it does not seem to be an invariable rule; in some families there may even be a regression in the

²⁶⁷ This is particularly interesting when one considers that the conclusions Maas drew from Penrose’s analysis of his results were completely at odds with Penrose’s analysis of Bell’s 1947 study which will be discussed in chapter four. Maas, “Observations,” 510.

²⁶⁸ Maas, “Observations,” 514, 523.

²⁶⁹ Maas, “Observations,” 510.

²⁷⁰ For example, the younger siblings might be diagnosed at an earlier age than their older siblings because the disease was already known to run in the family and the smallest signs would be taken as evidence of illness. Maas, “Observations,” 515.

²⁷¹ Maas, “Observations,” 514, 517, 524.

²⁷² Maas, “Observations,” 517-518.

²⁷³ Maas, “Observations,” 522.

²⁷⁴ Maas’s did not note a gender imbalance in these findings. Modern studies of myotonic dystrophy have found that the most severely affected children are those with affected mothers. Maas noted that of those children so badly affected by myotonic dystrophy that they needed to be institutionalised 10 had affected mothers and 10 had affected fathers. While mental symptoms were not commonly seen in earlier generations of the disease, Maas did not rule out the possible existence of such cases. Maas, “Observations,” 522.

incidence and severity of the disease.²⁷⁵ Maas' study concluded that both fraternal and generational anticipation occurred in myotonic dystrophy.²⁷⁶ In the case of generational anticipation he noted that "Dr. Penrose supposes that more than one factor is involved."²⁷⁷

In 1938, a study by Erich von Katzenstein-Sutro traced myotonic dystrophy through a Swiss family and its branches back to a common ancestor in the mid-1700s. In the third generation cataract showed up in one of three children. The unaffected son's descendents were traced, and showed no signs of cataract or myotonic dystrophy. The descendants of the affected son showed cataract in the second generation, mild dystrophic symptoms in the third generation and full blown myotonic dystrophy in the fourth generation.²⁷⁸ Katzenstein-Sutro therefore concluded that progressive heredity with anticipation was a feature of myotonic dystrophy.²⁷⁹ No indications of muscular disease or cataract in the generations preceded the first case of cataract. After the first generation with cataract the disease progressed in the same way in succeeding generations and the symptoms appeared at the same time in several branches of the family—i.e. a generation with senile cataract followed by a generation with pre-senile cataract and mild muscular symptoms succeeded by yet another generation with severe myotonic dystrophy and juvenile cataract.²⁸⁰

²⁷⁵ Maas, "Observations," 521.

²⁷⁶ This was despite the fact that he was well aware of Paterson's (1933) arguments against anticipation, which he referenced, and in spite of the fact that he and Paterson had collaborated on a paper on myotonic dystrophy in 1937 in which anticipation was not discussed. Maas, "Observations," 523-524. Otto Maas and A. S. Paterson, "Mental Changes in Families Affected by Dystrophia Myotonica," *The Lancet* 229 no. 5914 (2 January 1937): 21-23. As mentioned above, Maas and Paterson continued to collaborate on myotonic dystrophy. Although their 1939 and 1950 studies did not address anticipation, another one in 1943 did. It will be discussed below. Most of their collaborative papers dealt with the (incorrect) assertion that myotonia congenita, myotonic dystrophy, and paramyotonia were all related syndromes. Otto Maas and A. S. Paterson, "The Identity of Myotonia Congenita (Thomsen's Disease), Dystrophia Myotonica (Myotonia Atrophica) and Paramyotonia," *Brain* 62 no. 2 (1939): 198-212; Otto Maas and A. S. Paterson, "Myotonia congenita, dystrophia myotonica and paramyotonia; reaffirmation of their identity," *Brain* 73 no. 3 (1950): 318-336; Otto Maas and A. S. Paterson, "Myotonia congenita and dystrophia myotonica; further considerations indicating identity," *Monatsschrift für Psychiatrie und Neurologie* 126 no. 1 (July 1953): 27-33. An additional paper published in 1947 examined the clinical manifestations of myotonic dystrophy but did not deal with genetic aspects of anticipation. Otto Maas and A. S. Paterson, "Dystrophia Myotonica as a Generalised Disease," *Monatsschrift für Psychiatrie und Neurologie* 113 (1947): 79-99.

²⁷⁷ Maas, "Observations," 523.

²⁷⁸ Erich von Katzenstein-Sutro, "Beitrag zur Myotonischen Dystrophie," *Schweizer Archiv Für Neurologie und Psychiatrie* 42 (1938): 254-259.

²⁷⁹ von Katzenstein-Sutro, "Myotonischen Dystrophie," 295-297.

²⁸⁰ von Katzenstein-Sutro, "Myotonischen Dystrophie," 295-297.

Two American physicians, Abe Ravin and James Waring, carried out a study of the hereditary aspects of myotonic dystrophy in 1939.²⁸¹ They noted that “geneticists have studied this disease in an effort to express the method of inheritance in classical mendelian [*sic*] terms.”²⁸² However, as Ravin and Waring noted, this was easier said than done. According to classical Mendelian dominance the disease should pass from affected parent to affected child. Yet myotonic dystrophy “occurs commonly in the children of apparently normal parents, and is infrequently seen in two successive generations,” giving it “a very irregular type of inheritance.”²⁸³ They noted that “the fact that the parents of most patients with dystrophia myotonica are apparently normal suggest recessive inheritance.”²⁸⁴ This was, however, complicated by the fact that it *acted* like a Mendelian dominant in that there was no consanguinity seen in families suffering from the disease (which would have been expected if the trait had been recessive) and that once the disease had manifested itself within a family it passed from parent to child in the manner of a dominant gene.²⁸⁵ Because of this Ravin and Waring argued that the mode of heredity in myotonic dystrophy was one of “modified dominant inheritance.”²⁸⁶ They suggested that the gene for myotonic dystrophy would initially occur in a family as a dominant mutation that was “at first manifest by no signs or by very slight and few signs, notably cataract.”²⁸⁷ Then anticipation would begin to show itself; the cataract would appear earlier in succeeding generations until the disease finally manifested as full-blown myotonic dystrophy. Then within a few generations “a generation occurs in which the onset is before an age at which the patients mature and the disease ceases to appear in that family.”²⁸⁸ Ravin and Waring posited that this progression in severity of symptoms and age of onset was caused by an unstable mutation in the affected gene that worsened over succeeding generations, reducing the gene’s activity and causing degenerative

²⁸¹ Abe Ravin and James Waring, “Studies in Dystrophia Myotonica. I. Hereditary Aspects,” *American Journal of the Medical Sciences* 197 (1939): 593-609.

²⁸² Ravin and Waring, “Studies,” 594.

²⁸³ Ravin and Waring, “Studies,” 594.

²⁸⁴ Ravin and Waring, “Studies,” 599.

²⁸⁵ Ravin and Waring, “Studies,” 599-600.

²⁸⁶ Ravin and Waring, “Studies,” 602.

²⁸⁷ Ravin and Waring, “Studies,” 603.

²⁸⁸ Like some other authors, Ravin and Waring separated out the features of earlier onset age (always called anticipation or antedating) and worsening of disease over generations (called potentiation). Progressive inheritance or progressive heredity was said to occur when both anticipation and potentiation were occurring. Ravin and Waring, “Studies,” 603-604.

changes to occur earlier and more severely, no matter what the effect of allelic genes might be.²⁸⁹

In 1943, Maas and Paterson published a second large study on “Genetic and Familial Aspects of Dystrophia Myotonica.” In this paper Paterson seems to have changed his mind on anticipation (or progressive degeneration as it was called here) at least as regarded myotonic dystrophy.²⁹⁰ Maas and Paterson noted that progressive degeneration was occurring over generations in the families that they studied and that the development of mental defect in succeeding generations bore this out, since they found no “mental defective who definitely belonged to the first known generation affected by dystrophia myotonica.”²⁹¹ As had been noted in Maas’ 1937 article, there were occasional findings of “families in whom members of subsequent generations were less affected than those of the preceding ones,” a process that they termed “regeneration.”²⁹² It was clear to them, however, “that progressive deterioration is a more frequent event than regeneration in dystrophia myotonica, even when we take into consideration all possible statistical fallacies.”²⁹³ These assertions that anticipation, or rather “degenerate heredity,” which was the term they used, appeared to be really occurring in myotonic dystrophy—even when all possible statistical errors had been taken into account—and

²⁸⁹ This hypothesis was prescient, for the cause for anticipation was eventually found to be caused by expanding trinucleotide repeats—i.e. an unstable region of DNA that was prone to expansion when replicated. This helped to explain some of the hallmarks of the so-called “heredo-degenerative” diseases including why the disease appeared in the same form in the same generation (“homologous” heredity) and why onset occurred at approximately the same time in the same generation (“heterochomous” heredity). Ravin and Waring cited Goldschmidt (1928) as their reference on the “properties of genes.” In this 1928 paper Goldschmidt had discussed the issues of allelomorphs and modifying genes (he did not yet call them *dominigenes*). The discussion of variegation in plant colour seems to have been the source of Ravin and Waring’s belief in unstable genetic changes. Richard Goldschmidt, “The Gene,” *The Quarterly Review of Biology* 3 no. 3 (September 1928): 604-610.

²⁹⁰ It should be noted that in this paper Maas and Paterson included in their pedigrees and calculations individuals with myotonia congenita (Thompsons’ disease) and paramyotonia since they argued (erroneously) that their 1939 paper had shown that these three syndromes were “in our opinion essentially the same disease.” Otto Maas and A. S. Paterson, “Genetic and Familial Aspects of Dystrophia Myotonica,” *Brain* 66 no. 1 (March 1943): 55.

²⁹¹ Maas and Paterson, “Genetic,” 74-75.

²⁹² Maas and Paterson, “Genetic,” 75.

²⁹³ Maas and Paterson, “Genetic,” 76, see also 84. Despite the fact Fleischer (1918) and other authors had argued that the age of onset of disease in myotonic dystrophy seemed to be the same within each generation (termed homochronous heredity), Maas reiterated his 1937 argument that fraternal anticipation was taking place in myotonic dystrophy. Maas and Paterson posited that the causes for this finding might be related to the creation of additional defects in the germ-plasm, environmental factors including under-nourishment, and some sort of paternal inheritance effect. Maas and Paterson, “Genetic,” 77-82.

that regeneration also occurred, if much more rarely, were repeated in their conclusions.²⁹⁴

Comments made by Maas and Paterson concerning the genetic nature of myotonic dystrophy were equally interesting. As he had in 1937, Maas agreed with Penrose's suggestion that more than one factor was likely involved in the inheritance of myotonic dystrophy.²⁹⁵ Maas and Paterson, however, combined this with Goldschmidt's work on dominigenes to argue that "even if all the isolated factors were transmitted by recessive inheritance, it would still be possible for the factors in combination to be inherited by dominance, as "dominigenes" may change recessive inheritance into a dominant one."²⁹⁶ This led them to the conclusion that while the disease as a whole was "transmitted in a dominant manner," there were "multiple factors involved, which are recessive in isolation, but dominant when united."²⁹⁷ Clearly, attempting to explain the inheritance pattern of myotonic dystrophy was no easy task, even with the latest genetic thinking and most strenuous statistical examinations.

In 1942 the Argentine physician Alfredo Lanari published the first monograph on myotonic diseases. In his text Lanari reviewed the arguments concerning anticipation as they appeared in the literature.²⁹⁸ Lanari did not believe in "fraternal anticipation" (a finding reported by several authors, including Maas in 1937) i.e. a pattern in which the disease allegedly appeared at a successively earlier age in siblings within the same generation.²⁹⁹ However, his findings did confirm anticipation across generations. Among his patients he had seen a family in which the father had senile cataract with no muscular involvement, the next generation had cataracts and muscular symptoms in their thirties, and the third generation was showing signs of cataract at 10 years of age.³⁰⁰

²⁹⁴ Maas and Paterson, "Genetic," 84.

²⁹⁵ Maas and Paterson, "Genetic," 64, 74.

²⁹⁶ Maas and Paterson, "Genetic," 72.

²⁹⁷ Maas and Paterson, "Genetic," 83-84.

²⁹⁸ Alfredo Lanari, *Miotonias*, (Buenos Aires: El Ateneo, 1942), 17-18.

²⁹⁹ Lanari, *Miotonias*, 18.

³⁰⁰ Lanari, *Miotonias*, 18-19.

Diabetes

Diabetes had been one of the disorders associated with anticipation since Nettleship's 1909 and 1910 papers.³⁰¹ During the 1930s, Madge Macklin continued to observe anticipation in diabetes.³⁰² In her 1932 paper on "The Relation of the Mode of Inheritance to the Severity of an Inherited Disease" Macklin discussed patterns of inheritance in diabetes.³⁰³ She affirmed there that diabetes had an "erratic" mode of inheritance.³⁰⁴ Moreover, it had long been understood that diabetes with an early age of onset (now called juvenile or type 1 diabetes) was the most severe form of the disease and was invariably fatal without treatment in the form of insulin, as first discovered in 1922. Adult cases of the disease (what we more often call type 2 diabetes) were recognized as being generally milder in their effects.³⁰⁵ Macklin suspected that in cases with an average age of onset over thirty years and where diabetes appeared in a direct line of descent, "the disease may with a fair amount of justice be considered to have arisen through a mutation acting as a dominant character."³⁰⁶ In some families, however, she argued that it could be said to arise through a recessive mutation.³⁰⁷ In cases where "the disease [is] in its acute form which attacks the young [it] is inherited as a recessive."³⁰⁸ In 1933, Macklin wrote a paper directly addressing the question of anticipation in diabetes.³⁰⁹ She noted that while some scholars had previously denied that anticipation was at work in diabetes, others continued to affirm the opposite.³¹⁰ Some researchers found families with apparently dominant inheritance of diabetes, while others suggested that it was inherited according to recessive patterns of inheritance.³¹¹

³⁰¹ Edward Nettleship, "On Some Hereditary Diseases of the Eye," *Transactions of the Ophthalmological Societies of the United Kingdom* 29 (1909): 72; Edward Nettleship, *The Bowman Lecture on Some Hereditary Diseases of the Eye*, (London: Adlard and Son, 1909), 72; Edward Nettleship, "Some Points in Relation to the Heredity of Disease," *St. Thomas's Hospital Gazette* 20 (March 1910): 60-61.

³⁰² Not all researchers believed that anticipation featured in the inheritance of diabetes. See for example: Lenz, *Menschliche Erblehre*, 454-456.

³⁰³ Macklin, "Relation," 69-79.

³⁰⁴ Medical textbooks stated that "hereditary" cases of diabetes caused about 15% of cases while "familial" cases formed about 7 to 15% of cases and "sporadic" cases made up the rest. Macklin, "Relation," 70.

³⁰⁵ Macklin, "Relation," 72.

³⁰⁶ Macklin, "Relation," 73.

³⁰⁷ Macklin, "Relation," 73.

³⁰⁸ Macklin, "Relation," 73.

³⁰⁹ M. T. Macklin, "Inherited Anomalies of Metabolism: 1. Diabetes Mellitus," *Journal of Heredity* 24 no. 9 (1933) 349-356.

³¹⁰ Macklin, "Inherited," 350.

³¹¹ Macklin, "Inherited," 351-354.

The American physician R. T. Woodyat was also interested in the question of anticipation when diabetes appeared in several generations of the same family. In 1942, Woodyat and his colleague Marseille Spetz published a paper in which they assessed the existence of anticipation in diabetes in 100 families in which two or more generations had the disease.³¹² Woodyat and Spetz noted the arguments made against anticipation in the case of Huntington's disease made by Davenport and Muncy (1916) and the fact that while many researchers reported cases in which anticipation seemed to be taking place in diabetic families, most of them, with the exception of Macklin, let the observations pass "without commenting on it."³¹³ Their own research, they said however, showed significant signs of anticipation in the inheritance of diabetes.³¹⁴ In fact, they even suggested that most cases of juvenile diabetes appeared in families in which diabetes had been found in previous generations.³¹⁵

Neuromuscular Diseases

As part of her work for the *Treasury of Human Inheritance* Julia Bell ran calculations on the correlation between the ages of onset of disease in parents and children for a variety of neuromuscular disorders. On the question of anticipation in the hereditary ataxias, she reported that anticipation might be the mechanism behind the difference of the ages of onset in the parental and filial generations, but she cautioned that "it would be unwise to base any definite statement with regard to antedating on this too scanty material and on incomplete histories," noting that members of the children's generation might yet be affected by the disease at the same age as their parent, or even at a later date (postdating).³¹⁶

³¹² R. T. Woodyat and M. Spetz, "Anticipation in the Inheritance of Diabetes," *Journal of the American Medical Association* 120 (24 October 1942): 602-603.

³¹³ Woodyat and Spetz, "Anticipation," 603.

³¹⁴ Woodyat and Spetz, "Anticipation," 603-604.

³¹⁵ Woodyat and Spetz, "Anticipation," 604.

³¹⁶ Julia Bell, *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 3: On Hereditary Ataxia and Spastic Paraplegia*, assisted by E. Arnold Carmichael, ed., R. A. Fisher, (Cambridge: Cambridge University Press, 1939), 150-151.

In 1940, Julia Bell published a new paper in which she analysed material that would also later be published in *The Treasury of Human Inheritance*.³¹⁷ Bell admitted that calculations of such a pattern as fraternal anticipation were difficult, but she attempted it in her analysis of sex-linked, recessive, and dominant muscular disorders.³¹⁸ She found statistically significant differences in the age of onset of disease between parent and offspring in muscular dystrophy (6.6 years), peroneal atrophy (4.9 years), and Huntington's chorea (8.8 years) and between aunt/uncle and nephew/niece in muscular dystrophy (6.0 years), peroneal atrophy (4.8 years), and Huntington's chorea (6.2 years).³¹⁹ This finding, she noted, raised "the whole question of 'antedating' in human genetic populations."³²⁰ Bell was well aware that Pearson and others had long argued that the appearance of anticipation was likely caused by the faulty selection of relatively late ages of onset within the parental generation. She found that the age of onset in parents was, in fact, considerably older than that of unmarried individuals diagnosed with muscular dystrophy, Huntington's chorea, and peroneal atrophy, which supported the selection hypothesis.³²¹ Additionally, she remarked that the problem of incomplete generations could seriously affect the calculations and would require long-term studies to correct.³²² Bell concluded

that the methods employed have not revealed evidence of antedating. It seems probable that the *appearance of antedating* suggested by Table 11 [which contained the mean age of onset in parents and offspring and aunts/uncles and nephews/nieces] is brought about by the incomplete knowledge of the age factors in earlier generations being selective in character—the facts concerning those members who became affected early in life tending to be forgotten and to remain unrecorded.³²³

³¹⁷ Bell thanked J. B. S. Haldane "for his interest and a number of suggestions during the preparation of this paper." Julia Bell, "On the age of onset and the age of death in hereditary muscular dystrophy with some observations bearing on the question of antedating," *Annals of Eugenics* 10 (1940): 272-289.

³¹⁸ Bell, "Age of onset," 278-279.

³¹⁹ Bell, "Age of onset," 283.

³²⁰ Bell, "Age of onset," 283.

³²¹ Bell, "Age of onset," 283, 286.

³²² Bell, "Age of onset," 284.

³²³ Italics added. In this case, Bell argued that not only were late-onset cases being missed in the younger generation, but that early-onset cases were being missed in the older generations due to poor record keeping and family histories. These flaws, combined with the selection of older age of onset in parents, could give the appearance of anticipation. Bell, "Age of onset," 281, 283, 286.

These arguments were repeated when volume 4, part of the *Treasury of Human Inheritance* was published in 1943.³²⁴ Bell reiterated that

it seems probable that the appearance of ante-dating suggested by Table 9 [which contained the mean age of onset in parents and offspring and aunts/uncles and nephews/nieces] is brought about by the incomplete knowledge of the age factors in earlier generations being selective in character.³²⁵

She reported the same differences as in 1940 in ages of onset between the older and younger generations of families suffering from muscular dystrophy, peroneal atrophy, and Huntington's chorea.³²⁶ However, in 1943 she laid out a new table in which she examined the mean age of onset of disease in a group of cases of dominantly inherited muscular dystrophy. In this group, she reported, the difference in age of onset dropped to 3.23 years in muscular dystrophy (from 6.6/6.0 years) and to 3.83 years in Huntington's chorea (from 8.8/6.2 years).³²⁷ These results, she argued, though they might not "disprove the phenomenon" nevertheless "certainly fail to demonstrate its presence and I think they should have done so had ante-dating been a reality."³²⁸ Her scepticism about the reality of anticipation, even when faced with the evidence of decreasing age of onset across generations in aunts/uncles and nephews/nieces (which should have removed the selective pressure conveyed by parenthood requiring a relatively late onset of disease) is noteworthy. It would have strong resonances in Penrose's later work on the question of anticipation, but this is getting ahead of the story.

³²⁴ In fact, the text on this discussion is essentially the same as that which appeared in Bell's 1940 *Annals of Eugenics* paper, although some of the tables that appeared there did not appear in the *Treasury*. Julia Bell, *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 4: On Pseudohypertrophic and Allied Types of Progressive Muscular Dystrophy*, ed., R. A. Fisher, (Cambridge: Cambridge University Press, 1943), 294-295.

³²⁵ I believe that Bell is referring here not only to the problem raised by selection of later age of onset in the parental generation (by virtue of the affected individual having had sufficiently late onset of disease to allow them to have children) which she mentioned in the section immediately preceding this quotation, but also to the possible presence of forgotten early onset cases in the parental generation which was mentioned in her *Annals of Eugenics* paper. Bell, *Pseudohypertrophic*, 294-295.

³²⁶ Bell, *Pseudohypertrophic*, 295.

³²⁷ Bell, *Pseudohypertrophic*, 295.

³²⁸ This calculation could not help but to reduce the appearance of anticipation: it did so, because she was no longer comparing the individual differences in ages of onset between related parents and children or aunts/uncles and nephews/nieces, but rather the average of the combined ages of onset of a group of first generation individuals with that a group of a second generation individuals in diseases with a variable age of onset. Bell, *Pseudohypertrophic*, 295.

Ophthalmologic Diseases

Perhaps because the concept of anticipation was created by the prominent ophthalmologist Edward Nettleship, many ophthalmologists seemed to accept the idea and applied it to their hereditary work. The Swiss ophthalmologist and genetic researcher Adolphe Franceschetti reported anticipation in familial glaucoma in 1930³²⁹ and similar findings were noted by the Dutch ophthalmologist P. J. Waardenburg in 1932 who also found anticipation in certain families with hereditary cataract.³³⁰ However, Fritz Lenz, who was not an ophthalmologist, was critical of claims by Nettleship and other researchers to have seen evidence of anticipation in hereditary cataract and in glaucoma. He argued that these findings were the result of selection bias and constituted a statistical artefact, since those who were blinded at an early age rarely married and had children.³³¹ Julia Bell, who carried out meta-analyses of studies on ophthalmological disorders, glaucoma among them, was not herself an ophthalmologist by training.³³² Her mentor Karl Pearson had been a friend and colleague of Nettleship and thought so highly of him that he dedicated the second volume of the *Treasury of Human Inheritance* to Nettleship's memory.³³³ As we have seen, Bell took a guarded, even sceptical approach to the question of anticipation in general, and that was her stance in the case of glaucoma as well. While she could not *disprove* the existence of anticipation in hereditary glaucoma, she explained that her calculations of anticipation in glaucoma were

³²⁹ Adolphe Franceschetti, "Die Vererbung von Augenleiden." In *Kurzes Handbuch der Ophthalmologie*, ed. P. Eisler, A. Franceschetti, R. A. Pfeifer, R. Seefelder (Berlin: Verlag von Julius Springer, 1930), 669. In 1941, Franceschetti was one of the founding members of the Swiss Genetic Society. Through that society he later met and mentored David Klein—a physician with an interest in genetics who also believed in anticipation—whose work will be discussed in chapter four. David Klein, "Living History—Autobiography: Genetics and Environment From a Personal Perspective," *American Journal of Medical Genetics* 37 no. 3 (November 1990): 325-328.

³³⁰ Waardenburg, *Bibliographia*, 274-276.

³³¹ Lenz, *Human Heredity*, 242-244; Lenz, *Erbpathologie*, 16-18, 34-37; Lenz, *Menschliche Erblehre*, 336-339.

³³² Budney, "Julia Bell," 10-11; Harper, "Julia Bell," 422-432.

³³³ The second volume of the *Treasury—Anomalies and Diseases of the Eye* was subtitled *Nettleship Memorial Volume* to honour the late Edward Nettleship who had collected pedigrees that contributed significantly to the volume. As we have seen, Nettleship had been a friend and collaborator of Karl Pearson. As was discussed above in the section on theoretical approaches to anticipation and in chapter two, while Pearson seemed to make no bones about criticizing Mott's interpretation of anticipation, he had nothing but good words for Nettleship's studies of hereditary eye disorders. See for example: Karl Pearson, "Prefatory Note," in Julia Bell, *The Treasury of Human Inheritance*. Vol. 2. *Anomalies and Diseases of the Eye: Nettleship Memorial Volume. Part 1: Retinitis Pigmentosa and Allied Diseases Congenital Stationary Night-Blindness Glioma Retinae*, with a Memoir of Edward Nettleship by J. B. Lawford, (Cambridge: Cambridge University Press, 1922), vi; Pearson, "Inheritance," 362-380.

complicated by the fact that the pedigrees she was working from contained incomplete generations. This meant that only early onset disease might be observed in individuals in the last generation, and so this might hide possible cases of late onset disease which would not yet have manifested. For this reason she warned that “the reduced age of onset in the younger generation must not be taken as proof of a general tendency to antedating on the transmission of the disease” even though she regretted her “inability to make any definite statement regarding” anticipation.³³⁴

In 1928, Bell had published a study examining the age of onset in Leber’s disease (Hereditary Optic Atrophy) that was equivocal regarding anticipation—here she affirmed that better research was needed before deciding either way about anticipation.³³⁵ This discussion continued in 1931 when the issue of the *Treasury* devoted to Leber’s disease was published.³³⁶ Bell remained concerned that findings of anticipation were caused by selection bias—in that cases of disease in the younger generation were discovered early only because the family was already under observation and that late onset cases in that generation had not yet had the chance to develop. Moreover, she speculated that the “exact age of onset in members of the previous generation who came to be affected early in life is liable to be forgotten.”³³⁷ Based on her calculations, Bell concluded “that there is no evidence of antedating in the age of onset of hereditary optic atrophy in passing from one generation to the next.”³³⁸ In short, Bell clearly grew increasingly suspicious of anticipation over time.

³³⁴ Julia Bell, *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye*. *Nettleship Memorial Volume, Part 5: On Some Hereditary Structural Anomalies of the Eye and on the Inheritance of Glaucoma*, ed., Karl Pearson, (Cambridge: Cambridge University Press, 1932), 459-460.

³³⁵ For detailed discussion see chapter two. Julia Bell, “The Age of Onset in Hereditary Optic Atrophy,” *Annals of Eugenics* 3 (1928): 269-276.

³³⁶ Julia Bell, *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye, Part 4: Hereditary Optic Atrophy (Leber’s disease)*, ed., Karl Pearson, (Cambridge: Cambridge University Press, 1931).

³³⁷ It is unclear why Bell decided that cases of early onset disease were likely to be forgotten in the earlier generations (except that perhaps they were less likely to be recorded by the reporting physician and that the age of death was considerably easier to obtain), but this argument recurred in her future discussions of anticipation. Bell, *Optic Atrophy*, 335.

³³⁸ Bell, *Optic Atrophy*, 335.

Psychiatric and Mental Disorders

Anticipation had been associated with mental illness since Mott first discussed the concept in 1911.³³⁹ The German physician and eugenicist Ernst Rüdin had found anticipation in familial schizophrenia in his 1916 study.³⁴⁰ These findings were repeated by a variety of other authors thereafter, including Thurstone and Jenkins (1931).³⁴¹

By the late 1930s, however, even the long-time eugenicist A. F. Tredgold, the physician, authority on mental defect, and textbook writer, was having to adapt to the changing times. The sixth edition of his *Mental Deficiency* was considerably different from those preceding it.³⁴² Unlike in previous editions, the Intelligence Quotient (IQ) was now used as a defining criterion for sorting the normal from the feeble-minded.³⁴³ While discussion of the interaction between inheritance and environment as causative factors for mental illness continued to be seen as important, attention focused on a new class of genetically linked diseases, such as hereditary ataxia, Huntington's disease, and amaurotic family idiocy (Tay-Sachs) that were now recognised as having fairly clear-cut genetic causes.³⁴⁴ No longer was Nettleship's work cited as evidence for the effects of constitutional diathesis. Instead, Tredgold now directed his readers towards the discovery of specific diseases traditionally associated with mental defect that now were said to have a clearly genetic cause. Penrose's work on the Mendelian nature of the mental defect caused by an inborn metabolic error in the case of phenylketonuria (PKU) came in for repeated mention, for example.³⁴⁵ Tredgold continued to censure the American school and their work on the inheritance of mental defect—most notably their

³³⁹ See chapter one. For example: F. W. Mott, "A Lecture on Heredity and Insanity," *The Lancet* 1 (May 13, 1911): 1251-1259.

³⁴⁰ Ernst Rüdin, "Studien über Vererbung und entstehung geistiger Störungen. I. Zur Vererbung und neuentstehung der Dementia praecox," *Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie* 12 (1916): 123-138. Rüdin later retracted his support of the concept of anticipation, referring to it in 1923 as a statistical error. While this change was recognized in the German literature (e.g. by Lenz in his discussions on schizophrenia), Rüdin's 1916 paper continued to be referred to as supporting anticipation in schizophrenia in the English literature. See also chapter two.

³⁴¹ L. L. Thurstone and Richard L. Jenkins, *Order of Birth Parent-Age and Intelligence*, (Chicago: University of Chicago Press, 1931), 56, 94-96.

³⁴² A. F. Tredgold, *A Text-Book of Mental Deficiency (Amentia)*, 6th ed., (London: Baillière, Tindall & Cox, 1937).

³⁴³ Tredgold, *Mental Deficiency* (1937), 8-9.

³⁴⁴ Tredgold, *Mental Deficiency* (1937), 25.

³⁴⁵ Tredgold, *Mental Deficiency* (1937), 30-31.

belief that mental defect was inherited as a Mendelian recessive trait.³⁴⁶ Tredgold's alternative theory remained his idea that the cause of mental deficiency was an impairment of "germ developmental potentiality" which he termed "blastophthoria" or germ corruption.³⁴⁷ He argued that neuropathic diathesis was not caused by a specific mutation or mutations, "but that it is a general impairment of the vitality or the developmental potentiality of those genes which are responsible for the growth of the brain."³⁴⁸ Lasting changes in the germ-plasm could still be caused by harmful environmental influences (with his discussion now updated to include the latest research on X-rays), by chemical contamination (particularly by alcohol and lead), and by the effects of disease (syphilis) and heritage (consanguinity).³⁴⁹ Tredgold suggested that the Mendelian approach to inheritance was often not useful in the case of mental defect because multiple genes—both dominant and recessive—were likely to be involved as causative agents, along with a host of environmental and nutritional factors which might also play supporting roles in causing "the antedating of mental disease insisted upon by many experienced clinicians."³⁵⁰

By this time Tredgold no longer supported the passage of sterilization legislation for the mentally deficient. However, he was not entirely against eugenic legislation on the related issue of allowing marriage among the mentally defective. He hoped that, with proper education, people would choose to make the "correct" eugenic choices:

I see no reason whatever why the marriage of defectives, chronic epileptics, and persons who have suffered from recurrent insanity should not be prohibited by law, and even if this did not avail entirely to check their propagation, it would do something in this direction, and it would certainly be a great factor in the education of public opinion regarding the responsibility of marriage.³⁵¹

³⁴⁶ Tredgold, *Mental Deficiency* (1937), 31-33.

³⁴⁷ Tredgold, *Mental Deficiency* (1937), 33. Blastophthoria was one of the outdated ideas that Penrose warned medical students against during his lectures and that he attacked in his textbooks—he felt that attempts to incite germ line degeneration in a laboratory setting had failed and that it was time that the idea was abandoned. Penrose, *Mental Defect*, (1933), 54-55; Penrose, *Influence*, 16-17; Penrose, "Heredity and Medicine" Lecture at Maudsley in Postgraduate Course, 1936, Penrose Papers, 53/2; Penrose, "Syllabus of proposed course of lectures on Human Genetics", 1936, Penrose Papers, 53/3.

³⁴⁸ Tredgold, *Mental Deficiency* (1937), 34.

³⁴⁹ Tredgold, *Mental Deficiency* (1937), 35-42.

³⁵⁰ Tredgold, *Mental Deficiency* (1937), 44-45.

³⁵¹ Tredgold, *Mental Deficiency* (1937), 523.

This type of legislation prohibiting marriage was already on the books in several European countries and in various American states and Tredgold saw no reason why it should not be adopted in England as well.³⁵² He continued to espouse similar ideas in the second edition of his *Manual of Psychological Medicine: For Practitioners and Students*, published in 1945.³⁵³

Social and Economic Disorders

During the 1930s it was often assumed that there was a strong connection between social and economic “inefficiency” and some sort of physical or mental defect. Often the claim was made that such defects were hereditary. In 1932, during his introduction of Ernest Lidbetter at the Galton dinner, the President of the Eugenics Society, Sir Bernard Mallet, quoted the suggestion of the 1929 Mental Deficiency Committee:

if we could segregate as a separate community all the families in this country containing mental defectives of the primary amentia type, it would be found to include a much larger proportion of insane persons, epileptics, paupers, criminals (especially recidivists), unemployables, habitual slum dwellers, prostitutes, inebriates, and other social inefficients, than would a group of families not containing mental defectives.³⁵⁴

³⁵² Tredgold, *Mental Deficiency* (1937), 523.

³⁵³ Tredgold believed that it was the physician’s duty to correctly advise individuals who may have suffered from mental illness on the advisability of their marrying. In some cases, he felt, they were unlikely to pass along their disease to their offspring and could safely enter marriage and have children. In other cases, such as that of schizophrenia, he felt such a choice would be extremely unwise. He also argued that individuals should have the right to seek sterilization of their own free will, that it should not be not illegal, and that it was the practitioner’s duty to “satisfy himself, if necessary after consultation with an expert, that the risk is real.” Moreover, he advised that it “would also be wise to have a request in writing, and a statement signed by both husband and wife, to the effect that they fully realize the consequences of the operation.” A. F. Tredgold, *Manual of Psychological Medicine: For Practitioners and Students*, 2nd ed., (London: Baillière, Tindall and Cox, 1945, reprinted 1946), 20-23. The historian Mathew Thomson considers the Eugenics Society’s pursuit of legislation on sterilization “a strategic blunder.” He notes that sterilization operations were carried out in Britain throughout this period. Sterilization became legal in Britain in the 1960s, long after the operation had become common. Sterilization of the *non compos mentis*, however, “remained a highly contentious issue.” Thomson, *Problem*, 202-204.

³⁵⁴ During this period it was common to group the mentally defective in two categories. Those with “Primary Amentia” suffered from some inborn disposition towards mental defect or mental illness and they generally fell ill before the age of eighteen. “Secondary Amentia” referred to the condition of those who became mentally deficient from an external source such as illness, injury, or exposure to noxious substances. Anonymous, “The Society’s Further Projects,” *Eugenics Review* 14 (1932): 12; Tredgold, *Mental Defect* (1937) 23-63.

A link between physical or mental defect that ran in families and the tendency of members of such families to require public assistance had been asserted by Lidbetter in his capacity as General Relieving Officer of the Parish of Bethnal Green in London during the first decade of the twentieth century.³⁵⁵ During his collaboration with Nettleship, Lidbetter was introduced to the concept of anticipation, and he seized on this idea as a biological explanation for why some families sank into the pauper class.³⁵⁶

By the time of the publication of his master-work *Heredity and the Social Problem Group* in 1933, Lidbetter's simple pedigree approach to analyzing problems of inheritance had been overtaken by the new Mendelian science and by new mathematical methodologies of genetic analysis.³⁵⁷ Not only had statistical analysis of pedigrees become expected, but there was a new awareness of the impact of diet and environment on physical development.³⁵⁸ Even Leonard Darwin bowed to this new reality in his introduction to *Heredity and the Social Group*. He believed that bettering the economic and social conditions of slum-dwellers

should be welcomed by the eugenicist, not only by reason of the benefits they confer upon the community in general, but also because the more perfect the environment becomes, the more likely it will be that inborn defects would be recognizable as being due to natural inferiority.³⁵⁹

³⁵⁵ Mazumdar, *Eugenics*, 73-77, 144.

³⁵⁶ Nettleship's interest in this family had been in their eye disease and its apparent link to insanity. Lidbetter was interested in the idea that the family illustrated "insanity with destructive eye disease in four generations, with much collateral and associated pauperism." Lidbetter continued to remark on this family in articles in *Eugenics Review* (1932) and in his *Heredity and the Social Problem Group* (1933). E. J. Lidbetter, "The Social Problem Group: As Illustrated by a Series of East London Pedigrees," *Eugenics Review* 14 (1932): 7-12. In their 1943 paper, Maas and Paterson noted, as had Caughey in 1933, that authors who linked myotonic dystrophy with low social standing and intelligence were misinterpreting the evidence. Maas and Paterson noted that, in the case of myotonic dystrophy, "the mental defect and mental enfeeblement are not the result of their low social status, but rather the cause of the progressive descent of certain families in the social scale." Caughey, "Cataract," 66-70; Maas and Paterson, "Genetic," 83.

³⁵⁷ Mazumdar reports on the disputes between Lidbetter and R. A. Fisher over the former's use of simple pedigrees rather than statistical analyses of the same for his evidence. Moreover, she argues that the dissolution of his research programme "shows the crumbling of consensus within the [Eugenics] Society." Mazumdar, *Eugenics*, 131-143.

³⁵⁸ Amongst others, Penrose would rail against the notion of linking poverty and crime with an increased incidence of the birth of children with mental defect. Noting the effect of economics and environment on the intelligence of schoolchildren he argued rather "that mental defect may be to some extent due to criminal parents dwelling 'habitually' in slums." Penrose, *Mental Defect* (1933), 146. On the problem of environmentalism vs. heredity within the Eugenics Society, see Macnicol, "Eugenics," 148.

³⁵⁹ Lidbetter, *Heredity*, 7.

Despite these concerns, Lidbetter offered up his collection of pedigrees in 1933, promising that a further analysis would deal with such thorny questions.³⁶⁰ As it happened the additional volumes promised never saw publication.

“Pedigree No. 1” in *Heredity and the Social Problem Group* was, in fact, of a family that had previously been studied by Mott in *Brain* (1911 and 1913) and by Lidbetter and Nettleship (1913).³⁶¹ Lidbetter continued to affirm the incidence of anticipation within this family, but he recognized that the whole subject of anticipation itself needed additional study.³⁶² He commented on John George Adami’s theory of heredity—which hypothesized that environmental toxins (chemical, physical and bacteriological) could induce changes in the germ plasm which made succeeding generations increasingly sensitive to similar toxins—Lidbetter observed, as he had in 1913, that if this idea proved true, that it might provide an explanation for the findings of anticipation in a variety of disorders.³⁶³

THE QUEST FOR AN EXPLANATION: 1930-1945

The very existence of genetic anticipation, the various explanations for the hereditary effects attributed to it, and the possible social and political uses of the concept were all hotly debated between 1930 and 1945. This was particularly true in relation to the proposed voluntary sterilization legislation. Several groups clearly attempted to use the concept of anticipation to support their opinions, pro and con, on the sterilization dispute. However, membership in these groups was neither clear-cut, nor mutually exclusive. For example, within the Eugenics Society itself, there existed two groups of people both of which *supported* the proposed sterilization legislation, although their members held *opposing* views regarding of the concept of anticipation. The ‘mainstream’ Eugenics

³⁶⁰ Among other issues Lidbetter promised to explain how the analysis of his pedigrees would shed light on “1. Ante-dating, or anticipation, among the insane. ... 2. The necessary connection between public assistance and mental disability in its various forms. 3. The relations between insanity and mental deficiency. 4. The incidence of repetition in chargeability, insanity and other forms of defectiveness.” Lidbetter, *Heredity*, 19.

³⁶¹ Lidbetter, *Heredity*, 25.

³⁶² Lidbetter, *Heredity*, 27.

³⁶³ John George Adami, “A Study in Eugenics: Unto the Third Generation,” *Lancet* 180 no. 4653 (2 November 1912): 1199-1204; E. J. Lidbetter, and E. Nettleship, “On a Pedigree Showing Both Insanity and Complicated Eye Disease: Anticipation of the Mental Disease in Successive Generations,” *Brain* 35 no. 3 (February 1913): 195-221; Lidbetter, *Heredity*, 27. See also chapter two.

Society, at least as represented by the editor of *The Eugenics Review*, believed that anti-sterilization activists were misguided when they used Mott's interpretation of the "Law of Anticipation" to argue against eugenic action and for assuming that Nature would eventually take care of the issue by ending or mending the defective stock. However, Ernest Lidbetter's long-running "pauper pedigree project" (renamed after 1929 a study of the "social problem group") showed that a minority within the Eugenics Society remained in favour of anticipation. Lidbetter continued to call upon anticipation in the belief that it could be used to prove the degeneration of weak family lines and the long-held belief in a link between heredity and poverty.

Statistical and methodological arguments against anticipation were continuously voiced by a disparate group of individuals. Karl Pearson, an older eugenicist favoured the proposed sterilization legislation but was never a member of the Eugenics Society. Arthur Paterson, a young physician and psychiatrist, favoured the legislation and was a member of the Society. Lionel Penrose, a physician with psychiatric training whose interests in genetics and mathematics were influenced by the left-leaning scientific radicals of the period and a Quaker, argued against eugenics and sterilization as well as anticipation on scientific and ethical grounds. This period also saw the first attempt to provide anticipation with a standard Mendelian genetic explanation. Richard Goldschmidt, the only experimental geneticist then to attempt to theoretically explain (rather than explain away) anticipation, used fruit flies as his experimental subjects and formulated his arguments in mathematical Mendelian terms. His ideas were not accepted then, due at least in part to the fact to the novelty, if not idiosyncrasy, of the new terminology he was attempting to create but would have influence in the future. In the meantime, the use of the concept of anticipation was confined to work on individual disorders with which it had come to be associated. While many researchers were content with reporting the presence or absence of anticipation within the pedigrees they examined, others attempted to explain, or explain away, findings of anticipation according to their ability and interests. Years of accumulated clinical observations suggested to some physicians that anticipation was really occurring in certain disorders. Those with training in genetics and statistics, however, were sceptical about the physical reality of anticipation and preferred to believe that its appearance was caused by selection

bias and variable age of onset. The kind of progressive heredity suggested by anticipation could not easily be explained by the mathematical Mendelism that arose in the 1930s, because the theory held that a defective gene which caused disease might be present or absent but could *not* be growing progressively worse over succeeding generations. In 1948, Lionel Penrose ended this impasse by formulating a reinforced argument which proposed that anticipation did not exist offered an explanation for why it seemed to be occurring. It held sway over the disciplines of human and medical genetics for the next 30 years.

Chapter 4: Refuting the Concept of Anticipation (1945-1970)

CREATING A NEW FRAMEWORK

The period following the end of the Second World War was pivotal in the history of understanding anticipation. The scientific communities that had been attempting to prove or disprove the concept of anticipation from 1930 to 1945 quickly came to a consensus on the issue following the publication of Lionel Penrose's crucial paper "The problem of Anticipation in Pedigrees of Dystrophia Myotonica" in 1948.¹ At the same time, the intellectual communities that had previously interested themselves in anticipation were going through upheaval and intellectual foment. The early years of the period saw the unification of Mendelism and Darwinian biology in the work of population and quantitative geneticists who were forging the "Modern Synthesis." The field of genetics itself was fundamentally altered by the discovery that DNA was the genetic material in bacteria (1944) and viruses (1952), followed shortly thereafter by Watson and Crick's 1953 description of the structure of DNA.² The transformation of the discipline culminated in Crick's formulation in 1957 of the "Central Dogma," which elucidated the flow of genetic information as proceeding from DNA to protein.³ Geneticists who pursued unconventional research topics—including Richard Goldschmidt the one Mendelian who in the 1930s had ventured a guess as to the possible biological cause of anticipation—found their notions of heredity reshaped by the discovery of the molecular structure of the gene and by the concomitant rise of quantitative and molecular genetics. With no way to explain anticipation as a genuinely biological phenomenon according to the tenets of the—now dominant—mathematically

¹ Penrose, "The Problem of Anticipation in Pedigrees of Dystrophia Myotonica," *Annals of Eugenics* 14 (1948): 125-132.

² O. T. Avery, C. M. Macleod and M. McCarty, "Studies on the Chemical Transformation of Pneumococcal Types," *Journal of Experimental Medicine* 79 (1944): 137-158; A. D. Hershey, and M. Chase, "Independent Functions of Viral Proteins and Nucleic Acid in Growth of Bacteriophage," *Journal of General Physiology* 36 (1952): 39-56; J. D. Watson, and F. H. C. Crick, "Molecular Structure of Nucleic Acids. A Structure for Deoxyribose Nucleic Acid," *Nature* 171 (1953): 737-738. For an interesting look at the institutional side of Watson and Crick's discovery see Soraya de Chaderevian, *Designs for Life: Molecular Biology after World War II*, (Cambridge: Cambridge University Press, 2002).

³ F. H. C. Crick, "On Protein Synthesis," *The Symposia for the Society of Experimental Biology* 12 (1958): 138-163.

based Mendelian genetics, the newly orthodox forms of classical and quantitative genetics dismissed the issue entirely from the field of legitimate research.⁴

At the same time, in the wake of the Second World War, the fledgling fields of human and medical genetics underwent a period of rapid expansion and professionalization. As part of this process, the views on genetics held by members of this community were brought in line with those of the broader field of genetics. Additionally, many older human and medical geneticists who had once supported eugenics reinvented their vocabulary, if not their ideas, concerning the question of heredity and disease, following revelations of the uses to which eugenics had been put in Nazi Germany. The reconstituted field of human and medical genetics was Anglo-American centred, and the Galton Laboratory played a key role in research and postgraduate training under the direction of Lionel Penrose, who held strong views on the subject of anticipation. The quick integration of Penrose's arguments—that the concept of anticipation was fallacious rather than real—into medical genetics textbooks ensured that the new generation of human and medical geneticists would be inculcated with the idea that anticipation was an experimental artefact rather than a biological reality. Most researchers fairly quickly placed the concept of anticipation on the scrap heap of medical ideas, although there were occasional holdouts, mainly among older clinicians.

The British eugenics community that had previously concerned itself with the study of anticipation—evoked by some to argue against the need for the sterilization of the 'unfit' and by others to support such a policy—was shaken by the realization of the full extent of the Nazi eugenics policies and was never able to resume its campaign for the creation of legislation to allow voluntary sterilization. Moreover, the period of post-war economic expansion and the creation of the modern welfare state in Western Europe and North America undermined several of the social concerns that had once fuelled the interest in eugenics.⁵ Even though eugenics societies continued to exist in the post-war period, their interests turned away from the idea of anticipation. Between 1945 and 1970 mainstream scientific and medical views were turned so soundly against this notion that,

⁴ This disinterest in the concept of anticipation by non-medical geneticists seems to extend even today. See chapter six.

⁵ Pauline Mazumdar, *Eugenics, Human Genetics and Human Failings: The Eugenics Society, its sources and its critics in Britain*, (London: Routledge, 1992), 254-259.

when the first papers appeared suggesting anomalous modes of heredity in Huntington's disease in 1968 and 1969, these findings were interpreted within the analytical framework laid out by Penrose in 1948.

The almost total acceptance of Penrose's dismissal of anticipation following such a long period of controversy might well be deemed to signal the establishment of a paradigm in a Kuhnian sense. In his *Structure of Scientific Revolutions*, Kuhn identified paradigm formation as the creation of a consensus among scientists. The period of dispute before one concept is agreed upon is pre-paradigmatic. Following the creation of the paradigm scientists return to carrying out their experiments and return to a period of "normal science" until an anomaly arises that threatens to upset the current paradigm.⁶ While Kuhnian theory has fallen out of favour among many historians of science, the concept continues to be well accepted by some scientists and members of the general public.⁷ Indeed, the quick reversal in thinking concerning anticipation after the sequencing of genes involved in Fragile X, myotonic dystrophy, and Huntington's disease has been explicitly referred to as a paradigm shift.⁸ Within such a context, Penrose's 1948 paper can be seen as laying the groundwork for a paradigm which provided a basis for the period of "normal science" that occurred until the "revolution" of 1991-1992 which established a new paradigm concerning the concept of anticipation.

A PERIOD OF SCIENTIFIC AND INSTITUTIONAL CHANGE: 1945-1970

Between 1945 and 1970 the fields of genetics, human, medical, and clinical genetics, underwent a period of consolidation and expansion while at the same time the field of eugenics, which had previously had significant membership overlap with the medical and scientific community, was undergoing a period of eclipse and decline. This section will

⁶ Thomas S. Kuhn, *The Structure of Scientific Revolutions*, 2nd ed., enlarged, (Chicago: University of Chicago Press, 1970).

⁷ Several human geneticists use Kuhnian analysis, or some variation thereof in their historical narratives. See for example: Krishna Dronamraju, *The Foundations of Human Genetics*, (Springfield IL: Charles C Thomas, 1989); and F. Vogel and A. G. Motulsky, *Human Genetics: Problems and Approaches*. 3rd ed., (Berlin: Springer, 1997), 11-23. For a similar discussion in a non-scientific context see Anonymous, "Bittersweet anticipation: the logistics of inheritance," *Art & Research: A Journal of ideas, contexts, and methods* 1 no. 1 (Winter 2006/7), retrieved April 2, 2007, from <http://www.artandresearch.org.uk/v1n1/donachie.html>.

⁸ Anonymous, "Bittersweet anticipation." For more on the Kuhnian analysis of the history of anticipation and the discovery of trinucleotide repeats, see the discussion in chapter six.

offer a brief overview of developments in these fields with emphasis on how these changes affected the reception of anticipation by these communities.

Developments in Genetics: 1945-1970

As the historian Jan Sapp noted in 1987, three major developments in the field of genetics—Mendelian-chromosome theory, population genetics and the evolutionary synthesis, and the rise of DNA theory—have been extensively studied for this period while other aspects of the history of genetics have been ignored.⁹ Over the last two decades, scholars have added significantly to further our understanding of developments within genetics, but some areas remain to be explored—including the reception of the concept of anticipation. The late 1940s saw the completion of the synthesis of Darwinian evolutionary theory and Mendelism due to the work of the qualitative and population geneticists.¹⁰ The field of genetics underwent an explosive period of growth and development between 1945 and 1970. This was due in large part to the discovery of the molecular nature of the genetic material in bacteria (1944) and viruses (1952) which was followed shortly thereafter by the discovery of the structure of DNA (1953) and the creation of the “Central Dogma” (1957) which explained how the transfer of genetic information from DNA to protein took place.¹¹ These discoveries, and the elaboration of experimental systems in which they were made, fundamentally changed the field and ushered in an increasingly mechanistic and quantitative understanding of heredity.¹² The

⁹ Jan Sapp, *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*, (New York: Oxford University Press, 1987), xi.

¹⁰ See also chapter three. Peter Bowler, *Evolution: The History of an Idea*, 3rd ed., (Berkeley: University of California Press, 2003), 325-346.; Ernst Mayr, “Prologue: Some Thoughts on the History of the Evolutionary Synthesis,” in *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, Ernst Mayr and William Provine eds., (Cambridge MA: Harvard University Press, 1980), 1, 28-32, 39-44; William Provine, “England: Introduction,” in *The Evolutionary Synthesis: Perspectives on the Unification of Biology*, Ernst Mayr and William Provine eds., (Cambridge MA: Harvard University Press, 1980), 329-334; Robert Reid, *Biological Emergences: Evolution by Natural Experiment* (Cambridge MA: MIT Press, 2007), 38-65, Sapp, *Beyond the Gene*, xii-xiii.

¹¹ Avery, Macleod and McCarty, “Chemical Transformation,” 137-158; Hershey and Chase, “Bacteriophage,” 39-56; Watson and Crick, “Deoxyribose Nucleic Acid,” 737-738; Watson, and Crick., “Genetical Implications,” 964-967; Crick, “On Protein Synthesis,” 138-163.

¹² Because of the importance of the role of DNA in the study of genetics, many histories of genetics concentrate their narrative on the discovery of DNA and its uses. See for example: Elof Axel Carlson, *The Gene: A Critical History*, (Philadelphia: W. B. Saunders, 1966); Donald Chambers, ed., “DNA: The Double Helix: Perspective and Prospective at Forty Years,” *Annals of the New York Academy of Sciences* 758 (1995); Horace Freeland Judson, *The Eighth Day of Creation: Makers of the Revolution in Biology*, Expanded edition, (Planesview NY: Cold Spring Harbor Laboratory Press, 1996); Maxim Frank-

institutional expansion was aided by increased government funding and by directed funding from private organizations, such as the Rockefeller Foundation, which supported this new quantifiable approach to genetics.¹³ Research that did not fit into this model was marginalized.¹⁴

Richard Goldschmidt, who had been the only geneticist to examine the question of anticipation, reinterpreted his findings in light of this new reality. By the time that he wrote his 1952 textbook on genetics, he had given up attempting to get his personal terminology of dominigenes accepted and discussed his findings in terms of genetic modifiers instead.¹⁵ Anticipation was not mentioned, nor was the importance of modifying genes in human diseases such as myotonic dystrophy; but he noted the effect of modifying genes on fruit fly wings and mouse coat colour.¹⁶ As unexplainable according to the Mendelian mode of inheritance and without a working animal model, anticipation had never been of much interest to the field of genetics. From this time until the discovery of the molecular mechanism behind anticipation in the early 1990s, the concept of anticipation would be ignored by geneticists.

Kamenetskii, *Unravelling DNA: The Most Important Molecule of Life*, (Reading, MA: Addison-Wesley, 1997); Lily Kay, *Who Wrote the Book of Life? A History of the Genetic Code*, (Stanford CA: Stanford University Press, 2000); Evelyn Fox Keller, *The Century of the Gene*, (Cambridge, MA: Harvard University Press, 2000); Robert Olby, *The Path to the Double Helix: The Discovery of DNA*, (New York: Dover Publications, Inc., 1994); Franklin Portugal and Jack S. Cohen, *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*, (Cambridge MA: MIT Press, 1977); A. H. Sturtevant, *A History of Genetics*, introduction by Edward B. Lewis, (Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2001); N. A. Tiley, *Discovering DNA: Meditations of Genetics and a History of Science*, (New York: Van Nostrand Reinhold Company, 1983); Bruce Wallace, *The Search for the Gene*, (Ithaca: Cornell University Press, 1992). The subject of anticipation is not covered in these historical studies. A recent history of British molecular biology in the post-war period by Soraya de Chadarevian likewise concentrates on the impact of these important discoveries. Soraya de Chadarevian, *Designs for Life: Molecular Biology after World War II*, (Cambridge: Cambridge University Press, 2002).

¹³ Pnina Abir-Am, "The Rockefeller Foundation and the rise of molecular biology," *Nature Reviews Molecular Cell Biology* 3 (January 2002): 65-70; Chadarevian, *Designs for Life*, 199-235, 300-335; Lily Kay, *The Molecular Vision of Life*, (New York: Oxford University Press, 1993), 217-242; Daniel Kevles and Gerald L. Geison, "The Experimental Life Sciences in the Twentieth Century," *Osiris* 10 (1995): 97-121.

¹⁴ Sapp, *Beyond the Gene*; Jan Sapp, *Where the Truth Lies: Franz Moewus and the Origins of Molecular Biology*, (Cambridge: Cambridge University Press, 1990).

¹⁵ As mentioned in chapter three, Goldschmidt's term 'dominigenes' was obscure. It appears most likely that he was referring to the action of modifying genes on a mutant gene. However, he may have been referring to modifiers at the same locus (allelic variations) or to genes at different loci that acted to modify the disease gene. Richard Goldschmidt, *Understanding Heredity: An Introduction to Genetics*, (New York: John Wiley & Sons, 1952), 172-173.

¹⁶ Goldschmidt, *Understanding Heredity*, 173.

Developments in Human, Medical and Clinical Genetics: 1945-1970

After 1945 the fields of human, medical, and clinical genetics¹⁷ underwent marked expansion and institutionalization in the English-speaking world.¹⁸ The post-war educational expansion saw the creation of new departments of human genetics in a variety of institutions, and these benefited from directed funding provided by government and foundations.¹⁹ As the historian Daniel Kevles has noted, these fields developed from a small but influential nucleus dominated by Anglo-American researchers.²⁰

In the United States the professionalization of the human genetics community is generally said to date from the establishment of the American Society of Human Genetics in 1948 and its affiliated journal the *American Journal of Human Genetics* in 1949.²¹

¹⁷ Between 1945 and 1970 there were no hard and fast barriers between the fields of human, medical, and clinical genetics. Some individuals worked in two or more areas. For the purposes of this study human genetics was engaged with the more theoretical understanding of the genetics of humans while medical genetics examined heredity specifically in human disease and was concerned with its clinical manifestations. Clinical genetics generally refers to the activities of those engaged in genetic counselling and should not be confused with specialist clinicians like neurologists or ophthalmologists interested in hereditary diseases.

¹⁸ Recent studies of the history and professionalization of the fields of human and medical genetics in Canada and the United Kingdom have been carried out by Fiona Miller and William Leeming. William Leeming, "Medical Specialization and Medical Genetics in Canada (1947 and After)," Ph.D. thesis, York University, 1999; William Leeming, "Professionalization theory, medical specialists and the concept of 'national patterns of specialization,'" *Studies of Science* 40 no. 3 (2001): 455-485; William Leeming, "The Early History of Medical Genetics in Canada," *Social History of Medicine* 17 no. 3 (2004): 481-500; William Leeming, "Ideas about heredity, genetics, and 'medical genetics' in Britain, 1900-1982," *Studies in the History and Philosophy of Biological Biological and Biomedical Sciences* 36 (2005): 538-558; Fiona Alice Miller, "A Blueprint for Defining Health: Making Medical Genetics in Canada, c. 1935-1975," Ph.D. thesis, York University, 2000; Fiona Miller, "The importance of being marginal: Norma Ford Walker and a Canadian school of medical genetics," *American Journal of Medical Genetics* 115 no. 2 (2002): 102-110.

¹⁹ Diane Paul and Daniel Kevles have both observed that the institutional funding that supported the new human genetics in the United States "had eugenic motivations." Diane Paul, "Eugenic Origins of Medical Genetics," In *The Politics of Heredity: Essays on Eugenics, Biomedicine, and the Nature-Nurture Debate*, (Albany, NY: State University of New York Press, 1988), 137; Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity*, (Cambridge Mass.: Harvard University Press, 1995), 208-209, 252-254. The Rockefeller Foundation provided significant funding to European genetics institutes, including the Galton Laboratory, which will be discussed below. On the importance of Rockefeller Foundation funding in the development of the Institute of Human Genetics in Switzerland see, David Klein, "Living History—Autobiography: Genetics and Environment From a Personal Perspective," *American Journal of Medical Genetics* 37 no. 3 (November 1990): 325-329.

²⁰ Kevles, *Eugenics*, 205.

²¹ As noted in chapter three, recent historical research is pushing back the origins of the field of human and medical genetics to the inter-war period. However, institutional histories generally date the point of origin of the field to the formation of the American Society of Human Genetics. See for example: Laurence Snyder, "Old and New Pathways in Human Genetics," *American Journal of Human Genetics* 3 no. 1 (March 1951): 2; L. C. Dunn, "Cross Currents in the History of Human Genetics," *American Journal of Human Genetics* 14 (1962): 1-4; James Neel, "The 'Recovery' of Human Genetics," in *The History & Development of Human Genetics: Progress in Different Countries*, Washington DC, 6 October 1991, ed.,

The geneticist H. J. Muller was elected the first president of the American Society of Human Genetics. During his presidential address Muller warned his colleagues of “errors to be avoided” and urged researchers to separate themselves and their work from the discredited science of eugenics.²² From the beginning, the *American Journal of Human Genetics* worked towards creating a cohesive bibliography on human genetics and a survey of recent literature was published with every issue.²³

In 1945, Lionel Penrose returned to Britain from Canada to take up the post of head of the Galton Laboratory. J. B. S. Haldane—one of the most important British geneticists and who recommended him for the post—called Penrose “the greatest living authority on human genetics.”²⁴ Under Penrose’s leadership, the Galton would continue to turn away from eugenics and towards human genetics; as he informed one of his contacts at the Rockefeller Foundation in 1946, “we are now mainly interested in specific problems of human heredity rather than in the general question of eugenics.”²⁵ The quality of the genetic work done at the Galton was recognised by the Rockefeller Foundation which provided Penrose with repeated operating grants between 1945 and his retirement in 1965.²⁶ As the historian Daniel Kevles noted, during Penrose’s tenure “the

Krishna Dronamraju, (Singapore: World Scientific, 1992), 6-10; E. A. Carlson, “H. J. Muller and human genetics,” in *The History & Development of Human Genetics: Progress in Different Countries*, Washington DC, 6 October 1991, Krishna Dronamraju, ed., (Singapore: World Scientific, 1992), 21-47.

²² H. J. Muller, “Progress and Prospects in Human Genetics,” *American Journal of Human Genetics* 1 no. 1 (September 1949): 1-18.

²³ See for example, Anonymous, “Bibliography of Human Genetics,” *American Journal of Human Genetics* 1 no. 1 (September 1949): 105-112.

²⁴ J. B. S. Haldane to E. S. Pearson, 27 March 1944, Penrose Papers, 49/1; J. B. S. Haldane to Provost University College London, 9 August 1944, Penrose Papers, 49/1. Quotation from Kevles, *Eugenics*, 152.

²⁵ Penrose to Morison, 3 May 1946, folder 223, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC;

²⁶ On the recognition that research at the Galton was worth funding by the Rockefeller Foundation see: D. P. O’Brien to Warren Weaver, 20 June 1946, folder 223, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC.

On grants given to the Galton under Penrose see: Funding Motion RF 46085, 21 June 1946, folder 222, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, Rockefeller Archive Center, Sleepy Hollow, New York (hereafter designated RAC); Funding Motion RF 50315, 22 September 1950, folder 220, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Funding Motion RF 55078, 20 May 1955, folder 222, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Funding Motion RF 60160, 23 September 1960, folder 222, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC. On correspondence between Penrose and Rockefeller Foundation officers concerning grants see: Robert S. Morison to L. S. Penrose, 4 April 1946, folder 223, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Penrose to Morison, 3 May 1946, folder 223, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; R. R. Struthers to A. Gregg, 1 December 1950, folder 224, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Penrose to Struthers, 13 December 1949, folder 224, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Penrose to Gregg, 5 May

Galton was a mecca for aspiring human geneticists” from around the world and individuals trained there would go on to play a significant role in the field.²⁷ Between 1945 and 1970, Penrose published several textbooks on the topics of human genetics and mental defect in which he advocated the adoption of the newest forms of scientific research and decried eugenics and the uses to which it had been put.²⁸

As discussed in chapter three, prior to the 1940s a North American survey had shown that only one institution had included medical genetics in its medical curriculum; by 1953 that number had risen to 55 percent.²⁹ The number of medical geneticists did not reach significant levels until the 1960s, when the human geneticists began to fear that the field would be swamped by their medical colleagues.³⁰ Compared to human genetics, medical genetics appears, in the United States at least, to have gotten off to a somewhat

1949, folder 224, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; Penrose to Maier, 4 January 1955, folder 227, box 14, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC. For remarks made by Rockefeller Foundation officers on their visits to the Galton see: Alan Gregg officer’s diary, 13 October 1949, RG 1.1, Rockefeller Foundation Archives, RAC; R. R. Struthers Interview with L. S. Penrose, 3 May, 1950, folder 224, box 16, series 401a, RG 1.1, Rockefeller Foundation Archives, RAC; R. R. Struthers officer’s diary, 13 October 1949, RG 1.1 Rockefeller Foundation Archives, RAC. On the importance of Rockefeller Foundation funding to the development of the field of molecular biology see, Abir-Am, “Rockefeller Foundation and molecular biology,” 65-70.

²⁷ Kevles, *Eugenics*, 222. On the important role that research schools can play in the development of a scientific field see Gerald Geison, “Scientific Change, Emerging Specialties, and Research Schools,” *History of Science* 19 no. 1 (March 1981): 20-40.

²⁸ Penrose’s textbooks will be discussed in detail below.

²⁹ For a contemporary account of the slow but steady progress in introducing medical genetics into the medical school curriculum in America see, C. Nash Herndon, “Genetics in the Medical School Curriculum,” *American Journal of Human Genetics* 8 no. 1 (March 1956): 1-7. For historical accounts see, Nathaniel Comfort, “‘Polyhybrid Heterogeneous Bastards’: Promoting Medical Genetics in America in the 1930s and 1940s,” *Journal of the History of Medicine and Allied Sciences* 61 no. 4 (2006): 432-441; Angus McLaren, *Our Own Master Race: Eugenics in Canada, 1885-1945*, (Toronto: Oxford University Press, 1990), 128-145; Hubert Soltan, “Madge Macklin,” In *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*, ed., H. C. Soltan, (London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992), 11-26.

³⁰ In 1948, the membership of the American Human Genetics Society was made up of 25% medical professionals and the motion put forward to name the Society’s journal the *American Journal of Medical Genetics* was defeated. By 1968 the Society was made up of almost equal numbers of medical and non-medical members and complaints were being voiced that the field was becoming increasingly medicalized. The shift in textbook titles during the 1990s towards medical rather than human genetics may represent the results of the increase in the number of physicians interested in genetics or the result of increased funding for medicine over pure research. Of course, the term medical genetics currently appears to be undergoing a shift in the early twenty-first century towards the (perhaps still overly hopeful) term, genetic medicine. Victor McKusick, “The Growth and Development of Human Genetics as a Clinical Discipline,” *American Journal of Human Genetics* 27 (1975): 270; J. M. Opitz, “The American Journal of Medical Genetics—Forward,” *American Journal of Medical Genetics* 1 no. 1 (1977): 1-2.

slow start in terms of professionalization.³¹ The *American Journal of Medical Genetics* did not begin publication until 1977.³² In Britain, Lionel Penrose personally lectured physicians and medical students on the subject of eugenics and human genetics from the late 1940s. In a series of lectures given after 1948, Penrose argued that it was time for old modes of medical thinking—including eugenics as a whole and the concept of anticipation in particular—to be discarded in favour of the new (and more correct) science of human genetics. He cautioned his audiences to be most careful when engaging in genetic counselling.³³ Penrose was not alone in advocating the adoption of more modern methods in medical genetics and his early advocacy was continued by others. An extensive review of genetics in medicine by C. A. Clarke and his colleagues which urged physicians to avoid traditional pitfalls and adopt the latest scientific methods for their research was published in the *Quarterly Journal of Medicine* in 1968.³⁴

The field of clinical genetics was essentially concerned with the question of providing family planning advice and genetic screening. Victor McKusick has variously dated the point of origin of this field to the discovery of the correct number of human chromosomes in 1956 and to the discoveries of chromosome multiplication disorders in

³¹ The move towards professionalization appears to have gone more swiftly in Canada, perhaps because research institutions were confined to a few geographic areas. In fact, Hubert Soltan argues that medical genetics was the “strongest branch” of genetics in Canada. According to Soltan, a small group of pioneers introduced medical students to genetics which became widespread in the 1950s and 1960s culminating in the development of a professional accreditation and governing body in the Canadian College of Medical Genetics in 1975. H. C. Soltan, “The early history and development of human and medical genetics in Canada,” In *The History & Development of Human Genetics: Progress in Different Countries*, Washington DC, 6 October 1991, Krishna Dronamraju, ed., (Singapore: World Scientific, 1992), 57-82 and also H. C. Soltan, ed., *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*, (London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992).

³² Interestingly, the editor of the journal, J. M. Opitz, remarked in his inaugural introduction that the journal was intended to serve the publication needs of medical geneticists not clinical geneticists who were seen as being part of a separate field. Opitz, “Forward,” 2.

³³ See for example, B.M.A. Lecture – Eastbourne ; 24th October 1962 “Eugenics” Penrose Papers, 77/2; Lecture to the Harvey Society “The Futility of Eugenics” 11 February 1963, Penrose Papers, 77/2; “From Eugenics to Human Genetics – Lunch hour lecture, Thursday, 4th March [1965]” Penrose Papers, 77/2; English transcript of Penrose’s paper which was given in German at Forum Philippinum 1969: Vorschlag für das endgültige Programm. Penrose spoke 5 November 1969. Penrose papers, 103.

³⁴ Clarke and his colleagues agreed with Penrose that anticipation was likely to be the result of several sources of bias and adopted his iso-allele hypothesis as the cause of the variation in age of onset that contributed to findings of anticipation. This journal article was later followed up by a textbook on medical genetics that will be discussed below. C. A. Clarke, D. A. Price Evans, R. Harris, R. B. McConnell, and J. C. Woodrow, “Genetics in Medicine: A Review,” *Quarterly Journal of Medicine* 37 no. 145 (January 1968): 1-61.

1959.³⁵ No genetic markers had yet been discovered that would allow clinical geneticists to diagnose whether an individual was carrying the defective gene for Huntington's disease or myotonic dystrophy. These discoveries were not made until the 1970s and 1980s.

Developments in Eugenics: 1945-1970

As researchers and the public realized the uses the Nazis made of eugenics there were negative implications for eugenics movements elsewhere that affected the movement's institutions, research programmes, and membership. In the United States, attention to the Eugenics Record Office's role as an agent for Nazi propaganda, as well as scientific critiques of their methodologies, led the Carnegie Foundation to withdraw funding. The ERO consequently closed on 31 December 1939.³⁶ However, the American Eugenics Society continued to function for some years, and, despite a decrease in general membership in the post-war years, the president of the Society continued to attract scientists to the its board.³⁷ The British Eugenics Society also found its programmes—particularly the advocacy of voluntary sterilization legislation—coming under attack due to comparisons with the punitive eugenic legislation implemented by the Nazis.³⁸ In the post-war period the Eugenics Society, under the leadership of C. P. Blacker, had initially hoped to restart its programme of eugenic research and education which had been halted due to the war, but it was unable to gain any significant support.³⁹ Under Blacker's leadership the Eugenics Society had turned its focus more towards “positive” rather than

³⁵ McKusick, “Growth and Development,” 261; Victor McKusick, “History of medical genetics,” In *Emery and Rimoin's Principles and Practice of Medical Genetics*, Vol. 1, 4th ed., Eds., David Rimoin, J. Michael Connor, Reed Pyeritz, and Bruce Korf, (Edinburgh: Churchill Livingstone, 2002), 3-36.

³⁶ Garland E. Allan, “The Eugenics Record Office at Cold Spring Harbor, 1910-1940: An Essay in Institutional History,” *Osiris* 2 (1986): 250-254; David Micklos and Elof Carlson, “Engineering American society: the lesson of eugenics,” *Nature Review Genetics* 1 (November 2000): 156-157.

³⁷ Diane Paul, “From Eugenics to Human Genetics,” In *Controlling Human Heredity: 1865 to the Present*, (Atlantic Highlands NJ: Humanities Press International, 1995), 125.

³⁸ J.B.S. Haldane was among the Eugenics Society's most outspoken critics. In 1946, his articles in the *Daily Worker* decrying the eugenics movement came in for sharp criticism by the editor of the *Eugenics Review*. Nevertheless, the Eugenics Society did not seriously attempt to revive the voluntary sterilization campaign after the Second World War. Anonymous, “Notes of the Quarter,” *Eugenics Review* 38 no. 3 (October 1946): 111-115; C. P. Blacker, “Voluntary Sterilization: The Last Sixty Years,” *Eugenics Review* 54 no.1 (April 1962), 9-23; J. B. S. Haldane, “Eugenics: We need to know a great deal more about human heredity,” *Daily Worker*, Tuesday, June 4, 1946, page 2.

³⁹ C. P. Blacker, *Eugenics in Retrospect and Prospect: The Galton Lecture, 1945*, 2d ed., (London: The Eugenics Society and Cassell and Company Ltd., 1950), 28-38.

“negative” eugenics, and in 1946 turned its propaganda programme towards issues of positive eugenics and birth control advocacy.⁴⁰ The study of poor families that comprised what had been known from 1929 as the “social problem group” was re-named once more the “problem families group” but, despite investing further time and funds in research, the Eugenics Society could find no scientific evidence to support the contention that social inefficiency was hereditary.⁴¹ The question of the inheritance of mental deficiency, which had so engaged the Eugenics Society before the war fell by the wayside after 1945.

The historian Pauline Mazumdar argues that the combination of Penrose’s professional opinion on the question of the inheritance of mental deficiency and the institutional reconstruction brought about by the development of the Welfare State weakened the eugenics problematic.⁴² On the other hand, the historian Mathew Thomson noted that eugenicists—and particularly C. P. Blacker—played an active role in the planning the new postwar mental health service of the Welfare State.⁴³ Blacker and his colleagues viewed the creation in 1948 of the new National Health Service as part of a process of national consolidation that concomitantly undermined the position of the Board of Control (which had previously overseen the care and control of the mentally deficient) and served to marginalize mental health services and the care of the mentally defective as one very small branch of the NHS.⁴⁴ After the Second World War membership in the Eugenics Society began to decline, and by 1957 the Society began the process of changing into a charitable trust in order to continue to fund and support

⁴⁰ See for example, C. P. Blacker, “Positive Eugenics: A Proposal,” *Eugenics Review* 38 no. 1 (April 1946): 25-26; Mazumdar, *Eugenics*, 246-247; Anonymous, “Notes of the Quarter,” *Eugenics Review* 38 no. 4 (January 1947): 163-167; Schenk and Parkes, “Activities,” 155-156.

⁴¹ Ernest Lidbetter was no longer involved with the Problem Families Committee as it was reconstituted in 1947. Without Lidbetter’s support, the idea of anticipation faded from view. Mazumdar, *Eugenics*, 247-250; Faith Schenk and A. S. Parkes, “The Activities of the Eugenics Society,” *Eugenics Review* 60 (1968): 158.

⁴² Mazumdar, *Eugenics*, 250-252.

⁴³ Thomson also noted that the revelations of Nazi eugenic policies spurred on criticisms of the treatment of the mentally deficient and coincided with a rise in libertarian concerns about the exploitation of patients within the colony system but notes that eugenic concerns regarding the eugenic, social, and moral dangers posed by the so-called defectives were still alive and well during this same period. Mathew Thomson, *The Problem of Mental Deficiency: Eugenics, Democracy, and Social Policy in Britain c. 1870-1959*, (Oxford: Clarendon Press, 1998), 279-281.

⁴⁴ Thomson, *Mental Deficiency*, 282-293.

eugenic research projects.⁴⁵ The “education” efforts of the Eugenics Society ceased in 1989; it changed its name and retreated from the field of human heredity.⁴⁶

Assessing the scientific response to eugenics in the period between 1945 and 1970 is somewhat complex: the uses to which eugenics had been put by the Nazis were roundly condemned, but the idea of using eugenics “correctly” within a medical setting remained in play. Although scientists may have temporarily avoided the term in the years immediately following the Second World War, they did not completely disavow it.⁴⁷ Rather, eugenic concepts were transformed to suit the new post-war reality.⁴⁸

During his 1949 Presidential Address for example, H. J. Muller urged the adoption of a term other than eugenics to the American Society of Human Genetics.⁴⁹ The new field of genetic counselling in particular remained relatively close to its eugenic roots, although the emphasis came to be placed more on an individual’s privately making the “right” decision rather than on the application of public or legislative force to issues of birth control, sterilization, and selective abortion.⁵⁰ In other words, *pace* Mazumdar, very few human geneticists actively disavowed eugenics in the period immediately following the Second World War.⁵¹

In Britain, Lionel Penrose proved to be a powerful critic of the eugenics movement.⁵² In his inaugural lecture as Galton Chair, Penrose used the example of the

⁴⁵ The Galton Foundation, formed in 1968, was intended to act autonomously of the Eugenics Society and to provide funding for research and education. Money for this fund was drawn in large part from a memorial fund established by the reproductive endocrinologist Alan Parkes FRS in honour of his father and brother (E. T. Parkes and R. Parkes). Alan Parkes ran the Galton Foundation and was the Executive Editor of the journal that it sponsored (the *Journal of Biosocial Science* which succeeded the *Eugenics Review* in 1969). In 1987 the Galton Foundation was renamed the Parkes Foundation. Schenk and Parkes, “Activities,” *Eugenics Review* 60 (1968): 154-156, 157; Christopher Polge, “Sir Alan Sterling Parkes. 10 September 1900 – 17 July 1990,” *Biographical Memoirs of Fellows of the Royal Society* 52 (December 2006): 278-279.

⁴⁶ Mazumdar, *Eugenics*, 257.

⁴⁷ The historian Diane Paul notes that, with only two exceptions, most of those scientists educated before the Second World War continued to advocate some form of eugenics afterwards. Paul, “Eugenic Origins,” 135, 141. On the other hand, Elof Axel Carlson, one of H. J. Muller’s students, emphasises the distance that had arisen between American geneticists and the country’s eugenics movement in the years before the Second World War. Carlson, *The Unfit*, 337-352.

⁴⁸ Paul singles out James Neel in America and Lionel Penrose in Britain as the most significant critics of eugenics in the post-war period. Paul, “Eugenic Origins,” 138.

⁴⁹ H. J. Muller, “Our Load of Mutations,” *American Journal of Human Genetics* 2 (1950): 111-176.

⁵⁰ Paul, “From Eugenics,” 125-129.

⁵¹ Paul, “Eugenic Origins,” 135, 141.

⁵² See for example, Watt, “Part One,” 137-151; Watt, “Part Two,” 339-151. Penrose’s criticisms of eugenics dated back to the 1930s and continued after his retirement from the Galton Chair in 1965. For an

autosomal recessive condition phenylketonuria (PKU) to explain how sterilization of the affected individuals in one generation could have absolutely no impact on the number of affected individuals born in the next—except under a programme that undertook to sterilize all the carriers, estimated at a full one percent of the population—an act that Penrose declared “only a lunatic would advocate.”⁵³ He concluded that until the understanding of mental defect as a whole could be as well understood as phenylketonuria, “eugenic prognosis in the field of mental illness will remain, in most instances, a surmise based upon personal bias rather than scientific judgement.”⁵⁴ Such a harsh attack did not go un-answered, and C. P. Blacker defended the motives and actions of the Eugenics Society in an editorial published in the “Notes of the Quarter” in the *Eugenics Review*.⁵⁵ As discussed above, Penrose was playing a pivotal role at this time in transforming the Galton Laboratory from a centre for eugenic research to a centre of the new human genetics. Under his editorship the subtitle of the *Annals of Eugenics*, previously ‘a journal devoted to the genetic study of human populations’, was changed to ‘a journal of human genetics.’ The title was again eventually changed to *Annals of Human Genetics* in 1954.⁵⁶ In 1963, and after much effort, Penrose finally succeeded in having the very name of his Galton Chair itself changed from the Chair of Eugenics to the Chair of Human Genetics.⁵⁷

example of another direct confrontation between Penrose and the Eugenics Society see, L. S. Penrose, “Introduction,” in *Biological Aspects of Social Problems: A Symposium held by the Eugenics Society in October 1964*, J. E. Meade and A. S. Parkes, eds., (Edinburgh: Oliver & Boyd, 1965), 111-113.

⁵³ Phenylketonuria (PKU) is an autosomal recessive disease in which an individual is unable to metabolize the amino acid phenylalanine. This blockage in the metabolic pathway between phenylalanine and tyrosine leads to a range of symptoms including seizures and mental retardation. Damage can be avoided if a child with the disorder is diagnosed very early in life and fed a diet low in phenylalanine. Individuals carrying the gene for PKU appear normal and, in 1946, were undetectable members of the population. Since those affected by PKU were institutionalized and unlikely to procreate their sterilization would have absolutely no effect on the number of individuals born with PKU in the following generation. All affected children were born to apparently normal parents, who might have no idea that they carried the defective gene, and who had only a 25% chance of having a child with PKU in any given pregnancy. Lionel Penrose, “Phenylketonuria: A Problem in Eugenics,” *Lancet* 247 no. 6409 (29 June 1946): 949-951.

⁵⁴ Penrose, “Phenylketonuria,” 953.

⁵⁵ C. P. Blacker, “Notes of the Quarter,” *Eugenics Review* 38 no. 3 (October 1946): 115-117.

⁵⁶ Harry Harris, “Lionel Sharples Penrose 1898-1972 Elected F.R.S. 1953,” *Biographical Memoirs of Fellows of the Royal Society* 19 (1973): 538.

⁵⁷ When Penrose was hired as the Galton Chair in 1945, J. B. S. Haldane was the head of the Department of Eugenics and Biometry at University College. Penrose became head of the consolidated department of Eugenics Biometry and Genetics in 1957. He never liked the term “eugenics” in his title, so he had “The Galton Laboratory, University College” printed on his letterhead until 1963, when the chair changed to the Galton Professorship of Human Genetics. Harris, “Lionel Sharples Penrose,” 537-538.

By the 1960s, eugenics organizations in both Britain and America had bowed to both external and internal pressures and removed “eugenics” from the title of their periodical publications.⁵⁸ In 1968, *Eugenics Quarterly*, the journal of the American Eugenics Society, was renamed *Social Biology* and the British Eugenics Society retired its journal the *Eugenics Review* after its Jubilee volume, replacing it with the *Journal of Biosocial Science*. As the historian Diane Paul has noted, by the 1960s “eugenics” had become “a term of opprobrium among scientists.”⁵⁹ The term remains tainted into the early years of the twenty-first century.

ANTICIPATION IN THE SCIENTIFIC AND MEDICAL LITERATURE 1945-1948

Before the publication of Penrose’s influential 1948 paper on anticipation, the concept was treated in various ways by authors of human and medical genetics textbooks, by Penrose himself as he developed his theoretical approach to anticipation, and by a series of researchers who examined the possibility of anticipation in myotonic dystrophy. Let us consider these varied treatments individually before examining Penrose’s groundbreaking paper.

Human, Medical, and Clinical Genetics Textbooks: 1945-1948

In 1946 the Canadian-born botanist, geneticist, and anthropologist Reginald Ruggles Gates published a two-volume textbook titled *Human Genetics*.⁶⁰ The scope of this work was encyclopaedic, beginning with an introduction to human genetics and then progressing on to descriptions of a wide range of human illnesses.⁶¹ Gates included a discussion of anticipation in his chapter on “General Principles of Heredity in Man.”⁶² He generally referred to the idea explicitly as “anticipation” and began his discussion

⁵⁸ Paul, “From Eugenics,” 125.

⁵⁹ Paul, “From Eugenics,” 124.

⁶⁰ Gates’ anthropological research expressed contemporary racist and eugenic ideas although later in his career he became more concerned with the nature of racial differences rather than questions of racial superiority. J. A. Fraser Roberts, “Reginald Ruggles Gates. 1882-1962,” *Biographical Memoirs of Fellows of the Royal Society* 10 (November 1964): 83-106.

⁶¹ Reginald Ruggles Gates, *Human Genetics*, Vol. 1, (New York: The Macmillan Company, 1946).

⁶² Gates reviewed both the work of those who rejected anticipation—with whom he generally agreed (Davenport, 1916), and those who thought more favourably of anticipation and similar concepts including Nettleship (1909), Pieraccini (1901, 1932), and Macklin (1932). He mentioned Goldschmidt’s proposed hypothesis explaining anticipation, but accepted that later work by Waddington (1940) showed Goldschmidt’s wing mutation hypothesis to be incorrect. Gates, *Human Genetics*, Vol. 1, 6-49.

with the comment that “its existence has frequently been denied and in some cases it can be explained as a false statistical result arising from the fact that only those in whom it arises at a later age will live to reproduce,” but he also recognised that this was “probably not the whole explanation.”⁶³ Only in the case where “*all* affected individuals” in successive generations had a reduced age of onset over the previous generation, wrote Gates, could anticipation be firmly said to be occurring.⁶⁴ Should this be the case, he noted “there exists at present no biological explanation for it.”⁶⁵ Gates discussed the appearance of anticipation in a variety of diseases including cataract,⁶⁶ glaucoma,⁶⁷ deafness co-inherited in a pedigree with Huntington’s⁶⁸ (but strangely not in the case of Huntington’s disease itself),⁶⁹ diabetes,⁷⁰ myotonic dystrophy,⁷¹ hereditary cerebellar ataxia,⁷² bilateral trigeminal neuralgia,⁷³ neurofibromatoma,⁷⁴ and polycystic kidney disease.⁷⁵ Gates, although trained as a geneticist and leery of anticipation, sought to provide an encyclopaedic overview of human disease and, as such, he discussed the previous literature, and therefore anticipation, in his successive volumes.

Notably less interested in the concept of anticipation were those authors who had no specific inclination to consider concrete pathologies. In 1947, Francis Albert Eley Crew, known in scientific circles for his work as an animal geneticist, published the text *Genetics in Relation to Clinical Medicine* based on his lectures on genetics given to medical students at the University of Edinburgh.⁷⁶ As Crew noted, the importance of training medical students in genetics had become apparent to those “who are responsible

⁶³ Gates, *Human Genetics*, Vol. 1, 32-33.

⁶⁴ Emphasis in the original. Gates, *Human Genetics*, Vol. 1, 33.

⁶⁵ Gates, *Human Genetics*, Vol. 1, 33.

⁶⁶ Gates, *Human Genetics*, Vol. 1, 202.

⁶⁷ Gates, *Human Genetics*, Vol., 1, 224.

⁶⁸ Gates, *Human Genetics*, Vol., 1, 265-266.

⁶⁹ Reginald Ruggles Gates, *Human Genetics*, Vol. 2, (New York: The Macmillan Company, 1946), 1013-1019.

⁷⁰ Gates, *Human Genetics*, Vol., 1, 546-550.

⁷¹ Gates, *Human Genetics*, Vol. 2, 988-995.

⁷² Gates, *Human Genetics*, Vol., 2, 1030-1033.

⁷³ Gates, *Human Genetics*, Vol., 2, 1055.

⁷⁴ Gates, *Human Genetics*, Vol., 2, 1180.

⁷⁵ Gates, *Human Genetics*, Vol., 2, 1416.

⁷⁶ Crew lectured to medical students in genetics from 1919. His original textbook *Organic Inheritance in Man* (1927) was quickly rendered obsolete by new scientific discoveries. F. A. E. Crew, *Genetics in Relation to Clinical Medicine*, (Edinburgh: Oliver and Boyd, 1947), vii.

for the construction of medical curricula.”⁷⁷ These authorities had decided that “an introduction to genetical fact and to current genetical theory should be included at some point.”⁷⁸ In the same year, three American geneticists on the other side of the Atlantic published the textbook *Genetics, Medicine, and Man*.⁷⁹ This text reflected the latest advancements in genetic thinking, including the discovery made by Avery and his colleagues concerning the finding that DNA carried genetic information.⁸⁰ Neither text discussed anticipation; this is not surprising when one considers that their authors were (in whole or in part) trained as classical Mendelian geneticists and can therefore be assumed to be less receptive to the idea than physicians might have been.

Penrose’s Theoretical Discussions of Anticipation: 1945-1948

As part of his programme to urge the adoption of a human genetics approach rather than a eugenics approach to the study of human disease in general and psychiatric disease in particular, Lionel Penrose published a series of papers between 1945 and 1948 in which he argued for the adoption of mathematically-based Mendelism and of better methodological and statistical modes of analysis by researchers engaged in the study of human disease.⁸¹ As part of this programme, he continued to refine his thoughts on anticipation which he rejected in 1946 as an “illusion,” an “artefact,” and “a persistent fallacy derived from statistical data.”⁸² As we shall see below, Penrose continued to make these and similar arguments in his psychiatric and human genetics textbooks until his death in 1972.

⁷⁷ Crew, *Genetics*, 1.

⁷⁸ Crew, *Genetics*, 1.

⁷⁹ H. J. Muller, C. C. Little, Laurence H. Snyder, *Genetics, Medicine, and Man*, (Ithaca NY: Cornell University Press, 1947).

⁸⁰ Muller, Little, and Snyder, *Medicine*, 6.

⁸¹ Not all of these papers discussed anticipation. Penrose’s inaugural lecture as Galton Professor of Eugenics laid out the perils of attempting to apply eugenic thinking without a sound understanding of genetics. Penrose, “Phenylketonuria,” 949-953. His 1947 article on “The Importance of Statistics in Psychiatry” addressed three separate techniques (actuarial, biometric, and genetic) “which may be of special use in psychiatry.” Lionel Penrose, “The Importance of Statistics in Psychiatry,” *Proceedings of the Royal Society of Medicine*, 40 no. 14 (1947): 863-870. In the same year, Penrose published a paper in which he set out a statistical technique that would allow the analysis of variations by means of discrimination (described in the above paper as a biometric technique). Lionel Penrose, “Some Notes on Discrimination,” *Annals of Eugenics* 13 no. 4 (1947): 228-237.

⁸² Lionel Penrose, “Social Aspects of Psychiatry: The Importance of Statistics,” *Journal of Mental Science* 92 no. 389 (October 1946): 714.

In October 1946, Penrose published a paper on the importance of sound statistics in the analysis of mental illness.⁸³ In order to begin to treat psychiatric illness properly either within the hospital setting or within the community at large, Penrose argued, researchers needed to carry out up-to-date statistical and quantitative analyses. Seeking to “draw attention to some erroneous conclusions, which have been sometimes drawn from statistical data in the psychiatric field,” he discussed several “findings” made by the incorrect application of statistics.⁸⁴ Since the second decade of the twentieth century certain psychiatrists (including Mott) attempted to refute the assumption that the increase in the number of psychiatric admissions was a sign that mental disease was on the rise. Penrose assured his readers that “we must accept the paradox that more mental beds imply better mental health.”⁸⁵ In order to secure funding and to demonstrate the efficacy of their treatment programmes, he argued, most hospitals calculated their success based on the number of patients successfully discharged. Penrose called this a “major absurdity” as it did not take into account that patients were later re-admitted to hospital, sometimes several times over.⁸⁶ Another fallacy that Penrose addressed was “the illusion of anticipation in familial cases—progressive degeneration of the stock in succeeding generations.”⁸⁷ Penrose maintained that the finding of anticipation in mental disease was an experimental “artefact” created by the selection of parents with late onset disease and of children with early onset disease. He therefore concluded that it was “not a biological phenomenon.”⁸⁸ Penrose advocated treating mental illness as a chronic illness and argued that treatments must be evaluated over a long-term period.⁸⁹ He similarly advocated a long-term strategy for studying the genetics of mental disease by carrying out extended familial studies and attempting to ascertain the carriers of defective genes, whether dominant or recessive.⁹⁰

⁸³ Penrose, “Social Aspects,” 713-718.

⁸⁴ Penrose, “Social Aspects,” 713.

⁸⁵ In this paper Penrose argued—as had Mott in the 1910s and 1920s—that the stigma associated with mental illness needed to be removed so that patients would voluntarily seek treatment at the earliest opportunity. Penrose, “Social Aspects,” 713-714.

⁸⁶ Penrose, “Social Aspects,” 714.

⁸⁷ Penrose, “Social Aspects,” 714.

⁸⁸ Penrose here cited Heron (1914) and Paterson (1932).

⁸⁹ Penrose, “Social Aspects,” 715.

⁹⁰ Penrose, “Social Aspects,” 716-717.

Clinical Discussions of Anticipation: 1945-1948

Between 1945 and 1948, one small and two large, important publications on myotonic dystrophy included discussions of anticipation. The Swiss psychiatrist Adolphe Franceschetti and the Swiss psychiatrist, ophthalmologist, and geneticist David Klein wrote a short paper that dealt specifically with the question of anticipation in myotonic dystrophy.⁹¹ Two extensive studies on the same disease by the British physician and geneticist Julia Bell and by the Danish physician Eivind Thomasen, also considered the possible role of anticipation.⁹²

In 1946 Franceschetti Klein directly examined the question of anticipation (earlier age of onset in succeeding generations) and potentiation (progressive worsening) in myotonic dystrophy.⁹³ They remarked that several studies on myotonic dystrophy had established the features of the disease and its basic mode of heredity. However, there still remained questions as to whether anticipation and potentiation were occurring, and if so, which genetic factors might be causing such an unusual form of heredity.⁹⁴ Their own clinical examinations and analysis suggested that myotonic dystrophy *did* appear earlier and with more severe clinical manifestations—including psychological effects—in succeeding generations.⁹⁵ They agreed with previous researchers that the disease was clearly inherited as an autosomal dominant, and they echoed findings of homologous (the same kind of disease) and homochronous (in the same generation) heredity that had been

⁹¹ Adolphe Franceschetti and David Klein, “Über einen Stammbaum von myotonischer Dystrophie mit Anteponition und Potenzierung,” *Archiv der Julius Klaus-Stiftung für Vererbungsforschung Sozialanthropologie und Rassenhygiene* 21 (1946): 315-322. Franceschetti was one of the founding members of the Swiss Genetic Society in 1941. At one of its meetings he met David Klein—a Jewish physician who had completed his medical training at Basel in 1934 because of Nazi policies in his native Germany and who was then working at a psychiatric clinic in Zurich. The two began to collaborate and in 1945, Klein was invited by Franceschetti to establish a genetic unit in Geneva at the ophthalmology clinic, making Klein “the first full-time research worker in human genetics in Switzerland.” In 1955, Franceschetti and Klein founded the Institute of Human Genetics in Switzerland, one of only five such institutes active at the time in Europe. Unlike most other researchers, Franceschetti and Klein, who began his research on myotonic dystrophy at Franceschetti’s suggestion, continued to endorse the notion of anticipation even after Penrose’s 1948 arguments that it was merely a statistical artefact. Klein, “Living History,” 325-329.

⁹² Because Thomasen’s 1948 monograph was written prior to the publication of Penrose’s critical paper of the same year it is included in this section.

⁹³ Franceschetti and Klein, “Anteponition und Potenzierung,” 315-322.

⁹⁴ Franceschetti and Klein, “Anteponition und Potenzierung,” 315.

⁹⁵ Franceschetti and Klein viewed the appearance of mental symptoms in the youngest generation as a clear example of the progressive heredity at work in myotonic dystrophy. Franceschetti and Klein, “Anteponition und Potenzierung,” 315-319.

made by previous authors.⁹⁶ These findings were typical of what had previously been referred to as heredodegenerative disorders. The kind of progressive heredity that such findings suggested had, however, been under attack since the 1920s by a number of German-speaking researchers (including Rüdin, Weinberg, and Lenz) who felt that anticipation was a statistical fallacy and not a biological reality.⁹⁷ However, Franceschetti and Klein continued to believe that the work of Fleischer, and Henke and Seeger showed genuine anticipation with the development from senile cataract in one generation, cataract and dystrophic symptoms in the next, and early onset with mental disability in the last generation. Franceschetti's own research and that of others such as Waardenburg supported these findings.⁹⁸ Franceschetti and Klein felt that Goldschmidt's hypothesis of dominigenes provided, for the first time, a genetic explanation for these findings of progressive heredity and anticipation in myotonic dystrophy.⁹⁹ Moreover, they believed that this hypothesis might provide an experimental explanation for findings of progressive and regressive heredity, although the issue required further study.¹⁰⁰ Two further studies by Franceschetti, Klein, and Walthard which examined both myotonic dystrophy and myotonia congenital corroborated these findings.¹⁰¹ In the years after the publication of Penrose (1948), Klein was one of the few clinicians who continued to support the notion that anticipation was a biological reality in myotonic dystrophy. His later work will be discussed below.

In 1947, Julia Bell published her study on myotonic dystrophy and related diseases as part of the *Treasury of Human Inheritance*.¹⁰² It was the first detailed and

⁹⁶ Franceschetti and Klein, "Anteposition und Potenzierung," 319.

⁹⁷ Franceschetti and Klein, "Anteposition und Potenzierung," 319.

⁹⁸ Franceschetti and Klein, "Anteposition und Potenzierung," 319.

⁹⁹ Franceschetti and Klein, "Anteposition und Potenzierung," 320.

¹⁰⁰ Franceschetti and Klein, "Anteposition und Potenzierung," 322.

¹⁰¹ A. Franceschetti, D. Klein, and K. M. Walthard, "Klinisch-genealogische Untersuchungen über drei Fälle von Myotonia congenital (Thomsen) und acht neue Fälle von Dystrophia myotonica (Steinert-Batten) unter besonder Berücksichtigung der Differentialdiagnose der beiden Krankheitsformen," *Schweizer Archiv für Neurologie und Psychiatrie* 60 (1947): 48-79; A. Franceschetti, D. Klein, and K. M. Walthard. "Klinisch-genealogische Untersuchungen über drei Fälle von Myotonia congenital (Thomsen) und acht neue Fälle von Dystrophia myotonica (Steinert-Batten) unter besonder Berücksichtigung der Differentialdiagnose der beiden Krankheitsformen," *Schweizer Archiv für Neurologie und Psychiatrie* 61 (1948): 152-207.

¹⁰² Julia Bell, *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 5: Dystrophia Myotonica and Allied Diseases*, with clinical notes by J. Purdon Martin, ed., L. S. Penrose, (Cambridge: Cambridge University Press, 1947).

quantitative analysis of the genetics of the disorder.¹⁰³ During her examination of published pedigrees concerning myotonic dystrophy, Bell noted that previous scholars had discussed “antedating” in the case of myotonic dystrophy, and she did not think it possible here “to assert the contrary.”¹⁰⁴ Bell’s own statistical analysis had shown that it was “an exceedingly remote probability that the observed ages of onset in successive generations provide random samples of the same population.”¹⁰⁵ However, she argued “that it would be unwise to assert this as an undoubted example of inherent antedating.”¹⁰⁶ As to the question of whether cataract in the very earliest generations was a “forerunner to dystrophia myotonica,” Bell noted that it was “difficult to assess the reality of these observations,” but she did not doubt “the inherent association of the two conditions.”¹⁰⁷ As part of her study, Bell also analyzed the pattern of the inheritance of myotonic dystrophy. She concluded that “a dominant gene is the essential source of the disease” but that “some further hypothesis is required to account” for the peculiar forms of heredity seen in the disease.¹⁰⁸ At the end of her analysis Bell thanked Otto Maas for the use of his pedigrees and notes although she was sorry that her “conclusions and mode

¹⁰³ Bell noted many features of myotonic dystrophy (including the existence of congenital and childhood onset forms of the disease) that would be “rediscovered” by later researchers. For a discussion of the prescience of Bell’s work on myotonic dystrophy see Peter Harper, “Julia Bell and the *Treasury of Human Inheritance*,” *Human Genetics* 116 (2005): 429-431. Harper discusses Bell’s analysis of anticipation with regards to myotonic dystrophy and suggests that her cautious attitude towards anticipation might be the result of the influence of Lionel Penrose, the new Galton professor and editor of the *Treasury*. However, my analysis of Bell’s work suggests that her views on anticipation were more likely influenced by the work of Pearson and Heron and that her caution towards the concept of anticipation dates back at least as far as 1928. See chapter two for a discussion of Bell’s early views on anticipation.

¹⁰⁴ Bell, *Dystrophia Myotonica*, 352.

¹⁰⁵ Like earlier researchers, Bell noticed that siblings were far more likely to have a similar age of onset (0.65) than do parents and children (0.32) and found that there was a high degree of probability that children would have an earlier age of onset than their parents (χ^2 value of 47.558). Bell, *Dystrophia Myotonica*, 352-353.

¹⁰⁶ Bell listed four possible causes of bias: 1. Selection of late-onset cases in the older generations, 2. Early, almost pre-clinical detection of disease in later generations because the disease was known to run in the family, 3. Possibly missing late-onset cases in later generations who had not yet reached the age of onset, and 4. the early death rate in the sib-ships might be masking other trends. Bell, *Dystrophia Myotonica*, 352-353.

¹⁰⁷ Bell, *Dystrophia Myotonica*, 359-360.

¹⁰⁸ Bell suggested “the possibility of a source of disease resident in the plasma of the parent reproductive cell rather than located on a chromosome might account for a widespread diffusion of the disease in affected sib-ships with a lack of uniformity in manifestation, but on such an hypothesis the mother would presumably be a more potent transmitter than the father, and we find no evidence to support this.” Although Bell did not note any peculiarities in inheritance through female carriers, in the early 1970s the realization that congenital myotonic dystrophy occurred only in the children of affected mothers and not in those of affected fathers became widespread and reinvigorated the discussion of anticipation in this disease. This will be discussed in chapter five. Bell, *Dystrophia Myotonica*, 364.

of procedure sometimes diverge conspicuously from his expressed and authoritative views.”¹⁰⁹ She also thanked Lionel Penrose “for his interest and criticism and for an interesting discussion of the genetic basis of dystrophia myotonica, with an attempt to explain or elucidate the observed appearance of antedating, to be published shortly in the *Annals of Eugenics*.”¹¹⁰

The Danish physician Eivind Thomassen’s monograph on myotonic dystrophy, published in 1948, included an extensive literature review of previous works on myotonic dystrophy that preceded his own analysis of Danish myotonic dystrophy families.¹¹¹ Thomassen also discussed the debate in previous scientific literature on the existence and nature of anticipation, as well as its possible causes.¹¹² His own study, Thomassen said, observed “anticipation, and presumably also potentiation of the pathological picture in the youngest generation.”¹¹³ He believed that although the statistical selection of parents with later-onset myotonic dystrophy in the parental generations might be responsible for some of the findings of anticipation, “the possibility of real progression cannot be completely rejected.”¹¹⁴

A CRITICAL CONTRIBUTION: PENROSE (1948) AND ANTICIPATION

In 1948, Lionel Penrose published his own views in what came to stand for decades as the definitive paper on anticipation.¹¹⁵ In this study, Penrose noted that the observation of earlier onset of disease in children compared to their parents had led “many medical

¹⁰⁹ Bell, *Dystrophia Myotonica*, 365.

¹¹⁰ Bell, *Dystrophia Myotonica*, 365.

¹¹¹ Thomassen’s study is included in this section because it was written before the publication of Penrose’s seminal 1948 paper. Eivind Thomassen, *Myotonia: Thomsen’s Disease (Myotonia Congenita), Paramyotonia, and Dystrophia Myotonica. A Clinical and Heredobiologic Investigation*, (Denmark: Universitetsforlaget i Aarhus, 1948), 171-173.

¹¹² Thomassen, *Myotonia*, 178-179.

¹¹³ Thomassen noted that the parental generations showed cataract while the children’s generation showed fully developed myotonic dystrophy but the reverse was never seen. His generational studies revealed the by now common pattern: senile cataract in one generation, pre-senile cataract in the next, in the third generation classical myotonic dystrophy appeared, while the few children born into the fourth generation were the most seriously affected. Thomassen, *Myotonia*, 180.

¹¹⁴ Thomassen, *Myotonia*, 180.

¹¹⁵ Penrose, “Problem,” 125-132. See for example, Christiaan Höweler, “A Clinical and Genetic Study in Myotonic Dystrophy,” (Erasmus University of Rotterdam: MD thesis, 1986), 9, 13-18; Peter Harper, Helen G. Harley, William Reardon, and Duncan J. Shaw, “Anticipation in Myotonic Dystrophy: New Light on an Old Problem,” *American Journal of Human Genetics* 51 no. 1 (July 1992): 12-13. The incorporation of Penrose’s hypothesis on anticipation into the foundation texts for the fields of human, medical, and clinical genetics will be documented below.

investigators to postulate a process of progressive worsening of hereditary disease in succeeding generations.”¹¹⁶ Moreover, he reminded his readers, the idea of anticipation had considerable historical roots—including Galton who had argued that both positive and negative traits could be anticipated—and the phenomenon had been attested in research on diseases such as diabetes and mental illness. This record he acknowledged meant that “it is at first sight very difficult to believe that a fundamental biological process is not being observed.”¹¹⁷ F. W. Mott had, Penrose noted, “explained the phenomenon” in mental illness with a “theory of progressive degeneration of the germ plasm.”¹¹⁸ Yet although “Mott’s viewpoint is still generally considered valid by teachers of psychiatry,” it was nevertheless, Penrose argued, “very probably erroneous.”¹¹⁹

Penrose averred that “the tendency for anticipation to occur in pedigrees of hereditary disease is due to the manner of their statistical selection and is not a phenomenon of direct biological significance.”¹²⁰ Studies by Heron (1914) and Paterson (1933) had “indicated serious flaws in the interpretations advocated by Mott” but despite these criticisms “the belief in progressive degeneration persists.”¹²¹ Accordingly, Penrose sought to examine the phenomenon in myotonic dystrophy because it was the disease that showed the most “marked degree” of anticipation.¹²² Penrose used the findings of Bell (1947) as the basis for his examination of analysis of the genetics of myotonic dystrophy.¹²³ Her findings echoed those of earlier researchers; early generations showed mostly cataract in middle age while later generations showed myotonia, muscular dystrophy, and mental defect with a decreasing age of onset of the disease in succeeding generations.¹²⁴ Penrose calculated the correlation coefficient of age of onset between parents and offspring and between siblings, finding that “with respect to

¹¹⁶ Penrose, “Problem,” 125.

¹¹⁷ Penrose, “Problem,” 125.

¹¹⁸ Penrose, “Problem,” 125.

¹¹⁹ Penrose, “Problem,” 125.

¹²⁰ Penrose, “Problem,” 125.

¹²¹ Penrose, “Problem,” 125.

¹²² Penrose, “Problem,” 125.

¹²³ Penrose, “Problem,” 125.

¹²⁴ Penrose, however, did not discuss or attempt to explain the increasing severity of disease in succeeding generations. These hereditary peculiarities had, in 1939, led Ravin and Waring to posit that myotonic dystrophy was caused by an unstable mutation as the gene causing myotonic dystrophy could pass through several generations showing little or no signs of disease before suddenly progressing to the classic form of myotonic dystrophy. Penrose, “Problem,” 125-126; Abe Ravin and James Waring, “Studies in Dystrophia Myotonica. I. Hereditary Aspects,” *American Journal of the Medical Sciences* 197 (1939): 594-600.

the severity and type of disease, brothers and sisters have a relatively high degree of similarity.”¹²⁵ Yet, Penrose observed, these findings still awaited a sound genetic explanation. He argued that “the traditional hypothesis in current medical teaching . . . derives no support from researches by animal or plant geneticists.”¹²⁶ The lone animal model was Goldschmidt’s 1938 findings of allelic modification of fruit fly wings, which, Penrose allowed, gave “an appearance of anticipation in special circumstances.”¹²⁷ This did not mean that Penrose believed that anticipation was a real biological phenomenon; in fact it was quite the opposite.

Penrose listed “five points to be considered as possible ‘causes’ of anticipation”: in other words, he identified five reasons related to researchers’ selection and the variable age of onset of the disease to account for the appearance of anticipation.¹²⁸ He identified in the following order: 1. “Selection of affected parents in whom the onset of the disease is late” which occurred as those affected at an early age had reduced fertility, meaning that researchers selected those in the parental generation with a relatively late age of onset;¹²⁹ 2. “Selection of affected offspring in whom the onset of the disease is early”; this form of selection was likely because researchers were more likely to notice—and therefore publish—striking or severe cases of the disease which came with early onset;¹³⁰ 3. “Selection of cases with simultaneous onset in parents and offspring,” which was more likely to occur because investigations covered only a limited period of time and the investigator was likely to observe cases in which the disease appeared in the child at an earlier age than the parent but would likely miss “the complementary pairs of cases” in which the onset of the disease in the child occurred at a later age than the parent;¹³¹ 4.

¹²⁵ Penrose, “Problem,” 126.

¹²⁶ Penrose, “Problem,” 126.

¹²⁷ Allelic modification is the process by which the normal gene (allele) at a locus can modify or change the expression of a dominant or mutant gene (allele). If there is more than one allele (version of the gene) at the same locus there can be a range of phenotypic variations. In the case of Goldschmidt’s fruit flies, several alleles at the same locus resulted in a range of damage to the fruit fly wings ranging from slight to severe when in combination with the mutant gene. Penrose, “Problem,” 126.

¹²⁸ In his 1948 paper, Penrose dealt mainly with difficulties in selection bias which could lead to findings falsely indicative of anticipation. One of these difficulties was the effect that the age of onset of disease had on the ability of the researcher to observe or ascertain all affected members of a family. Hence ascertainment bias overlapped as a category with selection bias.

¹²⁹ These points appear in the order in which they were dealt with by Penrose. Penrose, “Problem,” 126.

¹³⁰ Penrose, “Problem,” 126

¹³¹ Penrose, “Problem,” 126-127. No evidence of these anticipated complementary pairs with later onset in the child than the parent were ever located, yet Penrose’s opinion on anticipation was accepted essentially

“Weakness of real correlation of onset ages in parents and offspring” which was necessary for an appearance of anticipation because a disease that appeared at the same age in succeeding generations would not suggest anticipation (Penrose argued that this did not mean that anticipation was actually occurring);¹³² 5. “General variability in age of onset.”¹³³

Analyzing Bell’s data, Penrose produced a table that compared the ages of onset in 51 pairs of parents and children who suffered from myotonic dystrophy.¹³⁴ This table revealed that the correlation was “not symmetrical” and that in the majority of pairs the disease occurred 20-40 years earlier in the offspring than in the parent. These were just the sort of findings that “could easily have been simultaneously observed.”¹³⁵ On the other hand, the empty regions of the chart should have contained cases in which the disease occurred later in the child than the parent but these cases “would not be so easily observed because of the long period of time, which would necessarily elapse between the date of onset of the disease in the parent and the date of onset in the child.”¹³⁶ Penrose used this contrast to infer “that at least as many pedigrees had been missed as had been recorded—perhaps not an unreasonable assumption.”¹³⁷ Therefore, he argued, “the exceptionally high anticipation index found in dystrophia myotonica is probably a direct consequence (in pedigree data collected in the usual manner) of the exceptionally low correlation age of onset in parent and child characteristic of this disease.”¹³⁸ It cannot be stressed too strongly that the existence of these “complementary pairs” which he posited was a crucial assumption of Penrose’s hypothesis concerning anticipation.¹³⁹

unchallenged until the work of Christiaan Höweler in the mid-1980s. Höweler, “Clinical and Genetic Study,” 14-16.

¹³² At this point in the argument Penrose inserted a comment by Dr Bell that was prescient with regard to the biological nature of anticipation as discovered in the early 1990s: “Dr Bell has pointed out to me that there is a possible exception to this rule. We might assume that the age of onset was lowered regularly by, say, 10 or 20 years at each generation by some unknown mechanism. This situation, if it should occur, would be consistent with a close though asymmetrical correlation between parent onset age and child onset age.” The unknown mechanism turned out in the 1990s to be expanding trinucleotide repeats in the affected gene. Penrose, “Problem,” 127.

¹³³ Penrose, “Problem,” 127-128.

¹³⁴ Penrose, “Problem,” 128.

¹³⁵ Penrose, “Problem,” 128.

¹³⁶ Penrose, “Problem,” 128.

¹³⁷ Penrose, “Problem,” 128.

¹³⁸ Penrose, “Problem,” 129.

¹³⁹ However, no previous studies—particularly those of Fleischer who had traced myotonic dystrophy through six generations and several branches of a family—had shown any evidence of the existence of

The question of why the age of onset should be so similar between aunts/uncles and nephews/nieces remained to be explained, he thought. Bell had first discussed this during her 1943 survey of pseudohypertrophic and allied types of progressive muscular dystrophy when she noted a correlation between the difference in ages of onset between parents and offspring and aunts/uncles and nephews/nieces.¹⁴⁰ Bell initially made this calculation in an attempt to get around the issue, first raised by Pearson (1912), that, by virtue of remaining healthy long enough to become parents, the parental generation was naturally selected for a later age of onset than the offspring generation, but it failed to do so since it revealed that the overall age of onset of disease was greater in the parental generation than in the filial generation—i.e. parents and their affected siblings developed the disease at much the same age and that this age was later than the age at which the disease affected individuals in the next generation. Bell included a similar table in her 1947 study of myotonic dystrophy, but did not discuss these findings.¹⁴¹ Moreover, there was a greater correlation of age of onset among siblings with myotonic dystrophy (0.66) than among parents and offspring (0.32) when both suffered from the disease.¹⁴² Penrose argued that “this relatively strong likeness among sibs tends to produce a well-marked anticipation effect in the uncle and nephew relationship because the uncles and aunts tend to be like their own sibs, the parents, who, in their turn, differ from their offspring.”¹⁴³ This finding undoubtedly suggested to Penrose that there was a real genetic component at work, rather than simply an illusion caused by the fact of parents living long enough to have offspring, although he thought that “the sib-sib correlation for age of onset is low enough to suggest a fair amount of variation among members of the same fraternity.”¹⁴⁴

these posited cases where children developed the disease at a later age than their parents. In fact, it was not until the work of the Dutch physician C. J. Höweler in 1986, that it became apparent that the absence of these posited complementary pairs was because *they did not exist* and not because their existence had somehow been missed by several generations of researchers. C. J. Höweler’s work will be discussed in some detail in chapter five. Höweler, “Clinical and Genetic Study,” 14-16, 22, 75-76.

¹⁴⁰ Julia Bell, *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 4: On Pseudohypertrophic and Allied Types of Progressive Muscular Dystrophy*, ed., R. A. Fisher, (Cambridge: Cambridge University Press, 1943), 294

¹⁴¹ Bell, *Dystrophia Myotonica*, 356.

¹⁴² Penrose, “Problem,” 129.

¹⁴³ Penrose, “Problem,” 129.

¹⁴⁴ The sib-sib correlation number was suspect because Penrose believed that siblings whose age of onset of disease differed by fifty years would likely have been missed. Moreover, as Heron (1914) and Paterson (1933) had argued, researchers were likely to diagnose disease at an earlier age in succeeding siblings on

In any case, Penrose argued, “the problem of finding a credible genetical hypothesis to account for dominance with anticipation in dystrophia myotonica can, thus, be narrowed down to the problem of accounting for a factor or factors, which can suitably modify the effects of a dominant gene.”¹⁴⁵ He felt that the simplest assumption was that “the main causes of variation in onset age are allelic genes.”¹⁴⁶ Penrose suggested that one rare gene, “**M**,” was dominant and caused myotonic dystrophy. That gene could be modified by its allelic partner, received from the other parent, and might be either “**m₁**”—causing severe disease and early onset—or “**m₂**”—causing mild disease and later onset.¹⁴⁷ This hypothesis suggested that parents and children would be unlikely to share the same allelic gene, while siblings would have a 50% chance of having the same allelic modifier.¹⁴⁸ Penrose remarked that Goldschmidt had put forth such a hypothesis of allelic modification in 1938 although he commented that Goldschmidt’s “treatment of the problem is obscure.”¹⁴⁹

The allelic modification hypothesis could not, however, completely account for the experimental findings, and so Penrose further assumed that some sort of ascertainment bias was at play. He supposed that there would be complete ascertainment of all cases when the disease appeared simultaneously in members of both the parental and offspring generations.¹⁵⁰ Following this line of thinking he posited two things: that, with a gap of a generation (30 years) between these two dates of onset, the level of ascertainment would drop by 50%; and that with two generations (60 years) separating the ages of onset, no cases would be noticed by the researcher since they would occur so far apart in time.¹⁵¹ Penrose did not explain the source of these suppositions and does not appear to have taken into account the fact that some researchers, most notably Fleischer

the basis of family history, dropping the apparent age of onset and creating the effect of fraternal anticipation that had been noted by Maas (1937). Penrose, “Problem,” 129.

¹⁴⁵ Penrose, “Problem,” 129.

¹⁴⁶ Penrose, “Problem,” 129-130.

¹⁴⁷ Penrose, “Problem,” 130.

¹⁴⁸ This meant correlation of age of onset in sib-sib pairs should have been 0.5; the actual correlation was 0.32 which Penrose would attempt to explain in a later section. Penrose believed that the actions of one of these allelic modifiers could, in and of itself, be negative even on an individual who did not carry the dominant gene for myotonic dystrophy. This, he felt, could explain both the high mortality rate among unaffected family members observed by Bell (1947) and the large number of suspicious cases noted by Maas (1937). Penrose, “Problem,” 130.

¹⁴⁹ For Goldschmidt’s hypothesis see chapter three. Penrose, “Problem,” 130.

¹⁵⁰ Penrose, “Problem,” 130.

¹⁵¹ Penrose, “Problem,” 130.

(1922) and Henke and Seeger (1927), had examined five generations of families with myotonic dystrophy and failed to report any severe cases in early generations. One can only assume that Penrose believed, as did Bell, that these severely affected individuals of the early generations were missing from the pedigrees due to bad record-keeping and faulty family memory.¹⁵² With these assumptions in mind, Penrose assigned frequencies to his hypothetical allelic genes and, assuming the posited rates of incomplete ascertainment, he calculated correlation coefficients for parent-child pairs of 0.33 and sib-sib pairs of 0.71.¹⁵³ These findings were, he noted, extremely close to the observed correlation coefficients of 0.32 for parent-child pairs and 0.71 for sib-sib pairs in myotonic dystrophy.¹⁵⁴ He concluded that “these observed values are thus in keeping with the hypothesis of two common allelomorphous modifying genes, which affect age of onset, in data which have been collected with a bias favourable to pairs, where the two members are affected simultaneously.”¹⁵⁵ There were even animal models in which such allelic modification had been observed—notably fruit fly wings¹⁵⁶ and the A_1 , O , and A_2 antigens in men—which meant that “the hypothesis that the peculiarities of inheritance of dystrophia myotonica are due to modification by one or more allelic genes is not biologically improbable.”¹⁵⁷

Why was Penrose (1948) so important?

One of the most curious features of the history of the concept of anticipation is just how quickly and completely the hypothesis put forward by Penrose’s 1948 paper, speculative as it was, came to be adopted as the explanation for findings of anticipation. Although

¹⁵² See for example Bell, *Pseudohypertrophic*, 294. The assumption that the missing cases of early onset disease were due to faulty family memory was adopted by other researchers; see for example de Jong who assumed that “a faulty family anamnesis often plays a part” in findings of progression of myotonic dystrophy over succeeding generations. Johannes Gerardus Ype De Jong, *Dystrophia Myotonica Paramyotonia and Myotonia Congenita*, Translation by Sister M. Lidwina van Weers and Sister M. Luke Gray, (Assen: Von Gorcum, 1956), 160-161.

¹⁵³ Penrose, “Problem,” 130-131.

¹⁵⁴ Penrose, “Problem,” 131.

¹⁵⁵ Penrose, “Problem,” 131.

¹⁵⁶ The fruit fly study in this case was that of Mohr (1932) which had been suggested to Penrose by Haldane as an example of a genetic locus with three genes that caused an array of phenotypes when combined. Penrose, “Problem”, 131; Otto Mohr, “On the potency of mutant genes and wild-type allelomorphs,” in *Proceedings of the Sixth International Congress of Genetics, Ithaca, New York, 1932*, Vol. 1, ed., Donald Jones, (Menasha WI: Brooklyn Botanic Garden, 1932), 190-212.

¹⁵⁷ Penrose, “Problem,” 131.

the concept of anticipation was popular among many English physicians and psychiatrists and was used by certain researchers in the Netherlands and Switzerland, the biological reality of anticipation had been under theoretical attack by the English biometricians Pearson and Heron since the 1910s and Mendelian explanations for the findings had been proposed from the 1930s. Most German researchers in the 1920s 1930s and 1940s soundly rejected it, and only a limited number of physicians in North America accepted it. Penrose, of course, had been refining his critiques of anticipation since at least 1932. His arguments in 1948 were not significantly different than those he put forward in 1936 and 1946, although they were more persuasively and elegantly made. Why then was Penrose (1948) accepted as proof that anticipation was nothing more than a statistical artefact often seen in diseases with a variable age of onset, a pattern that was itself, he thought, likely caused by a combination of allelic genes with the main disease-causing gene?

The simple answer is that Penrose was the right person, in the right place, who made the right argument, in the right way, and 1948 was the right time. Penrose's high-quality genetic work on mental deficiency was known internationally; he was the head of the prestigious Galton Laboratory and editor of its associated journal *Annals of Human Genetics*.¹⁵⁸ The small size of the Anglo-American human genetics community during the late 1940s and the influence of British geneticists within it no doubt added to the significance of Penrose's work.¹⁵⁹ Many important figures in the field of human and medical genetics during the second half of the twentieth century trained or worked with Penrose at the Galton, and his textbooks directly influenced the next generation of researchers in the fields of psychiatry and human and medical genetics.¹⁶⁰ He was well-respected even by those who did not completely agree with him in these fields and his influence was profound.¹⁶¹ In his 1948 paper, he made a rhetorically robust argument

¹⁵⁸ Harper, *Myotonic Dystrophy*, 2nd ed., (London: W. B. Saunders Company, 1989), 310; David C. Watt, "Lionel Penrose, F.R.S. (1898-1972) and Eugenics: Part One," *Notes and Records of the Royal Society of London* 52 no. 1 (1998): 138.

¹⁵⁹ Daniel Kevles, *In the Name of Eugenics: Genetics and the Uses of Human Heredity*, (Cambridge Mass.: Harvard University Press, 1995), 205.

¹⁶⁰ Book with names and addresses of Voluntary Workers at the Galton Laboratory, 1933-1966; Address book of visitors and workers in the Galton Laboratory, 1945-1959; Typed list of postgraduate workers in the Galton Laboratory, 1945-1965, Penrose Papers, 49/2.

¹⁶¹ Watt, "Part 1," 138.

against the biological reality of anticipation.¹⁶² He laid out all of the previous arguments against the concept in terms of selection bias and then attacked the research on myotonic dystrophy, the disease with the most marked and long-standing association with anticipation, in a way that highlighted the strength of his position.¹⁶³ Penrose provided persuasive tables that graphically showed how the correlation of the ages of onset in parent-child pairs was skewed towards those in which the onset of disease could be observed as occurring at the same point in time—i.e. cases where the disease occurred earlier in the children than in the parents. Moreover, the structure of these tables suggested that there should have been parent-child pairs in which the disease appeared later in the children than in the parent—and these missing children appeared to have been simply overlooked by scientific observers.¹⁶⁴

Having dismissed anticipation as nothing more than a statistical artefact due to a number of sources of selection bias, Penrose provided an explanation for the range of the age of onset that fit within the now-dominant Mendelian paradigm. However, Penrose's 1948 explanation (allelic modification of the dominant gene) was essentially the same as that which had been put forward by Penrose himself in 1936 and by Goldschmidt in 1938. The fact that it was better received at this point is a tribute not only to the clarity of Penrose's prose and the apparent reasonableness of his argument, but also to the rise to dominance of Mendelian concepts of heredity which ruled out ideas like 'germ plasm degeneration' or 'progressive mutation' that had been acceptable to earlier generations of researchers. Furthermore, Penrose capped his argument by purporting to "prove" his hypothesis. He carried out a thought experiment based on his hypotheses of allelic modification and his assumption that there was an incomplete ascertainment of parent-offspring pairs in whom disease did not begin at the same time. He then calculated the

¹⁶² Indeed, in the 1980s, it took the Dutch neurologist and researcher Christiaan Höweler multiple readings and four years of analysis before he could identify the problems with Penrose's 1948 study and test the hypothesis in his own PhD dissertation. Höweler, Correspondence with Judith Friedman, 18 March 2004.

¹⁶³ Penrose, "Problem," 125-128.

¹⁶⁴ The reasoning behind these tables was based on what turned out to be incorrect assumptions: that anticipation did not in fact exist; that there would be a symmetrical variation of age of onset of disease within the population; and consequently that there were individuals in the offspring generation in whom disease would begin at a later age than in their parent; the absence of these individuals was then assumed to be due to a combination of poor family memory and record-keeping, early diagnosis of expected cases, and the short time of the study compared to the length of human life which meant that late onset cases in the offspring generation would be missed. Penrose, "Problem," 128-129.

correlation coefficients of ages of onset between parents and children and between siblings and found that they were extremely close to the observed values in the case of myotonic dystrophy. This persuasively suggested that he was correct in his hypothesis that the appearance of anticipation was caused by this combination of factors and circumstances.¹⁶⁵

Penrose's 1948 article appeared at a critical time during the expansion and consolidation of the fields of medical, human, and clinical genetics. This resulted in the adoption of his ideas into most of the new textbooks designed to teach the growing number of human, medical, and clinical geneticists. Its acceptance is reflected in the clinical papers published by these newly trained researchers between 1948 and 1970. Moreover, the clinical literature of this period illustrates a divide between the new generation of human and medical geneticists who denied or ignored anticipation and clinicians and older clinically-oriented medical geneticists, who continued to report observations of anticipation.¹⁶⁶

¹⁶⁵ Penrose, "Problem," 130-131.

¹⁶⁶ As we have seen, Goldschmidt had noted, in 1938, that geneticists were sceptical of anticipation because it could not be explained by Mendelian heredity while physicians were inclined to believe that anticipation could be a real biological phenomenon. As shall be discussed below, in the period immediately following the publication of Penrose (1948) those clinicians (such as Caughey) or clinically oriented medical geneticists (such as Stein) who continued to report findings of anticipation had been educated during the 1930s when anticipation was still generally accepted by many physicians. However, this gap continued during the period between 1970 and 1989 as medical specialists (such as Höweler who was trained as a neurologist) were not taught about anticipation as part of their medical education. This made them more receptive to the idea that anticipation might be a real biological phenomenon than their colleagues in medical and human genetics who could not conceive of a mechanism that could account for findings of progressive heredity—that is, not until the discovery of expanding trinucleotide repeats in the early 1990s. H. Houston Merritt's *A Textbook of Neurology* (which went through several editions and reprints during this period) did not mention anticipation by name, but did note that the cataract associated with myotonic dystrophy was seen to appear earlier in succeeding generations in the fourth edition of his text (1967). That sentence was removed from the fifth edition (1973). Nor does the eleventh edition of *Merritt's Neurology*, published in 2005, mention anticipation by name, but it does describe the mutation causing myotonic dystrophy as "an expansion of a CTG triplet repeat within the DMPK gene." Richard Goldschmidt, " 'Progressive Heredity' and 'Anticipation': The Possibility of a Genetic Explanation of Certain Odd Hereditary Phenomena Observed in Man," *Journal of Heredity* 29 (1938): 140-142; Höweler, Correspondence with Judith Friedman, 18 March 2004; H. Houston Merritt, *A Textbook of Neurology*, 4th ed., (Philadelphia: Lea & Febiger, 1967), 547; H. Houston Merritt, *A Textbook of Neurology*, 5th ed., (Philadelphia: Lea & Febiger, 1973), 534; Lewis P. Rowland, *Merritt's Neurology*, 11th ed., (Philadelphia: Lippincott Williams & Wilkins, 2005), 905.

ESTABLISHING THE NEW GOSPEL: ANTICIPATION IN SCIENTIFIC AND MEDICAL LITERATURE 1948-1970

One of the most striking things about the history of the concept of anticipation as told by Penrose was just how quickly it went from an idea “formerly almost universally accepted” to being described as “merely a statistical artefact.”¹⁶⁷ Although many of the ideas put forward by Penrose in 1948 had been previously circulated as far back as Pearson in 1912, only after 1948 was the idea of anticipation soundly rejected by the majority of scientists and physicians.

By the early 1960s, even a casual suggestion that familial congenital heart disease that occurred in the sons but not in the father might “represent a further advance of genetic derangement” drew fire from a commentator who reminded the author that Penrose’s isoallele hypothesis was a more reasonable explanation.¹⁶⁸ This rebuke was accepted by the author who described it as “a plausible alternative” to his original suggestion.¹⁶⁹ Nevertheless, a few clinicians—mainly those whose training pre-dated the publication of Penrose (1948)—continued to affirm the biological reality of anticipation.¹⁷⁰ This section analyses how anticipation was discussed—or ignored—in various parts of the scientific and medical literature from 1948 to 1970.

(A) Anticipation in the Survey Literature

Human, Medical, and Clinical Genetics Textbooks

Between 1930 and 1948 most of the medical and human genetics textbooks published dealt with anticipation, whether or not the author(s) agreed with the concept, but after 1948 the situation changed dramatically, even as the number of textbooks published

¹⁶⁷ Lionel Penrose, *Outline of Human Genetics*, 1st ed., (London, Heinemann, 1959, Reprinted 1960), 44.

¹⁶⁸ Weil and Allenstein offered this suggestion for their findings having decided that recently discovered chromosomal rearrangements causing Turner’s syndrome and Down’s syndrome were likely responsible for the heart defects associated with those syndromes. Therefore they posited that similar rearrangements were possibly the cause of the mutations seen within their pedigree. Max Weil and Bertram Allenstein, “A Report of Congenital Heart Disease in Five Members of One Family,” *New England Journal of Medicine* 265 no. 14 (5 October 1961): 665; Frederick Hecht, “Correspondence: Genetic Defect,” *New England Journal of Medicine* 266 no. 1 (4 January 1962): 54.

¹⁶⁹ Max Weil, “Correspondence: Genetic Defect,” *New England Journal of Medicine* 266 no. 1 (4 January 1962): 54.

¹⁷⁰ The work of J. E. Caughey and David Klein, two clinical researchers who continue to believe that anticipation was occurring in myotonic dystrophy, will be discussed below.

increased.¹⁷¹ Systematic analysis of human, medical, and clinical genetics textbooks written between 1949 and 1970 reveals that the authors were just as likely to ignore anticipation as to discuss it, and where they did discuss it their comments were invariably critical. My analysis was carried out on medical, human, and clinical genetics textbooks available at Cambridge University, the Royal Society of Medicine Library (London), the University of Alberta, and the University of Victoria. Although not exhaustive, the collection includes the major texts—often published in several editions—that were used to instruct the new generation of human, medical, and clinical geneticists trained during the post-war period of expansion and professionalization of these fields. Together with an examination of successive editions this provides an accurate picture of the reception of anticipation within these expanding fields between 1949 and 1970.

In the first five years following the publication of Penrose (1948) three new human, medical, and clinical genetics textbooks were critical of the concept of anticipation. Two by authors who later wrote further editions of their popular studies. The first of these texts, and perhaps the most influential, was Curt Stern's *Principles of Human Genetics*. Published in 1949, it was the first to incorporate Penrose's hypothesis on anticipation and it played an important role in the dissemination of that hypothesis.

Born in Hamburg, Stern became in 1923 the youngest individual to date to be awarded his PhD from the University of Berlin. After graduating, he worked under Richard Goldschmidt at the Kaiser Wilhelm Institute in Germany before taking, at Goldschmidt's instigation, a Rockefeller Foundation fellowship to study genetics in the Morgan group's "fly room" at Columbia University between 1924 and 1926.¹⁷² A second fellowship took him to Cal Tech in 1932 to work with some of the most pre-eminent geneticists of the age including Morgan, Sturtevant and Dobzhansky. Due to the rise of Hitler and the Nazi party to power in 1933, Stern was unable to return to Germany at the end of his fellowship. Instead, he obtained a position at the University of Rochester where he taught courses in general and human genetics.¹⁷³ He moved in 1947 to

¹⁷¹ As mentioned above, the 1947 texts by Crew, and Muller, Little, and Snyder are two exceptions in that they ignored the subject of anticipation.

¹⁷² James Neel, "Curt Stern, 1902-1981," *Annual Review of Genetics* 17 (December 1983): 1-3.

¹⁷³ Neel, "Stern," 4. Curt Stern, *Principles of Human Genetics*, (San Francisco CA: Freeman and Co., 1949) viii.

Berkeley, when he was appointed professor of zoology and later, in 1958, professor of genetics. He retired in 1970.¹⁷⁴

Although Stern's own work concentrated mainly on fruit fly genetics, by 1949 he felt that "the time has arrived when human genetics can be presented as a course in fundamental genetics."¹⁷⁵ Because the teaching of human genetics had suffered from "the lack of a textbook," he wrote one "in an attempt to fill the need for an introduction to the study of human genetics."¹⁷⁶ Stern's text taught students the most up-to-date ideas on Mendelian genetics and the statistical methods used to analyse research findings and to calculate risk when undertaking genetic counselling.

On the question of anticipation, Stern provided his readers with the most recent theoretical approach to the topic—namely that of Penrose (1948). His discussion of the subject appeared in the chapter "Irregularities in the Expression of Genes" alongside subjects like "incomplete penetrance," "expressivity and specificity," and "genetic modifiers" which were concepts used to explain what Stern regarded as the "sound premise *that differences in genic expression are variable consequences of constant genes.*"¹⁷⁷ Anticipation, however, posed something of a difficulty. Although Stern recognized that belief in anticipation was "a widely held opinion among medical men, and some statistics seem to support it," he thought the notion that the severity of a disease could worsen over succeeding generations was merely a "presumed phenomenon."¹⁷⁸ Stern noted that "the concept of anticipation does not readily fit in with the system of genetic facts and interpretations" used by geneticists who had therefore "subjected to careful analysis the data which suggest anticipation."¹⁷⁹ If the variability in the age of onset of diseases commonly held to show anticipation was random, Stern suggested, there should be an equal number of pedigrees showing either earlier or later ages of onset in the younger generations. However, this was not the case, and Stern agreed that "it must be explained, therefore, why, in some diseases, pedigrees with earlier onset in older

¹⁷⁴ Neel, "Stern," 5.

¹⁷⁵ Stern, *Principles* (1949), vii-viii.

¹⁷⁶ Stern, *Principles* (1949), viii.

¹⁷⁷ Italics in original. Stern, *Principles* (1949), 265-302.

¹⁷⁸ Stern, *Principles* (1949), 296-297.

¹⁷⁹ Stern, *Principles* (1949), 297.

generations seem to be rarer than those with earlier onset in younger generations.”¹⁸⁰ He put forward a number of possible causes including environmental conditions by means of explanation but singled out several sources of selection bias as being most likely to cause the appearance of anticipation.¹⁸¹ Those individuals with early onset were likely to have no children and hence never be recorded (especially in early generations) while those with late onset would have children and would therefore be more likely noticed by the researcher. Those with earlier onset and more severe disease were most likely to be noted by the researcher; and the combination of early onset disease in the children and late onset disease in the parents was most likely to be noticed by the researcher.¹⁸² Stern, citing the work of Julia Bell, suggested that “it seems justified, until proved to the contrary, to consider anticipation as a statistical phenomenon which will disappear from the records when the methods of ascertainment have escaped all bias.”¹⁸³ Both Haldane’s (1941) hypothesis of modifying genes and Penrose’s (1948) hypothesis of allelic modification were discussed as possible genetic causes for the variability in age of onset that underlay the findings leading to the appearance of anticipation.¹⁸⁴ Stern felt that Penrose’s hypothesis, in particular, could explain why the ages of onset in siblings were more similar to each other than to their affected relatives in older generations.¹⁸⁵

Stern’s remarkably quick integration of Penrose’s theories into his textbook is worth some discussion. Penrose and Stern were well aware of each others’ work, having become acquainted during Penrose’s North American sojourn during the Second World War.¹⁸⁶ By January 1941, while Penrose was working at the Ontario Hospital, and Stern at the Department of Zoology at the University of Rochester, the two corresponded and

¹⁸⁰ Stern, *Principles* (1949), 297.

¹⁸¹ Stern, *Principles* (1949), 297.

¹⁸² Stern, *Principles* (1949), 297-298.

¹⁸³ Stern, *Principles* (1949), 298.

¹⁸⁴ Stern, *Principles* (1949), 298-299.

¹⁸⁵ Stern, *Principles* (1949), 299. This did not, however, explain why no generations had been found with siblings having a greater age of onset than their parents, and Stern did not question this. Perhaps he believed that such generations were among those who were missed in family studies and whose absence contributed to statistical bias.

¹⁸⁶ Penrose may have met Stern during his American tour before taking up his position with the Ontario Hospital and Western. H. Soltan, “Lionel Penrose,” in *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*, ed., H. C. Soltan, (London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992), 36-40.

arranged an ongoing exchange of reprints of their articles.¹⁸⁷ In later years they exchanged graduate students and corresponded on questions of the effects of nuclear radiation on humans. In the mid-1950s Stern spent two months working with Penrose in London at the Galton Laboratory at the end of which they co-authored a paper in the *Annals of Human Genetics* disproving the existence of a certain possible Y-linked gene.¹⁸⁸ Not only was Stern aware of Penrose's work on the subject of anticipation in the late 1940s, but his own research on *Drosophila* had led him to similar conclusions: in 1943 he had discovered that different variations of the same normal gene (called isoalleles) could lead to a variety of phenotypic effects when paired with a mutant gene.¹⁸⁹ Moreover, he had, as early as 1928, been aware that illnesses with similar symptoms could have different genetic causes, that led him to caution physicians over their belief in progressive heredity.¹⁹⁰ Stern was also clearly familiar with Wilhelm Weinberg's contributions to the mathematical analysis of Mendelian inheritance (and, one assumes, of his criticisms of anticipation) as Stern had in 1943 brought Weinberg's

¹⁸⁷ Lionel Penrose, London Ontario, to Curt Stern, Rochester NY, 16 January 1941, Curt Stern Papers, American Philosophical Society Archive, Philadelphia, Pennsylvania, USA.

¹⁸⁸ Lionel Penrose, London, to Curt Stern, Berkeley, 8 May 1952, Curt Stern Papers, American Philosophical Society Archive, Philadelphia, Pennsylvania, USA; Collection of Reports from the British Committee on the Medical Aspects of Nuclear Radiation, 1955, Curt Stern Papers, American Philosophical Society Archive, Philadelphia, Pennsylvania, USA; Margaret Penrose, London to Curt Stern, Berkeley, 7 February 1956, Curt Stern Papers, American Philosophical Society Archive, Philadelphia, Pennsylvania, USA; Lionel Penrose, London, to Curt Stern, Chalk River, Ontario, 1 October 1958, Curt Stern Papers, American Philosophical Society Archive, Philadelphia, Pennsylvania, USA; L. S. Penrose and C. Stern, "Reconsideration of the Lambert pedigree (ichthyosis hystrix gravior)." *Annals of Human Genetics* 22 no. 3 (1958): 258-283; Curt Stern to Margaret Penrose, Radlett England, 30 June 1972, Curt Stern Papers, American Philosophical Society Archive, Philadelphia, Pennsylvania, USA.

¹⁸⁹ In fact, according to Neel it was Stern himself who coined the term "isoalleles." Neel, "Stern," 4-5.

¹⁹⁰ Stern noted that progressive heredity was not seen in non-human genetics, and he urged researchers examining the subject in humans to move forward with extreme caution. He also singled out myotonic dystrophy as an odd phenomenon. Henke and Seeger's (1927) paper (which hypothesised that anticipation was caused by phenotypic induction or by progression from a pre-mutation form to a more severe form) was specifically mentioned by Stern in this regard. He noted that classical Mendelism could not account for the kind of progressive transmission seen in myotonic dystrophy. Stern observed that Henke and Seeger's methodological approach had been criticized and that more accurate methods would need to be utilized when examining myotonic dystrophy before the genetic facts could be correctly ascertained. Curt Stern, "Welche Möglichkeiten bieten die Ergebnisse der experimentellen Vererbungslehre dafür, daß durch verschiedene Symptome charakterisierte Nervenkrankheiten auf gleicher erblicher Grundlage beruhen?" *Nervenarzt* 2 (15 May 1929): 257-262. See also Neel, "Stern," 6.

discoveries to the attention of the English-speaking world.¹⁹¹ As well as arguing against anticipation in his textbook, Stern incorporated these ideas into his lectures.¹⁹²

Stern's *Principles of Human Genetics* merits detailed discussion because it was the first to adopt Penrose's (1948) arguments about anticipation, and significantly affected the developing field of human genetics, as evidenced by its status as "the first textbook of human genetics."¹⁹³ Some call it "the most successful textbook on human genetics ever written."¹⁹⁴ A large number of copies were sold as the text went through three English-language editions between 1949 and 1973—each extensively updated to reflect the latest information in the field—and it was translated into seven foreign languages.¹⁹⁵ Stern's textbook was well received from the outset. In his review of the original edition, J. B. S. Haldane declared that "the book is so good, and is so badly needed, that I hope there will be many further editions."¹⁹⁶ Penrose too found the text "very useful for students," although he admitted that "there are some points in it which we criticize, but that is only because we think it is so good."¹⁹⁷ Victor McKusick, whose considerable contributions will be addressed later, was beginning his own education in human genetics in the early 1950s. He judged Stern's "the most influential textbook" of those that he read.¹⁹⁸ Many of the papers published between 1948 and 1970 on diseases with which anticipation had been associated cited either Penrose (1948) or Stern (or both) in their criticisms of anticipation.

A second human genetics textbook, *Genetics and Disease*, was written by Tague Kemp and published in Edinburgh in 1951.¹⁹⁹ Kemp dealt with anticipation specifically in relation to eye diseases, most notably the case of hereditary cataract, which had been

¹⁹¹ Curt Stern, "The Hardy-Weinberg Law," *Science* 97 no. 2510 (5 February 1943): 137-138.

¹⁹² In a 1958 lecture entitled "Mental Disease" Stern includes anticipation in an analysis square with Penrose's postulated complementary pairs. The lecture included a note that "one gets more of these," referencing the late-onset-parent, early-onset-child part of the square, but he did not include any explanation for this in his notes. Curt Stern, Lecture on "Mental Disease," 1958, Curt Stern Papers, American Philosophical Society Archive, Philadelphia, Pennsylvania, USA.

¹⁹³ Eberhard Passarge, *Color Atlas of Genetics*, 2nd ed., revised and enlarged (New York: Thieme, 2001), 8.

¹⁹⁴ Neel, "Stern," 7.

¹⁹⁵ Neel, "Stern," 7.

¹⁹⁶ J. B. S. Haldane, "Principles of Human Genetics," *Annals of Eugenics* 15 (1950): 283.

¹⁹⁷ Penrose to Stern, 8 May 1952. Oral History Interview with Victor McKusick, 10-11 December 2001 (Ms. Coll. no. 316), Oral History of Human Genetics Collection, History & Special Collections Division, Louise M. Darling Biomedical Library, University of California, Los Angeles.

¹⁹⁸ He also read J. A. Fraser Roberts' text.

¹⁹⁹ Tague Kemp, *Genetics and Disease*, (Edinburgh: Oliver and Boyd, 1951).

associated with anticipation from the time of Nettleship's work in 1905.²⁰⁰ Although Kemp noted that anticipation had historically been noted in a wide range of conditions, from cataract and glaucoma to schizophrenia, diabetes, and myotonia, he concluded baldly that "the existence of anticipation has not been definitively proved."²⁰¹ This was the least dismissive comment made on anticipation in textbooks between 1948 and 1970.

The third textbook, *Clinical Genetics*, was the work of the British ophthalmologist and geneticist Arnold Sorsby.²⁰² In the first edition, published in 1953, Sorsby noted that "the general application of mendelian [*sic*] genetics to man in health and disease has emerged only during the past two or three decades," and "in consequence the theoretical basis of human genetics has broadened so quickly in recent years" that the theory as well as the description of genetic diseases needed to be fully addressed in textbooks.²⁰³ Conceding findings of anticipation in myotonic dystrophy, he argued that "there is little support for this view" and held it likely "that the concept of anticipation has emerged in the study of slowly evolving afflictions and that early cases are discovered incidentally as a result of systematic study of affected families."²⁰⁴ While cases of earlier onset in succeeding generations were often noted, he declared that the reverse—cases of later onset in later generations—had "also been observed," though he did not mention by which researchers.²⁰⁵ In a later section, Sorsby discussed previous findings of anticipation in the medical literature and offered Penrose's multiple allele explanation for the wide range in age of onset in myotonic dystrophy. He concluded that "whether or not there is progression in the younger generations with anticipation or whether the results are due to natural selection of the milder affected parents cannot be determined until more accurate data on several generations can be secured."²⁰⁶ He did not discuss findings of anticipation in Huntington's disease.²⁰⁷

²⁰⁰ Kemp, *Genetics and Disease*, 224-225; Edward Nettleship, "On Heredity in the Various Forms of Cataract," *The Royal London Ophthalmic Hospital Reports* 16 (October 1905): 190-199.

²⁰¹ Kemp, *Genetics and Disease*, 224-225.

²⁰² Arnold Sorsby, *Clinical Genetics*, (London: Butterworth & Co. (Publishers) Ltd., 1935).

²⁰³ Sorsby, *Clinical Genetics*, v.

²⁰⁴ Sorsby, *Clinical Genetics*, 6.

²⁰⁵ Sorsby, *Clinical Genetics*, 6.

²⁰⁶ Sorsby, *Clinical Genetics*, 300.

²⁰⁷ Sorsby, *Clinical Genetics*, 340.

Anticipation appeared in none of the next three textbooks published. Although Neel and Schull included no discussion of anticipation, either on its own or in relation to Huntington's disease or myotonic dystrophy, they did consider the question of variable age of onset of disease. In treating this they used Penrose's hypothesis of genetic modifiers to explain the recorded findings.²⁰⁸ The texts by Reed and by Colin for their part discussed neither anticipation nor the question of variability of age of onset in hereditary disease.²⁰⁹

Between 1959 and 1970, human, medical, and clinical genetics textbooks were equally divided on whether they included a discussion of anticipation. Half of these texts did not mention anticipation at all, including Penrose's own *Recent Advances in Human Genetics*.²¹⁰ The other twelve textbooks discussed anticipation negatively.²¹¹ A few of

²⁰⁸ James V. Neel and William J. Schull, *Human Heredity*, (Chicago: University of Chicago Press, 1954), 66-67.

²⁰⁹ Sheldon C. Reed, *Counseling in Medical Genetics*, (Philadelphia: W. B. Saunders Company, 1955); Colin, Edward C. *Elements of Genetics: Mendel's Laws of Heredity with Special Application to Man*, 3rd ed., (New York: McGraw-Hill Book Company, Inc., 1956).

²¹⁰ Texts published during this time that did not mention anticipation included: Ashley Montagu, *Human Heredity*, (Cleveland OH: The World Publishing Company, 1959); J. A. Fraser Roberts, *An Introduction to Medical Genetics*, 2nd ed., (London: Oxford University Press, 1959); L. S. Penrose, *Recent Advances in Human Genetics*, with the assistance of Helen Lang Brown, (London: J. & A. Churchill Ltd., 1961); C. A. Clarke, *Genetics for the Clinician*, (Oxford: Blackwell Scientific Publications, 1962); J. A. Fraser Roberts, *An Introduction to Medical Genetics*, 3rd ed., (London: Oxford University Press, 1963); Victor McKusick, *Human Genetics*, (Englewood Cliffs NJ: Prentice-Hall Inc., 1964); David Yi-Yung Hsia, ed., *Lectures in Medical Genetics: A Course for Medical Genetics*, (Chicago: Year Book Medical Publishers, Inc., 1966); J. A. Fraser Roberts, *An Introduction to Medical Genetics*, 4th ed., (London: Oxford University Press, 1967); C. O. Carter, *An ABC of Medical Genetics*, Reprinted from "The Lancet", May 17 to June 28 1969, with two additional chapters, (London: The Lancet Ltd., 1969); Henry T. Lynch, *Dynamic Genetic Counseling for Clinicians*, (Springfield IL: Charles C. Thomas, 1969); A. E. H. Emery, *Modern Trends in Human Genetics I*, (London: Butterworths, 1970); J. A. Fraser Roberts, *An Introduction to Medical Genetics*, (London: Oxford University Press, 1970). Although Clarke and McKusick did not mention anticipation in the first editions of their textbooks, they did discuss and reject it in their second editions.

²¹¹ These texts included the second edition of C. A. Clarke's *Genetics for the Clinician* in which he drew heavily on Penrose (1948) in his discussion on anticipation. Clarke argued that "faults in ascertainment" were of "overriding importance" in the perception of anticipation and that the variation of age of onset in myotonic dystrophy, in which anticipation was often said to take place, was caused by isoalleles. C. A. Clarke, *Genetics for the Clinician*, 2nd ed., (Oxford: Blackwell Scientific Publications, 1964), 160. Unusually, the American Maurice Whittinghill used Huntington's disease as the hallmark disorder showing anticipation in his textbook. He argued that a variable age of onset combined with a number of selection biases led to the appearance of anticipation, "no clear demonstration [of which] has withstood critical review." Maurice Whittinghill, *Human Genetics and Its Foundations*, (New York: Reinhold Publishing Corporation, 1965), 250-252. The first edition of the text by the Drs Thompson—in its 6th edition in 2001 under different editors—referred to anticipations as "apparent rather than real" and suggested that its appearance was caused by a combination of selection bias, ascertainment bias, variability in age of onset, and the unlikelihood of those affected at an early age to have children. They concluded that "chiefly for these reasons, most workers dismiss the phenomenon of anticipation as a statistical artefact; but at least one recent worker (Klein, 1958) believes that, in myotonic dystrophy, it has not been completely ruled out."

these textbooks are worth some further comment, including Penrose's first textbook on human genetics, published in 1959.²¹²

In this work, Penrose was highly critical of eugenics, arguing that the eugenicist project was beset by "theoretical as well as practical difficulties" not the least of which was the fact that "agreement has not been reached on the question of what are the most desirable hereditary characters."²¹³ Penrose cautioned those who would advocate breeding for one trait or another, and he argued that variety had significant hereditary value.²¹⁴ He also maintained that rather than being an eugenic threat, the larger families born to those of lower intelligence actually acted to counter the low fertility of the "normal" population without proportionately increasing the number of those with "inferior" mentality.²¹⁵ Moreover, Penrose argued that sterilization of the homozygous was ineffective (as their children would more than likely be normal in any event) and that sterilization of the heterozygous (even if they could be ascertained) "is theoretically possible but terribly wasteful" as most people were assumed to be heterozygous for a number of undesirable genes.²¹⁶ On the question of anticipation, Penrose here noted as

James S. Thompson and Margaret W. Thompson, *Genetics in Medicine*, (Philadelphia: W. B. Saunders Company, 1966), 62. In his *The Genetics of Neurological Disorders*, Pratt used the appearance of "anticipation" as a means by which to distinguish myotonic dystrophy (in which anticipation could be seen) from myotonia congenita (in which anticipation was not seen). He used Penrose's arguments against the reality of anticipation. R. T. C. Pratt, *The Genetics of Neurological Disorders*, (London: Oxford University Press, 1967), 161-162. Alan Emery argued that "it is difficult to visualize any biological explanation for anticipation" and he used many of the problems of ascertainment and statistical bias that were in Penrose (1948) to explain why anticipation appeared to exist. Alan Emery, *Heredity, Disease, and Man: Genetics in Medicine*, (Berkeley CA: University of California Press, 1968), 198. In his 1969 text, Cyril Clarke used essentially the same argument against anticipation as he had in his 1964 text. Cyril Clarke, *Selected Topics in Medical Genetics: A Review from the Nuffield Unit of Medical Genetics, Liverpool University*, (London: Oxford University Press, 1969), 3. Richard Goodman also discussed anticipation critically in his 1970 text *Genetic Disorders of Man*. Goodman called it "the so-called phenomenon of anticipation" and note that "it is generally thought that anticipation does not have a biological basis." He suggested that ascertainment bias caused the appearance of anticipation. Richard Goodman, *Genetic Disorders of Man*, (Boston: Little, Brown and Company, 1970), 92-93.

²¹² Lionel Penrose, *Outline of Human Genetics*, (London: Heinemann, 1959).

²¹³ Penrose, *Outline*, 1st ed., (1959), 108-109, 113. Penrose described uniform populations as "culturally uninteresting." Penrose, *Outline*, 1st ed., (1959), 119.

²¹⁴ Penrose, *Outline*, 1st ed., (1959), 108-110.

²¹⁵ Penrose, *Outline*, 1st ed., (1959), 116-118.

²¹⁶ Penrose, *Outline*, 1st ed., (1959), 119-120. It is interesting to note how Penrose's comments of the futility of sterilization parallel those made by Tredgold in 1927. Although Tredgold and Penrose seem to have been diametrically opposed in their ideas concerning the cause of mental defect and their support of eugenics, they agreed in their support of the policy of segregation over sterilization of the mentally deficient. A. F. Tredgold, "Mental Disease in Relation to Eugenics," *Lancet* 209 no. 5401 (5 March 1927): 528.

we have seen that the concept “was formerly almost universally accepted” but was “now generally believed to be erroneous.”²¹⁷ The “appearance of anticipation,” he believed, was due to the fact that it was easy for the researcher to observe cases of late onset in parents and early onset in children but difficult to observe the opposite—cases of early onset in parents and late onset in children.²¹⁸ Moreover, he said, those badly affected in childhood were unlikely to have children of their own. As a result he concluded that “the anticipation effect thus seems to be merely a statistical artefact.”²¹⁹ This textbook was reprinted in 1960 and went through a second edition in 1963 that was itself reprinted in 1964 and 1965.²²⁰ Penrose’s comments on anticipation remained essentially unchanged from 1959 to 1973.

In 1960, the second edition of Stern’s *Principles of Human Genetics* was published. This edition reiterated many of the opinions on anticipation that had been published in the 1949 edition. Stern continued to refer to anticipation as a “presumed phenomenon” that was likely caused by a combination of ascertainment bias and a variable age of onset, the genetic cause of which had been suggested by Penrose (1948).²²¹

Another influential text was produced by Widukind Lenz, who in 1961 discovered the link between Thalidomide and birth defects. He was the son of the German eugenicist Fritz Lenz whose work on anticipation was discussed in chapters two and three above.²²² In 1961, Lenz published his *Medizinische Genetik* to fill “a void in the market.”²²³ This went through six editions and was translated into four languages. Opitz

²¹⁷ Penrose, *Outline*, 1st ed., (1959), 44.

²¹⁸ Penrose, *Outline*, 1st ed., (1959), 44.

²¹⁹ Penrose, *Outline*, 1st ed., (1959), 44.

²²⁰ Lionel Penrose, *Outline of Human Genetics*, (London: Heinemann, 1959, Reprinted 1960), 43-44; Lionel Penrose, *Outline of Human Genetics*, 2nd ed., (London: Heinemann, 1963), 43-44. A third edition was published in 1973 after Penrose’s death. The comments on anticipation remained essentially unchanged in all three editions. Lionel Penrose, *Outline of Human Genetics*, 3rd ed., (London: Heinemann Educational Books, 1973), 42-43.

²²¹ Curt Stern, *Principles of Human Genetics*, 2nd ed., (San Francisco CA: W. H. Freeman & Co., 1960), 322-323.

²²² Widukind Lenz, “Living History—Biography: Nature and Nurture,” *American Journal of Medical Genetics* 37 no. 3 (November 1990): 356, 359-360; Friedrich Vogel, “Widukind Lenz—An Encomium,” *American Journal of Medical Genetics* 37 no. 3 (November 1990): 352, 354; John Opitz and Hans-Rudolf Wiedemann, “In Memorium: Widukind Lenz, 1919-1995,” *American Journal of Medical Genetics* 65 no. 2 (16 October 1996): 142-144.

²²³ Lenz, “Nature and Nurture,” 359.

and Wiedemann considered it to be “the best written on the subject at the time.”²²⁴ The English translation, titled *Medical Genetics*, was published in 1963.²²⁵ Lenz unsurprisingly took a negative approach to anticipation, and he referenced Penrose’s work on selection bias and on the effects of normal allele(s) in causing the observed range of ages of onset in affected individuals.²²⁶

Unlike its first edition, the second edition of the American geneticist Victor McKusick’s *Human Genetics* did deal with the question of anticipation. McKusick noted that the phenomenon of anticipation was usually seen in diseases with a range of manifestations and ages of onset.²²⁷ He echoed Penrose’s suggestions that the incidence of later age of onset in the parental generation caused the perception of anticipation and that the severity of the disease in cases with childhood onset was more easily recognized by physicians and researchers. He thus concluded that “anticipation has no genuine biological basis.”²²⁸ Additionally, the book’s glossary included the following definition of anticipation: “More severe expression of a disorder in a given generation than in preceding one(s). Based largely on bias of ascertainment, anticipation has no biological basis.”²²⁹ McKusick made similar statements concerning anticipation in his widely referenced compendium we will consider next.

Victor McKusick’s Mendelian Inheritance in Man

In 1966, McKusick and his colleagues at Johns Hopkins began publishing a compendium of all known human genetic diseases entitled *Mendelian Inheritance in Man* that continues to be added to today.²³⁰ This work began by listing autosomal dominant, autosomal recessive and X-linked diseases by their preferred name with a short

²²⁴ Opitz and Wiedemann, “Widukind Lenz,” 144. On the importance of Lenz’s textbook, see also Vogel, “Encomium,” 355.

²²⁵ Widukind Lenz, *Medical Genetics*, Translated by Elizabeth F. Lanzel, (Chicago: University of Chicago Press, 1963). Originally published as *Medizinische Genetik: Eine Einführung in ihre Grundlagen und Probleme* (Stuttgart: Thieme Verlag, 1961).

²²⁶ Lenz, *Medical Genetics*, 44-45.

²²⁷ Victor McKusick, *Human Genetics*, 2nd ed., (Engelwood Cliffs NJ: Prentice-Hall, 1969), 47-49.

²²⁸ McKusick, *Human Genetics*, 2nd ed., (1969), 49.

²²⁹ McKusick, *Human Genetics*, 2nd ed., (1969), 200.

²³⁰ Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, (Baltimore: The Johns Hopkins Press, 1966).

description of the disease and a key bibliography of important papers.²³¹ Over time, both the description and the bibliographies have grown, and as the location of diseases on various chromosomes has been discovered and their molecular nature has come to be understood, this information too has been added to the entries. Twelve print editions have since appeared, and some have come out in translation; in recent years the compendium became available online, first in 1987 from Johns Hopkins University, and from December 1995 at the National Library of Medicine.²³² McKusick states that the *Mendelian Inheritance in Man* and its online version “is intended to have wide usefulness to researchers, clinicians, and students”—particularly as an aid to differential diagnosis and as a source of background information for molecular biologists.²³³

As genetic diseases of long standing, both Huntington’s disease and myotonic dystrophy were included in *Mendelian Inheritance of Man* from its first edition. In the case of Huntington’s disease, McKusick commented upon its variable age of onset, but did not mention anticipation.²³⁴ The situation was different in the case of myotonic dystrophy, however; he remarked that in this condition “anticipation—earlier onset in more recent generation—is described but it is probably an artefact of ascertainment (Penrose, 1948).”²³⁵ The second edition, published in 1968, included more references, but the lack of discussion of anticipation in Huntington’s disease²³⁶ and the conclusion that anticipation in myotonic dystrophy was an artefact remained the same.²³⁷

²³¹ McKusick notes that he modeled the entries in *Mendelian Inheritance in Man* on the *Oxford English Dictionary*. Victor McKusick, “*Mendelian Inheritance in Man* and Its Online Version, OMIM,” *American Journal of Human Genetics* 80 no. 4 (April 2007): 600.

²³² McKusick, “*Mendelian Inheritance in Man*,” 588-591.

²³³ McKusick, “*Mendelian Inheritance in Man*,” 601. On the importance of databases such as OMIM for human genetics research see, Christine Fischer, Sabine Schweigert, Cord Spreckelsen, and Friedrich Vogel, “Programs, databases, and expert systems for human geneticists—a survey,” *Human Genetics* 97 (1996): 129-137.

²³⁴ McKusick, *Mendelian Inheritance in Man*, 1st ed., (1966), 72.

²³⁵ McKusick, *Mendelian Inheritance in Man*, 1st ed., (1966), 91.

²³⁶ Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 2nd ed., (Baltimore: The Johns Hopkins Press, 1968), 114.

²³⁷ McKusick, *Mendelian Inheritance in Man*, 2nd ed., (1968), 145. *Mendelian Inheritance in Man* would continue to discuss anticipation in this way until after the discovery in the early 1990s of expanding trinucleotide repeats in several diseases with which anticipation had been historically associated. The treatment of anticipation in *Mendelian Inheritance in Man* will be further discussed in chapters five and six.

Psychiatric Textbooks

Two prominent psychiatric textbooks published in Britain in 1947 and in 1949 advanced diametrically opposed ideas on the concept of anticipation. These were a new edition of the long-running, well-received, and popular *Textbook on Mental Deficiency* by A. F. Tredgold and the first edition of *The Biology of Mental Defect* by Lionel Penrose.

In his 1947 edition, which was reprinted without change the year after Penrose produced his seminal paper, Tredgold maintained his long-held views on anticipation and the cause of mental defect. Alfred Frank Tredgold's long experience with research into mental defect dated back to 1905 when he was appointed as an investigator to the Royal Commission on the Feeble-minded. The first edition of his textbook, *Mental Deficiency (Amentia)*, was published in 1908 and "was at once accepted as the most authoritative work on the subject," according to an obituary.²³⁸ This textbook went through several editions under slightly different titles, which were simultaneously published in Britain, Canada, and the United States—often being reprinted between successive editions.²³⁹ In 1947 the 7th edition of Tredgold's *Text-Book of Mental Deficiency* was published; it was reprinted apparently unchanged in 1949.²⁴⁰ As in previous editions, Tredgold remarked on the difficulties of studying the genetic composition of humans, particularly as compared to plants and animals, and especially in the case of mental abnormalities which usually had some kind of "exciting" environmental component.²⁴¹ As Tredgold put it, with the exception "of a few rare and special types of defect" it had so far "proved impossible to demonstrate such [Mendelian] ratios in the simple, but much more prevalent, type of defect."²⁴² Some researchers believed that this was because a number of genes were involved, some dominant, some recessive, some sex-linked, and others autosomal acting in combination. Their nature and effects were therefore difficult, if not impossible, to fully elucidate.²⁴³ Other researchers, including Tredgold himself, believed that a qualitative change of the genetic material was involved—"an impairment of

²³⁸ Anonymous, "Obituary: A. F. Tredgold, M.D., F.R.C.P.," *British Medical Journal* 2 (27 September 1952): 726; A. F. Tredgold, *Mental Deficiency (Amentia)*, (London: Ballière, Tindall and Cox, 1908).

²³⁹ For the sake of consistency I have tried, whenever possible, to examine the London editions of the texts.

²⁴⁰ A. F. Tredgold, *A Text-Book of Mental Deficiency (Amentia)*, 7th ed., (London: Baillière, Tindall & Cox, 1947. Reprinted 1949).

²⁴¹ Tredgold, *Mental Deficiency*, 7th ed., (1949), 38.

²⁴² Tredgold, *Mental Deficiency*, 7th ed., (1949), 38.

²⁴³ Tredgold, *Mental Deficiency*, 7th ed., (1949), 38.

vitality or developmental potentiality”—caused either by nutritional effects on the germ cells and their chromosomal contents or by genes that carried not only “*specific* tendencies” but also “some *general* force of vitality” that affected the development of the organism from conception.²⁴⁴ The latter explanation, Tredgold argued,

certainly affords a more satisfactory explanation of the progressive accentuation in the type of mental abnormality, and of the progressive increase in the number of affected persons, which has been observed; also of the antedating of mental disease which has been insisted upon by many experienced clinicians, than does the view that transmission is in accordance with Mendelian laws, which, in fact, has not been demonstrated.²⁴⁵

Nevertheless, Tredgold warned his readers that while biology and genetics could offer the physician “general rules” on which to base advice, they could not yet “forecast accurately what will be the result of one particular conception.”²⁴⁶ On the eugenic front, he argued that because families “in all social classes, which are sound and healthy” were not propagating “to the same extent as are the mentally disabled and socially inefficient,” the “sound” population was thus under threat “to be engulfed by these latter.”²⁴⁷ However, he advocated the adoption of birth control by these “inefficient” strata as a solution to this problem.²⁴⁸ Moreover, Tredgold felt, physicians were “in a position to render invaluable service to the State” by advising individuals on whether or not they should marry and by advising the government on health issues.²⁴⁹

Tredgold’s views contrast with those put forth in Penrose’s influential text, *The Biology of Mental Defect*, which was based in part on the author’s Colchester study. Penrose’s textbook was published in 1949 and it went through four editions before his death in 1972.²⁵⁰ The preface, written by the geneticist J. B. S. Haldane, laid out the changes that were then occurring in the field with regard to “exaggerated hopes” raised in

²⁴⁴ Tredgold, *Mental Deficiency*, 7th ed., (1949), 38-39.

²⁴⁵ Tredgold, *Mental Deficiency*, 7th ed., (1949), 39.

²⁴⁶ Tredgold, *Mental Deficiency*, 7th ed., (1949), 39.

²⁴⁷ Tredgold, *Mental Deficiency*, 7th ed., (1949), 497-498.

²⁴⁸ Tredgold, *Mental Deficiency*, 7th ed., (1949), 498.

²⁴⁹ Tredgold, *Mental Deficiency*, 7th ed., (1949), 499.

²⁵⁰ Watt, “Part 1,” 138; L. S. Penrose, *The Biology of Mental Defect*, With a preface by J. B. S. Haldane, (London: Sidgwick and Jackson Limited, 1949).

the past by both eugenic and treatment-oriented approaches to mental defect.²⁵¹ Haldane felt that “both schools of thought underestimated the immense complexity of the problem,” as revealed by Penrose’s Colchester survey.²⁵² Ethically, recent history had raised grave questions concerning the treatment of the mentally deficient; as Haldane put it “Hitler gave one answer; Penrose gives a very different one.”²⁵³

Penrose’s text included the most up-to-date thinking on the subject of mental defect. As part of this, he laid out arguments against what he felt were old-fashioned ideas of the role of heredity. First, he argued against the notion of germ plasm degeneration, or “blastophthoria” which Tredgold and other authors had advocated.²⁵⁴ Given recent discoveries—e.g. regarding the mutagenic nature of radiation—Penrose felt that the operation of environmentally induced mutations could not be entirely ruled out, but, in the case of alcoholism at least, he felt such changes were doubtful.²⁵⁵

Turning his attention to the question of whether anticipation was caused by the continued deterioration of vitiated germ plasm, Penrose noted that Mott had “strongly upheld this hypothesis.”²⁵⁶ Penrose linked this to Tregold’s “neuropathic diathesis” and the idea that, once injured, the germ plasm would continue to degenerate over generations.²⁵⁷ Observations of the negative effects of anticipation had been made in the case of mental illness by Rüdin²⁵⁸ and positive “anticipation,” he noted, had been

²⁵¹ The hope that the eugenic measure of sterilization or segregation could reduce or end mental defect has been much discussed above and in chapters two and three. However, as Haldane noted here, a number of treatment methods including hormones, psychotherapy, and specialized teaching methods had likewise been offered as possible solutions to the problem of mental deficiency, with mixed and somewhat disappointing results. Penrose, *Mental Defect*, (1949), v.

²⁵² Penrose, *Mental Defect*, (1949), v.

²⁵³ Penrose, *Mental Defect*, (1949), vi-vii.

²⁵⁴ Penrose, *Mental Defect*, (1949), 64.

²⁵⁵ Penrose, *Mental Defect*, (1949), 64-66. Over the last two decades, with the discovery of Fetal Alcohol Effect and Fetal Alcohol Syndrome, the effects of alcohol consumption during sensitive periods of fetal development have become apparent.

²⁵⁶ Penrose here referred only to Mott 1910 Huxley lecture, which was in fact written before Mott had learned of “anticipation” from Nettleship, though he did discuss degenerative heredity and Penrose’s refutation included Mott’s memorable phrase “rotten twigs were continually broken off the tree of life.” Penrose, *Mental Defect*, (1949), 66.

²⁵⁷ Penrose, *Mental Defect*, (1949), 66.

²⁵⁸ Here Penrose referenced Rüdin (1916) and was apparently unaware that Rüdin, whose Nazi associations were known from the 1940s, had changed his mind on the issue and had, in fact, rejected anticipation from the early 1920s onward. For a discussion of Rüdin on anticipation, see chapter two. Penrose, *Mental Defect*, (1949), 66.

observed by Galton.²⁵⁹ The main problems with “the hypothesis of anticipation,” Penrose noted, were “its total lack of support from observations in the field of animal genetics” and what he and other geneticists took to be the fact that “the effects of mutation do not get progressively worse.”²⁶⁰ Moreover, Penrose saw “good reasons for supposing the cause of the phenomenon lies in the special selection of data, which is inevitable in collecting human material, rather than any natural peculiarity of the germ plasm itself.”²⁶¹ These difficulties included: the long span of human life and human generations in comparison to the length of time of any given scientific study, the increased likelihood of recognizing hereditary disease when it was observed in parents and children at about the same time (i.e. the cases in which the age of onset was younger in the child than the parent), the rarity of noticing the “complementary types” he posited (i.e. cases in which the age of onset was older in the child than in the parent).²⁶² Cases showing “the converse of anticipation” were most often missed, he argued, because of the short period of time that any given family was under observation and because of the reduced fertility of those who suffered mental or physical illness from an early age.²⁶³

Although Huntington’s disease had been associated with anticipation since the early years of the twentieth century, Penrose did not mention anticipation in Huntington’s, which he treated as a dominant genetic disease with a (randomly) variable age of onset.²⁶⁴ However, Penrose did extensively discuss the question of anticipation in the case of myotonic dystrophy beyond noting a wide variation in symptoms and ages of onset in the disease.²⁶⁵ This variable age of onset, together with the facts that transmission could occur through apparently normal individuals, and that the ages of onset in siblings were closer than those of parent and child, meant that “the phenomenon of antedating is often very noticeable.”²⁶⁶ However, while some authorities might believe that “this antedating indicates a real process of worsening in succeeding generations,”

²⁵⁹ Penrose referred here to Galton’s *Hereditary Genius* first published in 1869. Penrose, *Mental Defect*, (1949), 66.

²⁶⁰ Penrose, *Mental Defect*, (1949), 66.

²⁶¹ Penrose, *Mental Defect*, (1949), 66-67.

²⁶² Penrose, *Mental Defect*, (1949), 67.

²⁶³ Penrose, *Mental Defect*, (1949), 67.

²⁶⁴ Penrose, *Mental Defect*, (1949), 127-128.

²⁶⁵ Penrose, *Mental Defect*, (1949), 131-132.

²⁶⁶ Penrose, *Mental Defect*, (1949), 132.

Penrose argued that “until the effect of selection of families by severe disease in the offspring has been fully examined, the inherently improbable hypothesis of progressive worsening cannot be entertained.”²⁶⁷ As he argued elsewhere in the same text, Penrose stated that the reduced fertility of early onset cases contributed to “observations” of anticipation.²⁶⁸

The eighth edition of Tregold’s *Mental Deficiency*, published in 1952, was written with the assistance of his son, Roger Francis Tredgold.²⁶⁹ Although the general text was somewhat updated from the previous edition, the sections dealing with anticipation and eugenics remained virtually unchanged.²⁷⁰ The arguments concerning anticipation that appeared in the second edition of Penrose’s *The Biology of Mental Defect*, published in 1954, were also virtually unchanged.²⁷¹ Penrose continued to argue against the whole series of what he considered older genetic ideas including “blastophthoria,” germ plasm degeneration, progressive heredity, and anticipation, warning his readers of the pitfalls posed by selection bias.²⁷² His discussions of modes of heredity in Huntington’s disease and myotonic dystrophy also remained the same as in the first edition.²⁷³

Over the course of the 1950s, Penrose’s views on questions of mental deficiency were increasingly in the ascendancy. The ninth edition of Tredgold’s *A Textbook of Mental Deficiency* (1956), now substantially re-written by R. F. Tredgold and K. Soddy, reflected the fundamental change in approach that had been occurring in the field of psychiatry.²⁷⁴ As the authors noted in their introduction “psychological theory has changed practically out of recognition since the first edition, and we have undertaken a complete rewriting of the chapters on the normal and the defective mind.”²⁷⁵ The textbook was completely revised, and the authors declared that they had “attempted to

²⁶⁷ Penrose, *Mental Defect*, (1949), 132-133.

²⁶⁸ Penrose, *Mental Defect*, (1949), 133.

²⁶⁹ A. F. Tredgold, *A Text-Book of Mental Deficiency (Amentia)*, Assisted by R. F. Tredgold, 8th ed., (Baltimore: The Williams & Wilkins Company, 1952).

²⁷⁰ Tredgold, *Mental Deficiency*, 8th ed., (1952), 38-40, 509-511.

²⁷¹ L. S. Penrose, *The Biology of Mental Defect*, with a preface by J. B. S. Haldane, 2nd (revised) ed., (London: Sidgwick and Jackson Limited, 1954).

²⁷² Penrose, *Mental Defect*, 2nd ed., (1954), 64-67.

²⁷³ Penrose, *Mental Defect*, 2nd ed., (1954), 127-128, 131-132.

²⁷⁴ R. F. Tredgold and K. Soddy, *A Textbook of Mental Deficiency. First compiled by A. F. Tredgold*, 9th ed., (London: Ballière, Tindall, & Cox, 1956). As were the previous editions of Tredgold’s textbook, this edition too was reprinted (in 1961) and was also published abroad.

²⁷⁵ Tredgold and Soddy, *Mental Deficiency*, 9th ed., (1956), ix.

include the results of current research” (much of it Penrose’s) into their text.²⁷⁶ This change in attitude was reflected in the lack of any mention of anticipation as well as in the now critical discussion of the concept of psychopathic diathesis.²⁷⁷

Similar critical comments concerning the concept of the psychopathic diathesis appeared in the textbook, *Mental Deficiency*, by L. T. Hillard and Brian Kirman and published in 1957.²⁷⁸ These authors considered Lionel Penrose’s Colchester Survey (1938) to be “the most important survey in the field,” and affirmed that the ideas concerning heredity and mental defect advanced there were “now shared by most workers.”²⁷⁹ They also supported Penrose’s criticisms of the hypothesis that there was an association between social inefficiency and mental deficiency.²⁸⁰ Their discussion of myotonic dystrophy included no mention of anticipation.²⁸¹ Criticisms of psychopathic diathesis and the hypothetical link between heredity and delinquency continued to appear in psychiatric texts.²⁸²

The third edition of Penrose’s *The Biology of Mental Defect* appeared in 1963.²⁸³ Although it too was revised to bring it up-to-date with current psychiatric research, the criticisms of anticipation were not. Penrose continued to argue that the idea was without any biological basis and that any observations to the contrary were the result of selection bias (those affected at an early age rarely had children) and experimental design (studies rarely tracked affected families long enough to pick up cases where the disease appeared in the children at a later age of onset than in their parents).²⁸⁴ The discussion of myotonic dystrophy was also brought into line with the latest experimental findings. Penrose continued to advocate the allelic modification hypothesis as the explanation for the

²⁷⁶ Tredgold and Soddy, *Mental Deficiency*, 9th ed., (1956), x.

²⁷⁷ Tredgold and Soddy, *Mental Deficiency*, 9th ed., (1956), 33-35.

²⁷⁸ L. T. Hillard and Brian H. Kirman, *Mental Deficiency*, (London: J. & A. Churchill, 1957), 33.

²⁷⁹ Hillard and Kirman, *Mental Deficiency*, 54-56.

²⁸⁰ Hillard and Kirman, *Mental Deficiency*, 273-274.

²⁸¹ Hillard and Kirman, *Mental Deficiency*, 347.

²⁸² See, for example, the 10th edition of Tredgold’s *Mental Deficiency*, now entirely revamped and brought in line with Penrose’s methods. R. F. Tredgold and K. Soddy, With the assistance of E. W. Dunkley, G. Rawlings, B. C. Marshall, J. F. Smith, D. A. Pond, and W. R. Trotter, *Tredgold’s Textbook of Mental Deficiency (Subnormality)*, 10th ed., (London: Baillière, Tindall, & Cox, 1963). 25-28.

²⁸³ L. S. Penrose, *The Biology of Mental Defect*, With a preface by J. B. S. Haldane, Completely revised with the assistance of J. M. Berg and Helen Lang-Brown, 3rd ed., (London: Sidgwick and Jackson Limited, 1963).

²⁸⁴ Penrose, *Mental Defect*, 3rd ed., (1963), 75-76.

variability seen in the disease in both symptomatology and age of onset.²⁸⁵ This variability, Penrose admitted, “allows the phenomenon of anticipation to be very noticeable” but he contended that while “some authorities” still believed that anticipation was occurring in myotonic dystrophy, with a proper analysis “this hypothesis is seen to be unnecessary.”²⁸⁶

Research and terminology in the field of mental defect continued apace throughout the rest of the decade. By the time of the appearance of the eleventh edition of Tredgold’s textbook the field had adopted the term “mental retardation” in place of “mental deficiency” as a descriptor.²⁸⁷ The previous policies of sterilization and segregation (effective sterilization) were under attack as a cause for “frustration and immaturity in patients” but, the new authors claimed, that “more enlightened policies” now prevailed.²⁸⁸ The scientific understanding was now that mental defect was caused by “a host of genetic and environmental influences.”²⁸⁹ Moreover, it was now recognised that “the decision as to whether an individual comes under care and is classified as retarded is in the main a social one.”²⁹⁰

In summary, the scientific understanding of the causes of mental defect had been radically transformed. By 1970, the hereditarian concerns that had once linked mental defect and social inefficiency were no more. Even the policy of segregation, once advocated by Tredgold and Penrose alike as a more humane way to care for those with mental defect, had come under attack. The concept of anticipation was no longer a concern for this research community.²⁹¹

²⁸⁵ In this edition Penrose included mention of the work of Renwick (1956) and his observations of allelic modification in nail-patella syndrome. Penrose, *Mental Defect*, 3rd ed., (1963), 137-138.

²⁸⁶ Penrose, *Mental Defect*, 3rd ed., (1963), 138.

²⁸⁷ This was also reflected in a change of title for Tredgold’s textbook. R. F. Tredgold and K. Soddy, with the assistance of E. W. Dunkley, G. Rawlings, J. Gibson, D. W. Smith, B.C. Marshall, J. F. Smith, D. A. Pond, and W. R. Trotter. *Tredgold’s Mental Retardation*, 11th ed., (London: Baillière, Tindall, and Cassell, 1970), vii.

²⁸⁸ Tredgold and Soddy, *Tredgold’s Mental Retardation*, 11th ed., (1970), 22-23.

²⁸⁹ Tredgold and Soddy, *Tredgold’s Mental Retardation*, 11th ed., (1970), 28.

²⁹⁰ Tredgold and Soddy, *Tredgold’s Mental Retardation*, 11th ed., (1970), 28.

²⁹¹ However, as shall be explored in chapter six, once a biological basis for anticipation was discovered in the early 1990s researchers again invoked this concept to explain patterns of heredity in schizophrenia and bipolar disorder.

(B) Anticipation in Various Disorders

Psychiatric Disease

Even though anticipation had been associated with psychiatric disease since the 1910s, the German psychiatric community turned against anticipation in the 1920s and British physicians and psychiatrists led by Pearson, Paterson, and Penrose did so in the 1930s.²⁹² Penrose's influential 1948 study and his psychiatric textbooks further turned the field against the concept of anticipation. Between 1948 and 1970, discussion of anticipation seems to have almost completely dropped from the psychiatric literature, except in relation to papers discussing the psychiatric effects of Huntington's disease and myotonic dystrophy.²⁹³

In 1966, Hopkinson and Ley published a paper on age of onset in manic-depressive disorders that considered the question of anticipation. Oddly, their paper stated that Penrose (1948) had "shown that when mental illness as a whole is considered, the age of onset is earlier in children than in their parents" but they credited Stern (1960) with casting doubt on anticipation, but "the position is still unclear."²⁹⁴ Although Hopkinson and Ley's research suggested that the age of onset was occurring earlier in succeeding generations, they concluded that this finding appeared, as Stern had suggested, "to be an artefact, rather than a genetic phenomenon."²⁹⁵

²⁹² See chapter two and three.

²⁹³ In fact, McInnis et al. argue that "no studies have addressed anticipation in psychiatric disorders since Kraepelin (1921) separated schizophrenia from bipolar affective disorder (BPAD) early in the century. Melvin G. McInnis, Francis J. McMahon, Gary A. Chase, Sylvia G. Simpson, Christopher A. Ross, and J. Raymond DePaulo, Jr., "Anticipation in Bipolar Affective Disorder," *American Journal of Human Genetics* 53 (1993): 385. Citation analysis reveals that only two indexed papers published on psychiatric subjects between 1948 and 1970 referenced either Mott (1910) or Penrose (1948). Only the paper by Hopkins and Ley—discussed below—dealt with the question of anticipation. The other paper, abridged from a 1965 PhD thesis written at the University of London (where Penrose worked), mentioned Mott (1910) in regard to discussing findings that when two family members suffered from mental disease women and same-sexed pairs were more likely to be affected. Although Penrose's hypothesis that mental illness could be affected by modifying genes was discussed, anticipation was not. However, the author did suggest that schizophrenia and affective disorders were both likely to be caused by many genes rather than by one gene, even one with allelic modifiers. Ming-Tso Tsuang, "A Study of Pairs of Sibs both Hospitalized for Mental Disorder," *British Journal of Psychiatry* 113 no. 496 (1967): 283-310.

²⁹⁴ This reading of the texts involved is peculiar because, as has been discussed above, Stern based much of his argument against anticipation on Penrose's 1948 study. G. Hopkinson and P. Ley, "The Age of Onset in Manic-depressive Families," *Psychiatria et Neurologia* 152 no. 4 (1966): 217.

²⁹⁵ Hopkinson and Ley, "Age of Onset," 220.

Diabetes

Diabetes literature was something of a hot-bed for the discussion of anticipation between 1948 and 1970 largely due to the work of the American physicians Arthur Steinberg and Russell Wilder who sought to discredit the work of R. T. Woodyat and Marseille Spetz. The latter had published a paper in 1942 arguing that significant anticipation was occurring in families with diabetes over several generations.²⁹⁶ In 1950 Steinberg and Wilder published the first of a series of papers in which they sought to “clarify the situation” regarding anticipation in diabetes.²⁹⁷ In discussing the concept they referred to Gates’ 1946 textbook and Penrose’s 1948 paper.²⁹⁸ Although their analysis of family histories of diabetics attending the Mayo clinic “confirms Woodyat and Spetz observations” that the age of onset of diabetes decreased in succeeding generations, they nevertheless strongly argued that anticipation did not occur in this disease.²⁹⁹ To reach this conclusion, Steinberg and Wilder assumed that the range of age of onset in diabetes remained the same in each generation. This would mean that individuals in the parental and grandparental generations would have older ages of onset of disease by virtue of having lived long enough to have children and grandchildren.³⁰⁰ Steinberg and Wilder concluded “that anticipation is a statistical and not a biologic phenomenon,” and they recommended “that the term ‘anticipation’ not be used” any longer in discussions with diabetic patients.³⁰¹

In 1952 Steinberg and Wilder published two additional papers attacking the presumption of anticipation in diabetes. Their paper “An Analysis of the Phenomenon of ‘Anticipation’ in Diabetes Mellitus,”³⁰² traced the idea of earlier onset of disease in succeeding generations back to Darwin’s *Variation of Animals and Plants Under*

²⁹⁶ For a discussion of Woodyat and Spetz (1942) see chapter three.

²⁹⁷ Arthur G. Steinberg, and Russell M. Wilder, “A Reconsideration of the Phenomenon of Anticipation in Diabetes Mellitus,” *Proceedings of the Staff Meetings of the Mayo Clinic* 25 no. 23 (8 November 1950): 626.

²⁹⁸ Steinberg and Wilder, “Reconsideration,” 625.

²⁹⁹ Steinberg and Wilder, “Reconsideration,” 626-627.

³⁰⁰ Steinberg and Wilder, “Reconsideration,” 628-629. Intriguingly, they noted that this analytic method “although independently arrived at, was suggested in 1912 by Pearson in a theoretical discussion of antedating in mental illness.” This suggests that these two were fairly wide read on the subject as Penrose (1948) mentioned Heron (1914) but not Pearson (1912). Steinberg and Wilder, “Reconsideration,” 629.

³⁰¹ Steinberg and Wilder, “Reconsideration,” 630.

³⁰² Arthur G. Steinberg and Russell M. Wilder, “An Analysis of the Phenomenon of ‘Anticipation’ in Diabetes Mellitus,” *Annals of Internal Medicine* 36 no. 5 (May 1952): 1285-1296.

Domestication, through Pieraccini's claim that he was the one to first devise the modern idea of anticipation,³⁰³ and then to Mott's 1910 Huxley lecture.³⁰⁴ They noted that Woodyat and Spetz—whose work had fostered the idea that anticipation occurred in diabetes—had agreed with Mott's hypothesis that anticipation resulted “from a progressive degeneration of the germ plasm” but Steinberg and Wilder noted that “most geneticists do not ascribe any biologic significance to the phenomenon of anticipation.”³⁰⁵ Even though they admitted that the geneticists' opinion on anticipation was “based on general considerations rather than actual investigation,” they were impressed by Penrose's analysis of the role of selection bias in the appearance of anticipation in myotonic dystrophy and felt that his hypothetical genetic explanation (allelic genes) “could lead to the observed data.”³⁰⁶ Although they knew “of no analysis in which anticipation was actually demonstrated to be a statistical phenomenon,” they argued that “even though data may appear most convincing, considerable caution must be shown before they can be accepted as proving that antedating is of physiologic importance in any given disease.”³⁰⁷ Much like Pearson, Steinberg and Wilder argued that the appearance of anticipation was caused by variable age of onset in the disease in which the parental generation was selected for late onset by virtue of having lived long enough to become parents. No such selective pressure was placed on the children's generation which could then display the disease at an age (but early onset would be most notable)³⁰⁸ They argued that the combination of this later age of onset in the parental generation with the earlier detection of disease in younger members of the family provided an explanation which was “applicable to many if not all reported instances of

³⁰³ Steinberg and Wilder referred here to Pieraccini's 1932 article in which he claimed priority of discovery and not to the 1901 paper in which Pieraccini in 1932 said he had announced the discovery. The 1901 article has proven impossible to access. A. Pierraccini, “On the Priority of the Biological Hereditary Law of ‘Anticipation’,” *Human Biology* 4 no. 4 (December 1932): 554-557.

³⁰⁴ In this lecture, Mott did not yet refer to “anticipation” as he had not yet been contacted by Nettleship. He did, however, refer to the findings of a number of other researchers—including Heilbronner—for the observation that certain diseases appeared earlier in succeeding generations. F. W. Mott, “The Huxley Lecture on The Hereditary Aspects of Nervous and Mental Diseases.” *The Lancet* 176 no. 4545 (8 October 1910): 1057-1059. Later in their paper Steinberg and Wilder would note the criticisms made of anticipation by Pearson, Heron and Paterson. Steinberg and Wilder, “Analysis,” 1286.

³⁰⁵ Steinberg and Wilder, “Analysis,” 1285-1286.

³⁰⁶ Steinberg and Wilder, “Analysis,” 1286.

³⁰⁷ Steinberg and Wilder, “Analysis,” 1286.

³⁰⁸ Steinberg and Wilder, “Analysis,” 1294.

‘anticipation’ in diseases with variable age of onset.”³⁰⁹ They concluded that “inasmuch as anticipation in diabetes is the result of statistical and not physiologic connotation,” the term should not be used in discussion of the earlier onset of disease in the children of affected parents.³¹⁰ Instead they urged that the term “prior onset” be used.³¹¹ Their second 1952 paper “A Study of the Genetics of Diabetes Mellitus,” continued to argue that the apparent decrease of the age of onset of diabetes in succeeding generations and “the apparent ‘anticipation’” were spurious.³¹² Their data appeared to further support the idea that anticipation was a statistical artefact rather than a biological reality.³¹³

In the late 1960s the Italian physicians L. Gedda, D. Casa, and G. Brenci also examined anticipation in diabetes. In their 1967 paper, “Chronon and the Problem of Anticipation,” they agreed with the ideas of Penrose, Stern, and Steinberg and Wilder, that “there is no real phenomenon of *anticipation*.”³¹⁴ This conclusion was recapitulated in their 1970 paper in which they advocated a polygenic (multiple gene) hypothesis for diabetes.³¹⁵ The variety of combinations that could be made by more than two alleles could, they felt, account better for the wide variety of type, severity, and age of onset seen in diabetes.³¹⁶ Under this model, they argued, anticipation could be explained as the result of variation in “the gene’s temporal unit” which they termed the “Chronon.”³¹⁷

Myotonic Dystrophy

Two studies published in 1954 called attention to the increasingly severe manifestations of myotonic dystrophy over succeeding generations. Both senior authors received their medical education before 1948. David Klein traced the progressive aspects of the disease through three generations of a family—complete with photographs of the affected grandmother, mother, and daughter who were stricken by the disease at

³⁰⁹ Steinberg and Wilder, “Analysis,” 1294.

³¹⁰ Steinberg and Wilder, “Analysis,” 1294-1296.

³¹¹ Steinberg and Wilder, “Analysis,” 1294-1296.

³¹² Arthur G. Steinberg and Russell M. Wilder, “A Study of the Genetics of Diabetes Mellitus,” *American Journal of Human Genetics* 4 no. 2 (June 1952): 116.

³¹³ Steinberg and Wilder, “Study,” 116.

³¹⁴ L. Gedda, D. Casa, and G. Brenci, “Chronon and the Problem of Anticipation (On two family cases of diabetes),” *Acta Geneticae Medicae et Gemellologiae* 16 no. 3 (July 1967): 218-219.

³¹⁵ L. Gedda, D. Casa, and G. Brenci, “Sulla Genetica del Diabete: Analisi di nove casi famigliari,” *Acta Geneticae Medicae et Gemellologiae* 19 no. 3 (July 1970): 385-398.

³¹⁶ Gedda, Casa, and Brenci, “Sulla Genetica,” 385, 395-396.

³¹⁷ Gedda, Casa, and Brenci, “Sulla Genetica,” 385, 395-396.

increasingly earlier ages and with increasingly severe manifestations.³¹⁸ In the same year, J. E. Caughey and J. Barclay discussed congenital defects seen during their examination of cases of myotonic dystrophy in New Zealand.³¹⁹ They concluded that these congenital defects should be considered as part of the manifestations of the disease and noted—quite significantly—that “from our own studies it seems probable that affected women of the ‘dystrophic generation’ are especially liable to have children with some congenital physical defect.”³²⁰ These findings significantly precede those of Harper and Dyken whose 1972 paper is usually seen as the one that identified the maternal transmission of congenital myotonic dystrophy.³²¹ The fact that Caughey’s findings were published—in essentially the same form—in his well-cited 1963 monograph on myotonic dystrophy co-authored with Ntinou Myriantopoulos leads me to suspect that this lack of recognition was not due to a lack of dissemination.³²²

The Dutch physician Johannes De Jong published his monograph on the three myotonic disorders in 1955.³²³ With regard to the pattern of inheritance of myotonic dystrophy, he noted that “the problem of the *progressive heredity* remains a difficult one.”³²⁴ The progression of the disease over succeeding generations from cataract, to mild myotonic dystrophy, to severe disease noted several times by previous researchers, was also seen in the families De Jong studied.³²⁵ He argued that it was “also certain that in the progression a faulty family anamnesis often plays a part.”³²⁶ That is, like other researchers, De Jong believed that family members forgot to include individuals with early onset disease in previous generations, a practice which he thought led to the perception of anticipation. Considering the various genetic explanations of myotonic

³¹⁸ Klein continued to favour Goldschmidt’s explanation of ‘dominigenes’ as the genetic cause of these findings. David Klein, “Manifestations progressives et extensives d’une dystrophie myotonique dans une famille argovienne,” *Confina Neurologica* 14 (1954): 169-175.

³¹⁹ J. E. Caughey and J. Barclay, “Dystrophia myotonica and the occurrence of congenital physical defect in affected families,” *Australasian Annals of Medicine* 3 no. 3 (August 1954): 165-170.

³²⁰ Caughey and Barclay, “Dystrophia myotonica,” 169.

³²¹ Harper and Dyken, “Early onset dystrophia myotonica. Evidence supporting a maternal environmental factor,” *Lancet* 2 (1972): 53-55. See for example, C. J. Höweler, “Clinical and Genetic,” 77.

³²² J. E. Caughey, “Congenital Mental and Physical Defects in Dystrophia Myotonia,” in J. E. Caughey and N. C. Myriantopoulos, *Dystrophia Myotonia and Related Disorders*, (Springfield IL: Charles C. Thomas Publisher, 1963), 124-137.

³²³ Johannes Gerardus Ype De Jong, *Dystrophia Myotonica Paramyotonia and Myotonia Congenita*, Translation by Sister M. Lidzina van Weers and Sister M. Luke Gray, (Assen: Von Gorcum, 1955).

³²⁴ De Jong, *Dystrophia Myotonica*, 160.

³²⁵ De Jong, *Dystrophia Myotonica*, 160-161.

³²⁶ De Jong, *Dystrophia Myotonica*, 160-161.

dystrophy, De Jong concluded that Goldschmidt's "dominogene" hypothesis was the most reasonable, but he also called Waardenburg's hypothesis that a mutation might include chromosomal as well as gene alterations "an opinion that I can subscribe to."³²⁷ In his view, the hypothesis of allelic modification required more elucidation, but he concluded that incomplete penetrance of the gene lay behind the variation of symptoms—where the penetrance of the gene was incomplete the disease would be mild and of late onset, while complete penetrance meant the disease would be severe and of early onset.³²⁸ These conclusions, he felt, "need not present difficulties with the broad mutation theory" of Waardenburg which he believed offered "the best theoretical explanation" for heredity in myotonic dystrophy.³²⁹ In a paper published in 1957, De Jong again briefly discussed progressive heredity in myotonic dystrophy which was clearly apparent in the families that he studied.³³⁰

Also in 1957, Margaret Lynas examined myotonic dystrophy in Northern Ireland.³³¹ Her study was unusual in that she calculated the correlation of age of onset in parent-child and sib-sib pairs under different onset conditions and found that "apparent anticipation" was not present when she included cataract in the symptoms, but did seem to occur when she calculated according to the age of onset of first symptoms.³³² In any event, her calculated index of anticipation was lower than that described by Penrose (1948).³³³ Lynas believed that mild cases of the disease in earlier generations were being

³²⁷ This hypothesis appeared in a discussion of a paper published in 1951. P. J. Waardenburg, "Discussion," *Folia Psychiatrica, Neurologica et Neurochirurgica Neerlandica* 54 (1951): 193. De Jong, *Dystrophia Myotonica*, 161.

³²⁸ Waardenburg had been speculating on the genetic causes of myotonic dystrophy since 1932. P. J. Waardenburg, *Bibliographia Genetica*, Vol. 7, *Das Menschliche Auge und seine Erblangen*, ed., J. P. Lotsy and W. A. Goddijn, (The Hague: Martinus Nijhoff, 1932), 298-304. Penetrance is the term used to describe the visible action of the gene (genotype) on the physical organism (phenotype). Where genes are highly penetrant almost every individual carrying the gene will express its effect. If a gene is only incompletely penetrant there will be individuals who carry the defective gene but exhibit few or no symptoms. De Jong used the theory of incomplete penetrance to explain why some individuals were only slightly affected by myotonic dystrophy while others were severely stricken by the disease. De Jong, *Dystrophia Myotonica*, 161-162.

³²⁹ De Jong, *Dystrophia Myotonica*, 162.

³³⁰ J. G. Y. De Jong, "Dystrophia Myotonica, Paramyotonia, and Myotonia Congenita," *Acta Genetica et Statistica Medica* 7 (1957): 313-313.

³³¹ Margaret Lynas, "Dystrophia Myotonica with Special Reference to Northern Ireland," *Annals of Human Genetics* 21 (1957): 318-351.

³³² Lynas, "Dystrophia Myotonica," 337.

³³³ Lynas, "Dystrophia Myotonica," 334.

missed and concluded that, in her series in any event, “apparent anticipation” was not present.³³⁴

In 1958 David Klein, whose earlier work was considered above, again examined anticipation in myotonic dystrophy, this time as part of an extensive study of myotonic dystrophy and congenital myotonia in Switzerland.³³⁵ In the families he examined the age of onset of disease decreased in succeeding generations—findings that confirmed those made by a number of previous authors—which meant, he believed, that the phenomenon of anticipation represented a biological reality.³³⁶ He recognized that many authors—Penrose in particular—had attributed such findings to a statistical error, but Klein held that his methodology avoided the alleged biases of selection.³³⁷ Klein preferred to adopt Goldschmidt’s dominigene hypothesis: he argued that anticipation was a real biological phenomenon, in which the most severe cases were caused by the changes provoked by modifying factors (Goldschmidt’s dominigenes).³³⁸ His statistical analysis showed that myotonic dystrophy was inherited as a simple Mendelian dominant gene with complete penetrance.³³⁹ Klein argued vehemently for the validity of the “law” of anticipation in myotonic dystrophy.³⁴⁰

After the Second World War improvements in neonatal treatment allowed the survival of infants who would otherwise have died before the significance of their symptoms could be ascertained and allowed researchers to recognize congenital-onset forms of disease.³⁴¹ T. M. Vanier’s 1960 study has been described as offering “the first clear description of myotonic dystrophy in young children.”³⁴² Vanier’s findings

³³⁴ Lynas, “Dystrophia Myotonica,” 337.

³³⁵ David Klein, “La dystrophie myotonique (Steinert) et la myotonie congénitale (Thomsen) en Suisse,” *Journal de Génétique Humaine* (Supplement) 7 (1958): 1-328.

³³⁶ Klein, “dystrophie myotonique,” 46.

³³⁷ Klein, “dystrophie myotonique,” 47.

³³⁸ Klein, “dystrophie myotonique,” 47.

³³⁹ To Klein the finding of complete penetrance showed that there were no missing individuals of the sort that Penrose had assumed must exist—i.e. there were no complementary pairs. Klein, “dystrophie myotonique,” 51.

³⁴⁰ The exact quotation is: “Notre impression générale tend donc plutôt à affirmer la validité de la loi d’antéposition dans la dystrophie myotonique,” Klein, “dystrophie myotonique,” 47.

³⁴¹ Several previous studies—including Maas (1937) and Bell (1948)—had remarked upon the high frequency of abortions, stillbirths, and infant deaths in families suffering from myotonic dystrophy. Harper, *Myotonic Dystrophy*, 1st ed., (1979), 170.

³⁴² Peter Harper, *Myotonic Dystrophy*, 1st ed., (Philadelphia: W. B. Saunders Company, 1979), 170. David Klein disputed this in his 1990 autobiography, arguing that he had published a description of just such a case in 1954 and repeated it in his 1958 monograph. Klein, “Living History,” 329.

suggested that the degenerative process which usually began at later ages in myotonic dystrophy had, in these cases, actually begun *in utero*.³⁴³ Moreover, he implied that all of these severely affected children were born to mothers who, with only one exception, had “minimal features of the disease.”³⁴⁴ He commented on anticipation, but dismissed it as likely a result of the fact that only the mildly affected reproduced.³⁴⁵

In the 1960s, Penrose’s hypothesis was the accepted explanation for any findings of decreasing age of onset or increasing severity of disease over several generations in studies of myotonic dystrophy.³⁴⁶ There were very few exceptions.³⁴⁷ The only defence of anticipation of any note in that decade was that made by the physician J. E. Caughey in his 1963 co-authored monograph on myotonic dystrophy written with the geneticist Ntinios Myrianthopoulos.³⁴⁸ Caughey had begun his study of myotonic dystrophy in the 1930s at about the same time that theoretical arguments against anticipation resurfaced.³⁴⁹ He remained unswayed by any of the arguments against anticipation. As he noted in the 1963 monograph, “My collaborator, Dr. Myrianthopoulos, and I do not see eye to eye in this regard.”³⁵⁰ Caughey believed that the decreasing age of onset of cataract in myotonic dystrophy over succeeding generations indicated anticipation; Myrianthopoulos felt that the age of onset of cataract was random and merely “another example of the pleiotropic

³⁴³ T. M. Vanier, “Dystrophia myotonica in childhood,” *British Medical Journal* 2 (29 October 1960): 1286.

³⁴⁴ As will be discussed in chapter five, these findings were later expanded upon by other researchers. Vanier, “Dystrophia myotonica,” 1286.

³⁴⁵ Vanier, “Dystrophia myotonica,” 1286.

³⁴⁶ See for example: Robert Gibson, “Dystrophia Myotonica in Association with Mental Defect,” *Canadian Medical Association Journal* 84 no. 22 (3 June 1961): 1234-1237; T. A. Vos, “25 Years Dystrophia Myotonica (D.M.)” *Ophthalmologica* 141 (1961): 37-45; Jack D Welsh, Gunter R. Haase, and T. E. Bynum, “Myotonic Muscular Dystrophy: Systemic Manifestations,” *Archives of Internal Medicine* 114 no. 5 (1964): 669-679; J. Junge, “Ocular Changes in Dystrophia myotonica, Paramyotonia and Myotonia congenital,” In *Documenta Ophthalmologica: Advances in Ophthalmology*. Vol. 12. G. von Bahr, G. B. Bietti, J. ten Doesschate, H. Fischer-von Büнау, J. François, H. Goldmann, K. Müller, Jean Nordmann, A. J. Schaefer, and Arnold Sorsby, Eds., (The Hague: Dr. W. Junk, 1966), 70-75; Sarah Budney and C. O. Carter, “Early recognition of heterozygotes for the gene for dystrophia myotonica,” *Journal of Neurology, Neurosurgery, and Psychiatry* 33 no. 3 (1970): 279-293.

³⁴⁷ Neville Parker felt that Penrose might have been correct in assuming that anticipation was an artefact, but he believed that attempts so far to explain the genetics behind the various manifestations of myotonic dystrophy were insufficient. Neville Parker, “Dystrophia myotonica presenting as congenital facial diplegia,” *Medical Journal of Australia* 2 no. 23 (7 November 1963): 939, 943-944.

³⁴⁸ J. E. Caughey and N. C. Myrianthopoulos. *Dystrophia Myotonica and Related Disorders*, (Springfield IL: Charles C. Thomas Publisher, 1963).

³⁴⁹ For Caughey’s early work on myotonic dystrophy see chapter three.

³⁵⁰ Caughey and Myrianthopoulos, *Dystrophia Myotonica*, 1st ed., (1963), 70.

effect of the gene” for myotonic dystrophy.³⁵¹ This recorded difference of views makes it likely Myriantopoulos alone wrote the discussion of anticipation. Although anticipation had been reported “from the earliest descriptions of the disease,” the text asserted that there was “no evidence that anticipation is a phenomenon of direct biological significance.”³⁵² Any findings which supported anticipation could “be adequately explained” on the basis of faulty selection.³⁵³ The explanations of Penrose (1948) and Stern (1960) were invoked to explain away findings of earlier age of onset in succeeding generations and Penrose’s multiple allele hypothesis was used to explain the variable nature of the disease which led to these mistaken findings of anticipation.³⁵⁴ In his 1986 dissertation, the Dutch neurologist C. J. Höweler has noted that Caughey was the last author to affirm the reality of anticipation in myotonic dystrophy in a study published between 1962 and 1979. After this point the opinions of the geneticists on anticipation came to dominate the field.³⁵⁵

The literature suggests that the tide had been turning against the concept of anticipation since shortly after the publication of Penrose (1948) and that it was only researchers trained in the period before the Second World War—such as Klein and Caughey—who kept anticipation alive in the scientific literature into the 1960s in the face of opposition from their more recently trained colleagues. Nevertheless, in the late 1960s evidence was emerging that would require the human and medical genetics communities to take anticipation seriously. In 1969 the American neurologist Paul Dyken presented a short paper at the American Academy of Neurology meeting in which he discussed myotonic dystrophy as a disease with three distinct syndromes.³⁵⁶ The first syndrome (S1) included the mildest cases, the second (S2) consisted of myotonic dystrophy in its classical presentation, and the third (S3) accounted for the most severe form of the disease, with congenital or childhood onset.³⁵⁷ The fact that the appearance

³⁵¹ Caughey and Myriantopoulos, *Dystrophia Myotonica*, 1st ed., (1963), 70.

³⁵² Caughey and Myriantopoulos, *Dystrophia Myotonica*, 1st ed., (1963), 200.

³⁵³ Caughey and Myriantopoulos, *Dystrophia Myotonica*, 1st ed., (1963), 200.

³⁵⁴ Caughey and Myriantopoulos, *Dystrophia Myotonica*, 1st ed., (1963), 200-204.

³⁵⁵ Höweler, “Clinical and Genetic Study,” 9-10, 21; Christiaan J. Höweler, Correspondence with Judith Friedman, 18 March 2004.

³⁵⁶ Paul R. Dyken, “The changing syndromes of dystrophia myotonica,” *Neurology* 19 no. 3 (March 1969): 292.

³⁵⁷ Dyken, “changing syndromes,” 292.

of these syndromes followed one another generationally—with the those suffering from S3 being the offspring of those with S2 who in turn descended from those with S1—was, he felt, truly significant.³⁵⁸ Myotonic dystrophy was, he stated, “genetically unique,” because it showed not only anticipation but also “changing expressivity” in succeeding generations, even if, “as yet no biological phenomena can definitely be offered as explanation” for these curious findings.³⁵⁹ As we shall see in chapter five, such findings mounted during the 1970s and 1980s without any acceptable genetic explanation being found.

Huntington’s Disease

The discussion of anticipation disappeared very quickly in the literature concerning Huntington’s disease after 1948. In her 1952 study, Stephanie Leese cited an “accepted theory of an abnormal autosomal dominant gene” as the cause of the disease.³⁶⁰ The 1953 study by Bickford and Ellison of Huntington’s disease in Cornwall noted that “ante-dating was formerly much stressed and seems to occur in our cases, but there is no evidence for this now, probably accounted for by the more accurate observation of cases and earlier detection of symptoms.”³⁶¹ Any such findings, they argued, were due to a combination of the selection of late age of onset in parental generations (as suggested by Davenport and Muncey) and to the unfortunate practice of publishing results before the disease manifested in members of the youngest generation.³⁶² The 1961 study by Campbell, Corner, Norman, and Urich, although it did not discuss anticipation, did acknowledge the “precocious development” and peculiar severity of Huntington’s disease in two sons of an affected father.³⁶³ The importance of this observation of parental transmission became evident by the end of the decade.

³⁵⁸ Dyken, “changing syndromes,” 292.

³⁵⁹ Dyken, “changing syndromes,” 292.

³⁶⁰ Stephanie M. Leese, “A Pedigree of Huntington’s Chorea: With a note on linkage data by R. R. Race,” *Annals of Eugenics* 17 (1952): 95.

³⁶¹ J. A. R. Bickford and R. M. Ellison, “The high incidence of Huntington’s chorea in the duchy of Cornwall,” *Journal of Mental Science* 99 (1953): 293.

³⁶² Bickford and Ellison, “high incidence,” 293.

³⁶³ A. M. G. Campbell, Beryl Corner, R. M. Norman, and H. Urich, “The Rigid Form of Huntington’s Disease,” *Journal of Neurology Neurosurgery and Psychiatry* 24 (1961): 71-73.

The 1960s also saw increasing recognition of the clinical variant of Huntington's disease that appeared in childhood. The American physician George Jervis who wrote on the subject in 1963 argued that "the condition must be exceedingly rare in children" but felt it likely that "instances of the disease in childhood go unrecognized" because the symptoms seen in the children, which often included seizure, differed from the chorea seen as characteristic of adult sufferers.³⁶⁴ Jervis noted that "one might consider all these cases extreme examples of 'anticipation'," but he felt that Penrose (1948) had shown these findings to be merely the result of allelic modification.³⁶⁵ An almost identical discussion on the subject was put forward by Ntinou Myriantopoulos in his 1966 study of Huntington's disease.³⁶⁶ He felt it "unfortunate that this concept still persists in medical and genetic literature."³⁶⁷

In 1967 two Irish physicians offered the first criticism of the theory that allelic genes were responsible for the variation in age of onset in Huntington's disease.³⁶⁸ Randolph Byers and John Dodge had examined four cases of juvenile Huntington's disease. In one of their families two half-siblings—the affected sons of an affected father—both developed the disease in childhood.³⁶⁹ They concluded that these findings diminished "the likelihood that the genetic constitution of the unaffected parent determines the early appearance of the disease in juvenile cases" of Huntington's disease.³⁷⁰ This conclusion was rebuked, however, by the authors of a later study. The French researchers P. Delmas-Marsalet, M. Bourgeois, Cl. Vital, and X. Fontages noted anticipation over three generations, but felt that Penrose's allelomorphic hypothesis

³⁶⁴ George Jervis, "Huntington's Chorea in Childhood," *Archives of Neurology* 9 no 3 (1963): 253. Interestingly, Jervis' childhood cases were all the children of men who were either known or suspected to have had Huntington's disease.

³⁶⁵ Jervis, "Huntington's," 253.

³⁶⁶ Ntinou Myriantopoulos, "Huntington's Chorea," *Journal of Medical Genetics* 3 (1966): 302-303.

³⁶⁷ Myriantopoulos, "Huntington's," 302.

³⁶⁸ Randolph K. Byers and John A. Dodge, "Huntington's chorea in children: Report of four cases," *Neurology* 17 no. 6 (1 June 1967): 587-596.

³⁶⁹ Byers and Dodge, "Huntington's," 591-594.

³⁷⁰ Byers and Dodge, "Huntington's," 596.

explained their findings.³⁷¹ In their pair of half-siblings—children of an affected mother—the disease did not begin at the same age.³⁷²

A presentation by A. Donald Merrit, P. M. Conneally, N. F. Rahman and A. L. Drew on juvenile Huntington's disease at the Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology, held in Montreal in 1967, first made the critical connection between the transmission of the disease by the male parent and the earlier age of onset of Huntington's disease in his affected offspring.³⁷³ This finding was confirmed in 1968 by G. W. Bruyn on the basis of evidence gleaned from his historical review of Huntington's disease.³⁷⁴ His discussion included a historical overview of findings of anticipation dating all the way back to Heilbronner (1903). He did remark that Penrose (1948) had suggested that allelic modification lay behind findings of anticipation.³⁷⁵ However, the findings of the paternal transmission of juvenile Huntington's disease remained to be explained and the causes underlying it remained unknown.³⁷⁶

ANTICIPATION DISCREDITED AS A BIOLOGICAL PHENOMENON: 1945-1970

Between 1945 and 1970 the concept of anticipation as a biological phenomenon was so severely discredited that even those findings suggestive of anticipation that Huntington's researchers made in the late 1960s were interpreted within the context set out by Penrose in 1948. The criticisms of anticipation on the basis of statistical methods, ascertainment bias, and experimental design put forward by Penrose were essentially no different than those already laid out by Pearson (1912, 1931), Heron (1914), and Paterson (1932, 1933).

³⁷¹ In this family the children born into the third generation inherited the Huntington's disease gene from their mother. P. Delmas-Marsalet, M. Bourgeois, Cl. Vital, and X. Fontages, "Formes rigide de la maladie de Huntington (étude d'une famille avec un cas anatomo-clinique)," *Revue Neurologique* 118 (1968): 278.

³⁷² Delmas-Marsalet et al., "Formes rigide," 278.

³⁷³ A. Donald Merrit, P. M. Conneally, N. F. Rahman and A. L. Drew, "Juvenile Huntington's Chorea," in *Progress in Neurogenetics. Proceedings of the Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology*, Vol. 1, eds., André Barbeau and Jean-Réal Brunette, (Amsterdam: Excerpta Medica Foundation, 1969), 645-650.

³⁷⁴ G. W. Bruyn, "Huntington's Chorea—Historical, Clinical and Laboratory Synopsis," in *Handbook of Clinical Neurology*, Vol., 6, Eds., P. J. Vinken and G. W. Bruyn, (Amsterdam: North-Holland Publishing Company, 1968), 316-323.

³⁷⁵ Bruyn, "Huntington's," 306.

³⁷⁶ In a note on page 323 Bruyn comments "Dr. L. N. Went from Leyden proposed an attractive explanatory hypothesis for this [paternal juvenile transmission] at the Montreal Congress (1967)." However, Bruyn did not discuss this hypothesis nor does it seem that Went's hypothesis was published in the conference proceedings. Bruyn, "Huntington's," 322-323.

The genetic explanation he suggested as the cause of the phenotypic variability—particularly in age of onset—that underlay perceptions of anticipation was essentially that of Goldschmidt (1938). In his 1948 paper, Penrose combined the points raised by his predecessors to produce an elegant hypothesis that explained anticipation as an artefact of selection bias and short study length in a disease with a high degree of phenotypic variation that he believed was due to allelic modification. He then conducted a highly persuasive *thought experiment* to test his hypothesis and found the results in line with the expected experimental results. As the Dutch researcher Christiaan Höweler would later note, the hypothesis put forward by Penrose remained untested, and no researcher ever successfully located the complementary pairs whose existence Penrose had posited must exist in order to support his belief that there had to be an equal variation in age of onset over the generations.³⁷⁷

I posit that several factors lay behind the ease with which the arguments put forward by Penrose in 1948 rose to prominence. Penrose was a well-respected and influential member of several research communities. His research into the genetic causes of mental deficiency had not only opened new ground for the psychiatric community but had earned him the respect of the human and medical genetics communities as well. As the new Galton Chair, he was in a position of institutional power, and he played an important role in educating the next generation of human and medical geneticists. The fact that his paper appeared near the beginning of the post-war period of expansion and institutionalization of the new fields of human and medical genetics was also significant. The quick adoption of Penrose's analysis of perceptions of anticipation in the post-war textbooks written to educate increasing numbers of human and medical geneticists (and the absence of any mention of anticipation in other available texts) helps to explain why researchers so completely dropped the concept of anticipation. As we have seen, only clinically inclined researchers whose education pre-dated the Second World War continued to support anticipation in the years between 1948 and 1970. However, Penrose's ideas would not have been so completely accepted had it not been for important changes within the broader field of genetics. There was no room for a form of heredity that could not be made to fit within the increasingly mathematical and

³⁷⁷ The work of Höweler will be discussed fully in chapter five.

mechanistic view of Mendelism that was then rising to dominance, spurred on by the elucidation of the nature, structure, and function of DNA between 1944 and 1958.

Chapter 5: Gradually Re-Conceptualizing Anticipation (1970-1990)

CONCEPTUALIZING ANTICIPATION: 1970-1986

By 1970, as was noted in the previous chapter, the overwhelming majority of geneticists and human geneticists had accepted Penrose's assertion that anticipation not an actual biological phenomenon, but was merely an experimental artefact caused by ascertainment bias and faulty experimental design.¹ Although some clinicians continued to argue that anticipation was in fact real, their claims were summarily dismissed by their genetically inclined colleagues. Perusal of the contents of human genetics publications reveals how resistant the scientific community in general at this time was to re-conceptualizing anticipation even in the wake of discoveries made concerning early-onset or congenital forms of Huntington's disease and myotonic dystrophy between 1970 and 1990.

Nevertheless, some authors of medical monographs on specific disorders retained the old concept of anticipation in their texts—even if only to deride it. Following the Dutch physician Christiaan Höweler's surprise discovery in 1986 that Penrose's hypothesis on anticipation was seriously flawed, meaning that anticipation seemed to have a genuine physical basis, a few others, most notably the British human geneticist Peter Harper, the author of medical monographs on both Huntington's disease and myotonic dystrophy, began the process of re-conceptualizing anticipation for the scientific and medical communities.²

¹ See for example, Lionel Penrose, "Social Aspects of Psychiatry: The Importance of Statistics," *Journal of Mental Science* 92 no. 389 (October 1946): 714.

² In chapters one through four I was able to analyze the developments in the fields of heredity, eugenics, genetics, and medicine against their historical, social, and institutional backgrounds. With chapter five we move in to the period of recent history with all of the difficulties that this poses to the researcher in terms of a lack of archival, primary and secondary source material. For this reason I have been forced to rely mainly on the analysis of scientific papers and oral and written interviews although the latter were only available from the 1980s. Relatively little has been written on the technological developments of this period and their impact. See for example, Thomas Caskey, "DNA-Based Medicine: Prevention and Therapy," in *The Code of Codes: Scientific and Social Issues in the Human Genome Project*, Daniel J. Kevles and Leroy Hood Eds., (Cambridge MA: Harvard University Press, 1992), 112-135; Horace Freeland Judson, "A History of Science and Technology Behind Gene Mapping and Sequencing," in *The Code of Codes: Scientific and Social Issues in the Human Genome Project*, Daniel J. Kevles and Leroy Hood Eds., (Cambridge MA: Harvard University Press, 1992), 37-80; Daniel Kevles, "Out of Eugenics: The Historical Politics of the Human Genome," in *The Code of Codes: Scientific and Social Issues in the Human Genome Project*, Daniel J. Kevles and Leroy Hood Eds., (Cambridge MA: Harvard University Press, 1992), 3-36.

ANTICIPATION IN THE SCIENTIFIC AND MEDICAL LITERATURE: 1970-1986

In order to carry out an analysis of the reception of the concept of anticipation in scientific and medical literature I have consulted genetics, medical genetics, human genetics, and clinical genetics texts. While the list of medical genetics textbooks consulted for this purpose was not exhaustive, it is fairly comprehensive and reveals an accurate picture of what the medical and medical genetics professions believed about anticipation. Moreover, in an attempt to track changes in the reception of the idea of anticipation over time, I sought book series that produced several editions in order to track changes in the conceptualization of anticipation over time.

This analysis revealed just how thoroughly the idea of anticipation had been discredited within the broader genetics community. Many of the genetics textbooks contained absolutely no discussion of anticipation whatsoever.³ The medical genetics community had likewise rejected the concept and medical genetics textbooks commonly contained no direct mention of anticipation at all.⁴ For example, the sixth and seventh editions of J. A. Fraser Roberts' popular *An Introduction to Medical Genetics* did not even mention anticipation.⁵ Levitan and Montagu did not discuss anticipation *per se*, but did address the question of variable age of onset in dominant disorders which they ascribed to Penrose's suggested hypothesis of normal isoalleles acting to moderate the effect of the mutated gene.⁶ Bodmer and Cavalli-Sforza ascribed the variation in severity of symptoms of myotonic dystrophy to the penetrance of the mutant gene—the disease

An exception to this trend was Paul Rabinow's monograph on the creation of PCR. Paul Rabinow, *Making PCR: A Story of Biotechnology*, (Chicago: University of Chicago Press, 1996). Some institutional histories detail developments in the field of molecular biology, but unfortunately the institutions examined did not intersect with those discussed here. See for example, Soraya de Chaderevian, *Designs for Life: Molecular Biology after World War II*, (Cambridge: Cambridge University Press, 2002).

³ For this reason I have not included a list of every genetics textbook consulted for the period between 1970 and 1986.

⁴ See for example: H. Eldon Sutton, *Introduction to Human Genetics*, 2nd ed., (New York: Holt, Reinhart and Winston, 1975); D. J. Weatherall, *The New Genetics and Clinical Practice*, (Oxford: Oxford University Press, 1982); D. J. Weatherall, *The New Genetics and Clinical Practice*, 2nd ed., (Oxford: Oxford University Press, 1985).

⁵ J. A. Fraser Roberts, *Introduction to Medical Genetics*, 6th ed., (London: Oxford University Press, 1974); J. A. Fraser Roberts and M. E. Pembry, *Introduction to Medical Genetics*, 7th ed., (Oxford: Oxford University Press, 1978); J. A. Fraser Roberts and M. E. Pembry, *Introduction to Medical Genetics*, 8th ed., (Oxford: Oxford University Press, 1985), 167-168.

⁶ Max Levitan and Ashley Montagu, *Textbook of Human Genetics*, (New York: Oxford University Press, 1971), 244-245.

was least severe when the gene was least penetrant and most severe when the gene was fully penetrant—they did not mention anticipation at all.⁷

Where the authors of medical genetics textbooks did discuss anticipation, they often used the opportunity to teach that the appearance of anticipation was likely due either to ascertainment bias or to the fact that the diagnoses of younger individuals were more likely when the disease was known to run in the family.⁸ Some researchers used their contributions to these texts to make polemical arguments against the existence of anticipation. In his contributions to clinical genetics texts in the 1970s, N. C. Myriantopoulos, who had argued against the existence of anticipation in the 1963 monograph co-authored with the clinician J. E. Caughey, continued to campaign against the existence of the concept. He argued that the ideas of anticipation and progression in diseases like myotonic dystrophy “seem to have had such a mesmerising appeal to workers who studied the disease as to be uncritically perpetuated to the present day” when “neither is a phenomenon of direct biological significance” but were instead “artefacts stemming from the mode of ascertainment of cases or families.”⁹ In their 1979 text, *Clinical Genetics: A Source Book for Physicians*, L. G. Jackson and R. N. Schimke even declared that the very term anticipation “should be removed from the genetics literature.”¹⁰ In his textbook *Elements of Medical Genetics* (1979) A. E. H. Emery also took a very negative view of anticipation describing it as merely the result of ascertainment bias or the survivor effect, where one saw only the least affected survivors of the grandparental and parental generations while seeing the earliest affected of the most recent generation.¹¹ Victor McKusick, the author of the often-updated and important compendium *Mendelian Inheritance in Man*, mentioned anticipation only in relation to inheritance in myotonic dystrophy with which it had been historically

⁷ W. F. Bodmer and L. L. Cavilli-Sforza, *Genetics, Evolution, and Man*, (San Francisco: W. H. Freeman and Company, 1976), 37-41.

⁸ See for example A. Sorsby, “Clinical Varieties of Genetic Disease,” in *Clinical Genetics*, 2nd ed., A. Sorsby ed., (London: Butterworths, 1973), 76.

⁹ N. C. Myriantopoulos, “Disorders of Muscle,” in *Clinical Genetics*, 2nd ed., A. Sorsby ed., (London: Butterworths, 1973), 232.

¹⁰ L. G. Jackson and R. N. Schimke, *Clinical Genetics: A Source Book for Physicians*, (New York: John Wiley & Sons, 1979), 20.

¹¹ Alan Emery, *Elements of Medical Genetics*, 5th ed., (Edinburgh: Churchill Livingstone, 1979), 223; Emery, *Elements of Medical Genetics*, 6th ed., (Edinburgh: Churchill Livingstone, 1983), 230, 263; Alan Emery and R. F. Mueller, *Elements of Medical Genetics*, 7th ed., (Edinburgh: Churchill Livingstone, 1988), 312.

associated, and took his arguments against anticipation directly from Penrose's 1948 paper.¹² As we saw in the previous chapter, it tended to be clinicians working with multi-generational families who continued to believe in the existence of anticipation, even over the protests of their colleagues.

THE RECOGNITION OF EARLY ONSET VARIETIES OF DISEASE: 1970-1986

Nettleship first defined anticipation in 1905 as a means of explaining the earlier onset of disease in individuals in succeeding generations. However, from as early as 1912 this finding came under attack by members of the Galton Laboratory. Julia Bell, who had often examined this vexed question, made the most prolonged criticisms of this idea. She concluded that findings of earlier ages of onset in succeeding generation were more often perceived than real, and were due to methodological problems including the analysis of incomplete pedigrees.¹³ Therefore, the discovery of distinct congenital and early onset forms of Huntington's disease and myotonic dystrophy, diseases with which anticipation had been historically associated, had far-reaching implications for the study of anticipation, even if this was not immediately evident.

¹² Victor McKusick's compendium *Mendelian Inheritance in Man* had its beginning in an attempt to collate and track human hereditary diseases. An analysis of succeeding editions reveals just how much the understanding of human genetics has changed over time. For an overview of the development of *Mendelian Inheritance in Man* see: Victor McKusick, "Mendelian Inheritance in Man and Its Online Version, OMIM," *American Journal of Human Genetics* 80 no. 4 (April 2007): 588-604. Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 3rd ed. (Baltimore: Johns Hopkins University Press, 1971), 198; Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 4th ed. (Baltimore: Johns Hopkins University Press, 1975), 224; Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 5th ed. (Baltimore: Johns Hopkins University Press, 1978), 268; Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 6th ed. (Baltimore: Johns Hopkins University Press, 1983), 366-368; Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 7th ed. (Baltimore: Johns Hopkins University Press, 1986), 509; Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 8th ed. (Baltimore: Johns Hopkins University Press, 1988), 511. In the 9th edition, McKusick noted that "with only rare exception it is the mother who transmits the disease." I can only assume that this is a misprint and that he meant that the mother transmits the congenital form of the disease as the next sentence was McKusick's comment that anticipation, although described, was undoubtedly an experimental artefact of the sort described by Penrose (1948). Victor McKusick, Clair A. Francomano, and Stylianos E. Antonarakis, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 9th ed., (Baltimore: Johns Hopkins University Press, 1990), 639.

¹³ For a discussion of Bell's work, see chapters two, three and four.

In the years just before and after the death of Lionel Penrose in 1972, several scientists reported the discovery and elucidation of congenital and/or early-onset forms of Huntington's disease and myotonic dystrophy, findings that were suggestive of anticipation. A variety of explanations were sought to explain or explain away these findings but none were particularly successful. In the meantime, evidence was growing that in the case of myotonic dystrophy, maternal transmission led to the earlier onset of disease in the succeeding generation while in the case of Huntington's disease, it was the male parent who transmitted the early onset form of the disease to the next generation. Although these new findings were being discussed in journals, medical genetics textbooks on the whole continued to be dismissive of anticipation as a factor in hereditary illness or simply ignored the concept altogether.

HUNTINGTON'S DISEASE: 1970-1986

Recognizing Early-Onset Huntington's disease: 1970-1986

Sporadic cases of juvenile-onset Huntington's disease had been reported in medical literature from the early years of the twentieth century, but no clear inferences were drawn from these findings. In a paper delivered at the Second International Congress of Neuro-Genetics and Neuro-Ophthalmology in 1967 A. D. Merrit and his colleagues first made the observation that parental transmission led to an earlier age of onset of disease in children. These findings, however, were not published until 1969.¹⁴ In his 1968 historical and literature review of Huntington's disease, G. W. Bruyn followed up on the conference report and noted that evidence supporting the paternal transmission of juvenile Huntington's disease was scattered throughout the literature.¹⁵ A. Barbeau confirmed this pattern of inheritance in 1970.¹⁶ Several other researchers then followed suit, examining their own populations to see if the paternal transmission of juvenile

¹⁴ A. Donald Merrit, P. M. Conneally, N. F. Rahman and A. L. Drew, "Juvenile Huntington's Chorea," in *Progress in Neurogenetics. Proceedings of the Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology*, Vol. 1, eds., André Barbeau and Jean-Réal Brunette, (Amsterdam: Excerpta Medica Foundation, 1969), 645-650.

¹⁵ G. W. Bruyn, "Huntington's Chorea—Historical, Clinical and Laboratory Synopsis," in *Handbook of Clinical Neurology*, Vol., 6, Eds., P. J. Vinken and G. W. Bruyn, (Amsterdam: North-Holland Publishing Company, 1968), 316-323.

¹⁶ André Barbeau, "Parental ascent in the juvenile form of Huntington's chorea," *Lancet* 296 no. 7679 (31 October 1970): 937.

Huntington's disease was universal.¹⁷ The sheer weight of these findings excluded the possibility that ascertainment bias was solely responsible for the observations of earlier onset of disease in later generations.¹⁸ Other researchers would show that the observations were identical independent of race.¹⁹ Several studies of the U.S. Huntington's roster, which contained the largest data set of Huntington's families, confirmed that the earlier onset of disease was associated with paternal rather than maternal inheritance.²⁰ Yet, two studies²¹ of small populations failed to find paternal transmission, as did one large study that looked at the age of death due to Huntington's disease.²² Those studying the progression of Huntington's disease through multiple generations of the same family made one of the most interesting findings. Two studies found that juvenile cases of Huntington's disease became more common after several

¹⁷ These studies include: E. D. Bird, A. J. Caro, and J. B. Pilling, "A sex related factor in the inheritance of Huntington's chorea," *Annals of Human Genetics* 37 (1974): 255-260; M.R. Hayden, "Huntington's chorea in South Africa," PhD Thesis, University of Cape Town, 1979; R. G. Newcombe, D. A. Walker, and P. S. Harper, "Factors influencing age of onset and duration of survival in Huntington's chorea," *Annals of Human Genetics* 45 (1981): 387-396; R. H. Myers, J. J. Madden, J. L. Teague, and A. Falek, "Factors related to onset of Huntington's disease," *American Journal of Human Genetics* 34 (1982): 481-488; G. A. Chase, L. E. Markson, R. Brookmeyer, and S. E. Folstein, "Covariate-dependent genetic counseling in Huntington's disease," *Journal of Neurogenetics* 3 (1986): 215-223.

¹⁸ Susan Folstein, *Huntington's Disease: A Disorder of Families*, (Baltimore: The Johns Hopkins University Press, 1989), 113.

¹⁹ S. E. Folstein, G. A. Chase, W. E. Wahl, A. M. McDonnell, and M. F. Folstein, "Huntington's disease in Maryland: Clinical aspects of racial variation," *American Journal of Human Genetics* 41 (1987): 168-179.

²⁰ M. Boehnke, P. M. Conneally, and K. Lange, "Two models for a maternal factor in the inheritance of Huntington's Disease," *American Journal of Human Genetics* 35 (1983): 845-860; P. M. Conneally, "Huntington's disease: genetics and epidemiology," *American Journal of Human Genetics* 36 (1984): 506-526; L. A. Farrer and P. M. Conneally, "A genetic model for age at onset in Huntington's disease," *American Journal of Human Genetics* 37 (1985): 350-357; R. M. Ridley, C. D. Frith, T. J. Crow, and P. M. Conneally, "Anticipation in Huntington's disease in inherited through the male line but may originate in the female," *Journal of Medical Genetics* 25 (1988): 589-595; R. M. Ridley, C. D. Frith, L. A. Farrer, and P. M. Conneally, "Patterns of inheritance of the symptoms of Huntington's disease suggestive of an effect of genomic imprinting," *Journal of Medical Genetics* 28 (1991): 224-231.

²¹ M. B. Jones and C. R. Phillips, "Affected parent and age of onset in Huntington's chorea," *Journal of Medical Genetics* 7 (1970): 20-21; C. J. Brackenridge, "A genetic and statistical study of some sex-related factors in Huntington's disease," *Clinical Genetics* 2 (1971): 287-297; C. J. Brackenridge, "The relation of type of initial symptoms and line of transmission to ages at onset and death in Huntington's disease," *Clinical Genetics* 2 (1971): 287-297.

²² L. N. Went, M. Vegter-van der Vlis, G. W. Bruyn, and V. S. Volkers, "Huntington's chorea in the Netherlands: the problem of genetic heterogeneity," *Annals of Human Genetics* 47 (1983): 205-214; L. N. Went, M. Vegter-van der Vlis, and G. W. Bruyn, "Parental transmission in Huntington's disease," *Lancet* i (1984): 1100-1102.

generations of transmission of the affected gene from father to son.²³ However, a later study failed to confirm these findings.²⁴

Explaining Early-Onset Huntington's Disease: 1970-1986

The hunt was now on to find a way to explain these mysterious findings. Linkage analysis suggested that whatever genetic mechanism lay behind the paternal transmission effect operated independently of the Huntington's disease gene.²⁵ One proposed mechanism that was quickly discarded was the hypothesis that a unique mutation of the Huntington's gene caused juvenile Huntington's disease.²⁶ The idea that juvenile Huntington's disease might be caused by homozygosity (possession of two copies of the mutant gene) was similarly dismissed.²⁷ Three hypotheses were then left as to possible causes of this paternal inheritance effect: the maternal factor hypothesis, the modifier gene hypothesis, and the genomic imprinting hypothesis.

The maternal factor hypothesis suggested that some factor inherited from the mother somehow 'protected' or delayed the age of onset of disease in children of affected women as compared to those of affected men. Two research groups proposed that either a cytoplasmic or a mitochondrial factor was involved.²⁸ The mitochondrial theory proposed by Myers *et al.* suggested that the earlier age of onset of Huntington's disease seen during paternal transmission might be due to mitochondrial genes, which were contributed almost exclusively by the mother. They based this idea on the theory that

²³ D. L. Stevens, "Huntington's chorea: a demographic genetic and clinical study," University of London: MD thesis, 1976; R. G. Newcombe, D. A. Walker, and P. S. Harper, "Factors influencing age of onset and duration of survival in Huntington's chorea," *Annals of Human Genetics* 45 (1981): 387-396.

²⁴ R. H. Myers, D. S. Sax and M. Schoenfeld, "Late onset of Huntington's disease," *Journal of Neurology, Neurosurgery and Psychiatry* 48 (1985): 530-534.

²⁵ L. A. Farrer, P. M. Conneally, and P. Yu, "The natural history of Huntington's disease: possible role of ageing genes," *American Journal of Medical Genetics* 18 (1984): 115-123; Folstein, *et al.*, "Racial variation," 168-179.

²⁶ Peter Harper, ed., *Huntington's Disease*, (London: W. B. Saunders, 1991), 309.

²⁷ Harper, *Huntington's Disease*, (1991), 309.

²⁸ When a human embryo is formed it received nuclear genetic material in equal amounts from both parents. However, the cellular contents (cytoplasm, organelles etc.) come almost exclusively from the mother as her contribution to the egg cell. Mitochondria (cellular energy plants) are a type of organelle which contains its own DNA separate and apart from nuclear DNA. For this reason mutations in mitochondrial DNA or problems with the cytoplasm result in particular patterns of inheritance, passing down from the mother to all offspring. A mutation in mitochondrial DNA is the cause of Leber's disease whose peculiar pattern of inheritance was at one time considered possibly due to anticipation. R. H. Myers, D. Goldman, and E. D. Bird, "Maternal transmission in Huntington's disease," *Lancet* 321 no. 8318 (29 January 1983): 208-210; M. Boehnke, *et al.*, "Two models," 845-860.

oxidative stress caused by free radical formation during oxidative phosphorylation could act toxically on cells, including neurons, and could be a causative factor in the degeneration of neurons in Huntington's disease.²⁹ Males and females carrying the Huntington's disease gene who lived long enough to reproduce would already have been selected for having mitochondria that were more "efficient" and less prone to create excess free radicals. In the case of paternal transmission, the *mother's* mitochondria would have undergone no such selection. Inheriting a less efficient mitochondrial system from the mother could then lead to neuronal damage and an earlier onset of Huntington's disease.³⁰ However, this hypothesis failed to explain why earlier ages of onset occurred in nearly all cases of paternal transmission. Surely some mothers would have had mitochondria as efficient as (or more efficient than) their husbands, resulting in the same or a later age of onset of Huntington's disease in their children. By 1991, this hypothesis was falling out of favour.³¹

In his 1948 paper, Penrose had suggested that modifying genes might be a cause of variability in the ages of onset of dominant disorders and so contribute to the perception of anticipation. This modifier gene hypothesis was put forward in the case of juvenile transmission of Huntington's disease. Boehnke *et al.* suggested that the paternal transmission effect could be caused either by an autosomal or by an X-linked gene acting to modify the effect of the Huntington's gene.³² While this group could not distinguish whether an autosomal or X-linked gene might be to blame, other researchers believed that an X-linked was the likeliest candidate.³³ Unfortunately, locating genes that might have a modifying action on the mutant Huntington's gene via linkage analysis to prove or disprove this hypothesis was a difficult undertaking.

²⁹ Myers *et al.* believed that damage caused by free radical release from the mitochondria during the process of cellular energy production contributed to the neuronal damage typical of Huntington's disease. The level of this oxidative stress could vary from individual to individual, they felt, depending on the "efficiency" of the mitochondria. The more efficient the mitochondria, the less oxidative stress, and the fewer damaged neurons. Myers *et al.*, "Maternal transmission," 208-210.

³⁰ Folstein, *Huntington's Disease*, 86-87; Myers *et al.*, "Maternal transmission," 208-210.

³¹ Harper, *Huntington's Disease*, (1991), 309.

³² Boehnke *et al.*, "Two models," 845-860.

³³ The idea of an X-linked factor was initially put forward by Stevens (1976) and was later taken up by Laird. Harper, *Huntington's Disease*, (1991), 309; C. Laird, "Huntington's disease: proposed mechanism of mutation, inheritance and expression," *Trends in Genetics* 6 (1990): 242-247.

The final hypothesis was that of genomic imprinting or methylation. Experiments with mice had shown that the methylation of a parental gene could have a substantial influence on the expression of the gene in the offspring.³⁴ In 1985, R. Erikson proposed that chromosomal imprinting might explain why Huntington's disease seemed to vary according to which parent transmitted the affected gene.³⁵ Similarly, W. Reik suggested in 1988, that genomic imprinting might be the cause of the paternal transmission of juvenile Huntington's if such imprinting caused the Huntington's disease gene to be expressed earlier or at a higher level.³⁶ This hypothesis, however, could not explain the occasional findings of maternal transmission of the juvenile onset form of Huntington's disease. The final test of this hypothesis could not be made, however, until the gene causing Huntington's disease was located and could be examined by restriction enzyme analysis.³⁷ Ridley *et al.* suggested that such a mechanism might be able to explain findings of anticipation in Huntington's disease if the higher degree of methylation that the Huntington's gene received when passing through the ovum delayed or reduced the production of the protein, thereby resulting in a later onset of the disease.³⁸ It was becoming increasingly clear that a determination of the mechanism that caused juvenile onset in Huntington's disease would rest at least in part on locating and sequencing the gene involved. Several research labs around the world began the hunt to do just that.

Incorporating New Ideas on Heredity in Huntington's Disease: 1970-1986

Between 1970 and 1986, most medical genetics textbooks ignored the concept of anticipation. The few textbooks that did discuss it generally followed the precedent set by Stern in 1949 and attributed the perception of anticipation to ascertainment bias or

³⁴ The addition of methyl groups to DNA is a control mechanism which decreases the expression of the gene without changing the DNA itself in any way. The more highly methylated the gene, the lower the expression of the protein product. Harper, *Huntington's Disease*, (1991), 332.

³⁵ R. P. Erikson, "Chromosomal imprinting and the parent transmission specific variation in Huntington's Disease," *American Journal of Human Genetics* 37 (1985): 827-829.

³⁶ Genetic imprinting is the process by which certain genes are expressed according to whether they were turned off or turned on in their parent of origin. In this case Reik proposed that because the defective Huntington's gene was inherited in a turned on mode, that it could be expressed more strongly in the offspring. W. Reik, "Genomic imprinting: a possible mechanism for the prenatal origin effect in Huntington's chorea," *Journal of Medical Genetics* 25 (1988): 805-808.

³⁷ Harper, *Huntington's Disease*, (1991), 332-333.

³⁸ Ridley *et al.*, "Anticipation in Huntington's disease," 589-585; Ridley *et al.*, "Patterns of inheritance," 224-231.

faulty experimental technique.³⁹ Unlike the case of myotonic dystrophy, the historical link between Huntington's disease and anticipation had been severed, and so the two were never discussed together. Instead, Huntington's disease was most often used as an example of an autosomal dominant disorder, which struck most often in middle age, although with some variability.

Victor McKusick was quick to incorporate the new discovery that paternal inheritance seemed to play a role in the development of early-onset Huntington's disease, when he discussed the issue in the third edition of *Mendelian Inheritance in Man*, published in 1971.⁴⁰ As new hypotheses were put forward to explain this pattern of inheritance they too were discussed in later editions of *Mendelian Inheritance in Man*; however the editors made did not acknowledge that this pattern of inheritance might be caused by anticipation.⁴¹ As shall be seen in a later section, what discussion of anticipation there was in *Mendelian Inheritance of Man* presented it solely historically as a false explanation for the patterns of inheritance seen in myotonic dystrophy.

In a similar fashion, the hypotheses attempting to explain the odd pattern of heredity in Huntington's disease made their way fairly quickly into medical monographs. Susan Folstein's 1989 monograph *Huntington's Disease* is a good example.⁴² As a physician who was educated after anticipation had been discredited and writing at a time when anticipation and Huntington's disease were no longer linked in the literature, Folstein, not unusually, did not mention anticipation when discussing the heredity of Huntington's disease. However, she did note the paternal transmission effect and discussed the three as-yet untested explanatory mechanisms: the mitochondrial hypothesis (her preferred hypothesis), the modifier gene hypothesis, and the gene methylation hypothesis.⁴³

³⁹ See for example: Emery, *Elements of Medical Genetics*, 5th ed., (1979), 223; Emery, *Elements of Medical Genetics*, 6th ed., (1983), 230, 263; Emery and Mueller, *Elements of Medical Genetics*, 7th ed., (1988), 312. The third and final edition of Penrose's *Outline of Human Genetics*, published the year after his death, continued to argue that anticipation was merely a statistical artefact. Lionel Penrose, *Outline of Human Genetics*, 3rd ed., (London: Heinemann Educational Books, 1973), 43.

⁴⁰ McKusick, *Mendelian Inheritance*, 3rd ed., (1971), 155-156.

⁴¹ For example, the different allelic forms hypothesis was discussed in the fourth edition. McKusick, *Mendelian Inheritance*, 4th ed., (1975), 175.

⁴² Folstein, *Huntington's Disease*.

⁴³ Folstein, *Huntington's Disease*, 86-87, 114-115.

MYOTONIC DYSTROPHY: 1970-1986

Recognizing Congenital and Early-Onset Myotonic Dystrophy: 1970-1986

While many early researchers considered myotonic dystrophy a disease that most commonly affected adults, some studies noted a high rate of stillbirths and deaths in early childhood in families with myotonic dystrophy although the cause of these deaths was not understood.⁴⁴ Improvements in health care following the Second World War allowed more of these children to survive, and beginning in 1960, specific congenital and childhood forms of myotonic dystrophy were identified. T. Vanier was the first to recognise myotonic dystrophy in young children in 1960.⁴⁵ Later researchers described the features of the disorder as seen in infancy⁴⁶ and identified diagnostic features, like the hallmark facial appearance of congenitally affected infants.⁴⁷ It was also discovered that the mental retardation sometimes seen in myotonic dystrophy cases could be linked to the congenital-onset form of the disease.⁴⁸ Other studies raised awareness that, despite modern medical advancements, the congenital form of the disease could be fatal for neonates.⁴⁹

Peter Harper and Paul Dyken's work of Harper and Dyken in the United States in the early 1970s is generally seen as the first to recognize that cases of congenital myotonic dystrophy were almost always found in the children of mothers carrying the affected gene. Harper and Dyken assumed that the most likely cause of this form of inheritance was some toxic or hormonal factor in the intrauterine environment. They noted, however, that there were some problems with this hypothesis. To begin, this factor somehow did not appear to affect genetically normal children who were born

⁴⁴ Otto Maas, "Observations on Dystrophia Myotonica," *Brain* 60 (December 1937): 498-524; Julia Bell, *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 5: Dystrophia Myotonica and Allied Diseases*, with clinical notes by J. Purdon Martin, ed., L. S. Penrose, (Cambridge: Cambridge University Press, 1947).

Treasury of Human Inheritance (1948). See also chapter three and four.

⁴⁵ T. M. Vanier, "Dystrophia myotonica in childhood," *The British Medical Journal* 2 (29 October 1960): 1284-1288.

⁴⁶ P. R. Dodge, I. Gamstorp, R. K. Byers, and P. Russell, "Myotonic dystrophy in infancy and childhood," *Pediatrics* 35 (1966): 3-19.

⁴⁷ G. V. Watters and T. W. Williams, "Early onset myotonic dystrophy," *Archives of Neurology* 17 (1967): 137-152.

⁴⁸ R. Calderon, "Myotonic dystrophy: a neglected cause of mental retardation," *Journal of Pediatrics* 68 (1966): 423-431.

⁴⁹ D. B. Bell and D. W. Smith, "Myotonic dystrophy in the neonate," *Journal of Pediatrics* 81 (1972): 83-86; J. D. Aicardi, D. Conti, and F. Goutières, "Les formes néo-natales de la dystrophie myotonique de Steinert," *Journal of the Neurological Sciences* 22 (1974): 149-164.

normal and healthy but rather acted only on children carrying the defective gene whose development was affected in utero.⁵⁰ Moreover, this toxic factor did not affect children when born to fathers with the disease or cases of maternal transmission of classical rather than early-onset myotonic dystrophy.⁵¹ These findings were confirmed in 1972.⁵²

After returning to Britain, Harper continued his research into myotonic dystrophy. In 1975, he published two articles outlining the clinical and genetic aspects of congenital myotonic dystrophy.⁵³ In his discussion of the genetics of congenital myotonic dystrophy, Harper confirmed that some maternal inheritance factor was operative but it could not be explained by the old argument of ascertainment bias. He also recognised that many mothers who had congenitally affected children were themselves only mildly affected by the disease. This raised two significant questions: why the form of the disease was so different in mother and child; and how one could explain the appearance of congenital cases of the disease only in children born to mothers affected with the classical form of the disease if myotonic dystrophy was an autosomal dominant that should have been present or absent, but not mutable in its effects.⁵⁴

Explaining Congenital and Early-Onset Myotonic Dystrophy: 1970-1986

These perplexing findings surrounding the mode of inheritance of congenital myotonic dystrophy called out for explanation. Some of the usual excuses such findings were rather quickly examined and dismissed while others required more examination. For some time, scientists were unable to come to a consensus as to the cause of these puzzling findings.

In 1972, Harper and Dyken overturned a long held idea by presenting evidence that ascertainment bias was not a likely cause of anticipation in the case of myotonic

⁵⁰ Peter Harper and Paul R. Dyken, "Early onset dystrophia myotonica—evidence supporting a maternal environmental factor," *Lancet* 300 no. 7767 (8 July 1972): 53-55.

⁵¹ Maternal transmission of classical myotonic dystrophy with adult onset disease would usually occur earlier in the pedigree and these children would appear normal at birth. It was the children of mothers with classical disease who would have congenital or early-onset forms of myotonic dystrophy. Harper and Dyken, "Early onset," 53-55.

⁵² Paul R. Dyken and Peter Harper, "Congenital dystrophia myotonica," *Neurology* 23 no. 5 (May 1973): 465-473.

⁵³ Peter S. Harper, "Congenital myotonic dystrophy in Britain. 1. Clinical aspects," *Archives of Disease in Childhood* 50 (1975): 505-513; Peter S. Harper, "Congenital myotonic dystrophy in Britain. 2. Genetic basis," *Archives of Disease in Childhood* 50 (1975): 514-521.

⁵⁴ Harper, "Genetic Aspects," 514-521.

dystrophy. They discarded ascertainment bias because selection methodologies had improved considerably since 1948. Since congenital cases of myotonic dystrophy were only seen in the offspring of female sufferers, decreased male fertility relative to female fertility was also considered and deemed insufficient to explain the results. The hypothesis that the early onset form might be caused by a separate allele was considered “unlikely to be an adequate explanation, since not only were the mothers of the early-onset cases frequently mildly affected, but also sibs were observed with the more typical form of the disease.”⁵⁵ Harper and Dyken believed that an intrauterine factor lay at the root of anticipation, even though they could not locate such a factor.⁵⁶

In his 1975 paper, Harper laid to rest the perennial argument that childhood cases of myotonic dystrophy were being recognised because the disease was already known to be present in the family. Instead, his survey found instead that in many cases it was the birth of an affected child that led to the diagnosis of myotonic dystrophy in the mother, in whom symptoms were so slight as to have been hitherto undiagnosed.⁵⁷

In their 1972 study, Budney and Carter had raised the idea that genetic heterogeneity might cause the variations in age of onset in myotonic dystrophy, that is that what had been classified as one disorder could in fact be two or more different disorders.⁵⁸ Genetic heterogeneity could express itself either by different mutations in the same gene causing different degrees of severity or by mutations in completely different genes. Budney and Carter suggested that what was called myotonic dystrophy might be made up of two or three different disorders, possibly caused by different mutations in the same gene, and that the variety of mutations produced overlapping ages of onset of disease.⁵⁹ Harper noted several problems with their hypothesis.⁶⁰ First, their findings conflicted with work done earlier by Bell.⁶¹ Secondly, their work depended on being able to judge the age of onset of myotonic dystrophy symptoms accurately. Because age of onset was often extremely difficult to determine accurately in the case of

⁵⁵ Harper and Dyken, “Early onset,” 54.

⁵⁶ Harper and Dyken, “Early onset,” 53-55.

⁵⁷ Harper, “Genetic basis,” 514-521.

⁵⁸ Sarah Budney, and C. O. Carter, “Genetic heterogeneity for dystrophia myotonica,” *Journal of Medical Genetics* 9 (1972): 311-315.

⁵⁹ Budney and Carter, “Genetic heterogeneity,” 311-315.

⁶⁰ Peter S. Harper, *Myotonic Dystrophy*, (London: W. B. Saunders, 1979), 219-220.

⁶¹ Bell, *Treasury of Human Inheritance* (1947).

myotonic dystrophy, the data might be significantly skewed. Finally, Budney and Carter defined all their early onset cases as those manifesting under 30 years of age but they did not separate out the congenital cases that might have another cause.⁶² The possibility that myotonic dystrophy might be caused by mutations taking place in more than one location of the genome was ruled out based on linkage analysis studies.⁶³

A number of earlier workers including Goldschmidt and Penrose had suggested that the variability of effect might be caused by the action of other genes on the main myotonic dystrophy gene. While this hypothesis had been suggested as a way to explain congenital myotonic dystrophy, Harper and Dyken rejected it early on since the mildly-affected mothers of early-onset children could have siblings with the typical form of myotonic dystrophy.⁶⁴

Harper and Dyken favoured a maternal factor hypothesis as the explanation for congenital myotonic dystrophy.⁶⁵ They believed that an intrauterine factor provided an explanation for the appearance of anticipation although the nature of the factor remained elusive.⁶⁶ Harper later confirmed these findings with his large study of congenital myotonic dystrophy in Britain. He argued that congenital myotonic dystrophy was caused by the interaction of the gene and some maternally transmitted factor. This hypothesis could explain uterine onset and why symptoms were worst in the neonatal period with slow improvements in childhood before deterioration in adolescence and adulthood. He believed that the missing adult features of the disease could be explained by the action of the gene occurring in utero.⁶⁷

Incorporating New Ideas on Heredity in Myotonic Dystrophy: 1970-1986

As established earlier, most medical genetics textbooks began this period either ignoring the concept of anticipation entirely or warning that it was deeply flawed. Generally, if

⁶² Harper, *Myotonic Dystrophy*, (1979), 219-220.

⁶³ Harper, *Myotonic Dystrophy*, (1979), 221.

⁶⁴ Harper and Dyken, "Early onset," 54.

⁶⁵ Harper and Dyken, "Early onset," 54.

⁶⁶ Harper and Dyken, "Early onset," 53-55.

⁶⁷ Harper, "Genetic basis," 514-521.

they discussed anticipation at all, the authors of these textbooks maintained this stance on anticipation throughout the period under examination in this chapter.⁶⁸

Because myotonic dystrophy had, almost from the time of its discovery, been so closely associated with anticipation, an analysis of the literature's treatment of the new finding of maternally inherited congenital or early-onset forms of myotonic dystrophy is illuminating for charting effective reception of innovation into the scientific mainstream. In 1983 this new material began to be incorporated into medical genetics textbooks. After this date many authors noted that congenital or early-onset cases of myotonic dystrophy were maternally inherited, even while they continued to ignore the possibility of anticipation.⁶⁹ This information, of course, was important for genetic counselling purposes—particularly as linkage analysis made possible pre-natal screening for factors linked to the myotonic dystrophy gene.⁷⁰ Once the oddity of this form of inheritance was dealt with, it was sometimes dismissed with the note that the causes of this sort of variability were not well understood.⁷¹ After 1983, McKusick's *Mendelian Inheritance in Man* also noted that some maternal factor was likely involved in cases of congenital myotonic dystrophy. But, through the rest of the decade he continued to agree with Penrose that anticipation was most probably an artefact, rather than a biological reality.⁷²

Between 1970 and 1986, two major monographs appeared on myotonic dystrophy, one published in 1973 by Zellweger and Ionasescu, and a second by Peter Harper in 1979. Zellweger and Ionasescu's monograph contained a historical review of anticipation in myotonic dystrophy. They noted that while some researchers had credited the idea of anticipation, others—most notably Penrose—had doubted its existence. They felt that of all of the arguments marshalled against anticipation, the most notable was that

⁶⁸ See for example: Emery, *Elements of Medical Genetics*, 5th ed., 1979, 223; Emery, *Elements of Medical Genetics*, 6th ed., 1983, 230, 263; Emery and R. F. Mueller, *Elements of Medical Genetics*, 7th ed., 1988, 312.

⁶⁹ See for example: Michael Baraister and Robin M. Winter, *A Colour Atlas of Clinical Genetics*, (London: Wolfe Medical Publications Ltd., 1983), 122; K. Garver and S. Marchese, *Genetic Counselling For Clinicians*, (Chicago: Year Book Medical Publishers, Inc., 1986), 103.

⁷⁰ For example see: H. M. Kingston, *ABC of Clinical Genetics*, (London: British Medical Association, 1989), 13.

⁷¹ L. P. Rowland, D. S. Wood, E. A. Schon, and S. DiMauro eds., *Molecular Genetics in Diseases of Brain, Nerve, and Muscle*, (New York: Oxford University Press, 1989), 110.

⁷² McKusick, *Mendelian Inheritance*, 6th ed., (1983), 366-368; McKusick, *Mendelian Inheritance*, 7th ed., (1986), 509; McKusick, *Mendelian Inheritance*, 8th ed., (1988), 511.

which focussed on “the life span of the investigator.”⁷³ During the course of his or her career this theory ran, a researcher would see illness develop during the parental generation, recognize late onset cases in the grandparental generation, and encounter cases of early onset in the filial generation. However, such a researcher would most likely miss any late-onset cases that might develop in the filial generation (the complementary pairs that had been postulated by Penrose) as they would most likely not appear within the researcher’s lifetime.⁷⁴ This would lead to the appearance of anticipation.

Zellweger and Ionasescu did remark upon the recent discovery of the maternal inheritance effect in myotonic dystrophy. They largely agreed with Harper and Dyken that congenital myotonic dystrophy was likely caused by some interaction between the maternal myotonic dystrophy gene, an intrauterine environmental factor, and the myotonic dystrophy gene in the foetus. They did not, however, discount Budney and Carter’s alternative hypothesis that early onset myotonic dystrophy was caused by a different mutation than that of classical myotonic dystrophy.⁷⁵

Peter Harper’s own research into myotonic dystrophy and Huntington’s disease helped to place him at the centre of changing ideas on anticipation and through examination of how his ideas to anticipation developed over time we can track points of contact between research communities and how the spread and integration of the new discoveries of the 1970s and 1980s began to lead to the re-conceptualization of anticipation.⁷⁶ Harper went on to publish several more volumes on myotonic dystrophy and Huntington’s disease, and he has played an important role in disseminating the ideas about anticipation as they have been re-conceptualized since this period.

⁷³ H. Zellweger and V. Ionasescu, *Myotonic Dystrophy and its Differential Diagnosis*, (Copenhagen: Munksgaard, 1973), 17.

⁷⁴ Zellweger and Ionasescu, *Myotonic Dystrophy*, 17.

⁷⁵ Zellweger and Ionasescu, *Myotonic Dystrophy*, 16.

⁷⁶ Harper’s familiarity with the work of Dutch physician and researcher C. J. Höweler (whose work will be discussed below) also played an important role in the development of his own ideas on anticipation. Harper and Höweler first met in 1978 when Harper gave a paper on myotonic dystrophy in Leiden. Höweler’s supervisor Herman Busch invited both men to dinner at an Indonesian restaurant. That evening they discussed Höweler’s work on anticipation and Harper agreed that he was pursuing a worthwhile topic. C. J. Höweler, Correspondence with Judith Friedman, 20 June 2007. The importance of Harper as a populariser of the new concept of anticipation will be dealt with more fully in chapter six.

Peter Harper published the first edition of his monograph *Myotonic Dystrophy* in 1979. In the chapter on the genetics basis of myotonic dystrophy Harper summarised the history of the genetics of myotonic dystrophy and discussed all the theories then circulating on possible causes of variation in the disorder.⁷⁷ He also noted that the disease displayed all of the hallmarks of being an autosomal dominant disorder.⁷⁸ The variability of the symptoms and age of onset, he commented, had led some researchers to question whether the variation might be caused by a incomplete penetrance of the gene—that is a situation in which some individuals might have the mutant gene and yet show no or limited signs of illness. Recent studies, however, had shown that the disease was fully penetrant, with the expected 50 percent of offspring being found to carry the faulty gene.⁷⁹ Normal autosomal dominant disorders did not show the same kinds of maternal inheritance effects as myotonic dystrophy did; this required an explanation. Not surprisingly given his own research findings, Harper favoured the maternal inheritance hypothesis, according to which some combination of a normally mutated gene in the mother and some as yet unknown maternally transmitted factor combined to affect only children carrying the mutant gene in utero. He reviewed and dismissed the theories of genetic heterogeneity and ascertainment bias or observer effect.⁸⁰

In his monograph, Harper discussed the long-standing controversy in the field as to whether observations of anticipation in myotonic dystrophy represented a genuine biological phenomenon, or simply resulted from biases that favoured recording families in which grandparents were mildly affected, parents were classically affected, and children were congenitally affected. Harper noted that “in general, neurologists have accepted anticipation as a genuine event whereas geneticists have not.”⁸¹ While there was still no way to explain how a gene might “worsen” in succeeding generations, Harper believed that the maternal environmental factor could provide “a genuine biological basis for anticipation.”⁸²

⁷⁷ Harper, “The Genetic Basis of Myotonic Dystrophy,” chap. 10 in *Myotonic Dystrophy*, (1979), 207-231.

⁷⁸ Harper, *Myotonic Dystrophy*, (1979), 208-211.

⁷⁹ Harper, *Myotonic Dystrophy*, (1979), 211-213.

⁸⁰ Harper, *Myotonic Dystrophy*, (1979), 200-204.

⁸¹ Harper, *Myotonic Dystrophy*, (1979), 221.

⁸² Harper, *Myotonic Dystrophy*, (1979), 222.

Harper also contributed to Emery's 1983 *Principles and Practice of Medical Genetics*. Although this chapter was published between editions of his monograph, it marks an interesting step in the development of his ideas concerning anticipation. To the three points concerning anticipation listed in his 1979 monograph discussed above Harper added: "It would not surprise the author if some unexpected additional factor were to be operating, particularly in relation to the origin, mutational or otherwise, of the mildest cases."⁸³ He concluded that the issue was only likely to be solved once the gene for myotonic dystrophy was located and studied.⁸⁴ Even in the absence of a clear explanatory mechanism, by 1983 Harper had clearly come to the working position that there was some biological basis for anticipation.

LAYING THE GROUNDWORK FOR CONCEPTUAL CHANGE: 1986-1989

By 1986, the stage was therefore set for a re-examination and re-conceptualization of the question of anticipation in hereditary illness in general and in myotonic dystrophy in particular. One of the longstanding explanations for the variable symptoms of myotonic dystrophy was that it was caused by the incomplete penetrance of the gene involved. Better diagnostic procedures and statistical analyses allowed researchers to see that by young adulthood symptoms had appeared in the expected 50% of offspring predicted according to Mendelian inheritance of a dominant gene.⁸⁵ This discovery left unexplained why some carriers of the myotonic dystrophy gene never developed more than slight symptoms while others developed more severe forms of the disease.⁸⁶ Moreover, the discovery that the congenital form of the disease was found solely in the offspring of female sufferers failed to explain observations of anticipation in preceding generations, or the fact that the disease equally affected both sexes.⁸⁷ Finally, despite much diligent searching, no sign of severe myotonic dystrophy had been found among

⁸³ Harper, "Myotonic dystrophy and related disorders," in *Principles and Practice of Medical Genetics*, vol. 1, A. E. H. Emery and D. L. Rimoin eds., (Edinburgh: Churchill Livingstone, 1983), 434.

⁸⁴ Harper, "Myotonic dystrophy and related disorders," 434.

⁸⁵ Confirmed in T. O'Brien and P. S. Harper, "Course, prognosis and complications of childhood-onset myotonic dystrophy," *Developmental Medicine and Child Neurology* 26 (1984): 62-67. See also W. Pryse-Phillips, G. J. Johnson, and B. Larsen, "Incomplete manifestations of myotonic dystrophy in a large kinship in Labrador," *Annals of Neurology* 11 (1982): 582-591.

⁸⁶ Harper, *Myotonic Dystrophy*, (1979), 213.

⁸⁷ Harper, *Myotonic Dystrophy*, (1979), 215-303.

siblings in earlier generations of families affected by the disorder and no mild cases were found in the later generations.⁸⁸ In short, many of the important supporting points of Penrose's hypothesis had been weakened or disproved. The stage was thus set for a revision of ideas on anticipation.

The work of the Dutch physician and clinical researcher Christiaan Höweler proved pivotal to highlighting the need to re-evaluate the old ideas of anticipation. While waiting to enter a neurology programme, Höweler had been employed as a research assistant of the neurologist Dr. Herman Busch who was studying myotonic dystrophy. Before beginning his research, Höweler knew nothing of anticipation—it had not been included in his medical training. While familiarizing himself with the literature in the field he read Penrose's 1948 paper and “found his arguments so persuasive that I had no doubt they were true.”⁸⁹ Höweler's research involved re-examining the pedigrees of extended families with myotonic dystrophy. To his surprise, he found “anticipation in all parent-child pairs.”⁹⁰ In 1975, Professor Busch presented those results in Leiden at a conference on clinical genetics.⁹¹ To the surprise of both, the geneticists attending the session simply ignored their findings.⁹² At this point Höweler “became aware of the split in thinking on the existence of anticipation in M.D. between the geneticists and clinicians and recognised this, not only in the book of Caughey and Myriantopoulos, but also in the papers of Dyken and Harper (*Neurology* 1973) and Harper and Dyken (*Lancet* [*sic*] 1972). The neurologist Dyken believed in anticipation (1973), while the geneticist Harper neglected it (1972).”⁹³ In his dissertation Höweler set about disproving the

⁸⁸ See for example, Dyken and Harper, “Congenital dystrophia myotonica,” 465-473. See also W. Pryse-Phillips *et al.*, “Incomplete manifestations,” 582-591.

⁸⁹ Christiaan Jacob Höweler, Correspondence with Judith Friedman, 18 March 2004. See also Jacqueline Donachie and Darren G. Monckton, *Tomorrow Belongs to Me*, (Glasgow: University of Glasgow, 2006), 171-184.

⁹⁰ Höweler, Correspondence with Judith Friedman, 18 March 2004.

⁹¹ H. F. M. Busch and C. J. Höweler, “Dystrophia Myotonica,” *Early diagnosis and prevention of genetic diseases*, L. N. Went, C. Vermeij-Keers and A. G. J. M. van der Linden Eds., (Leiden: Leiden University Press, 1975), 26-32.

⁹² In the discussion section L. N. Went remarked that he found it interesting that the congenital form of myotonic dystrophy was transmitted through affected mothers when it was affected fathers whose offspring were most severely affected in the case of Huntington's disease. The geneticist Arno Motulsky was also in the audience but he completely ignored Herman Busch's direct comments on anticipation and progression in the case of myotonic dystrophy and instead commented solely upon the difficulty of screening for the disease. Busch and Höweler, “Dystrophia Myotonica,” 32. Höweler, Correspondence with Judith Friedman, 18 March 2004, 19 March 2004.

⁹³ Höweler, Correspondence with Judith Friedman, 18 March 2004.

theoretical underpinnings of Penrose's hypothesis dismissing anticipation. This left the way open for a re-conceptualization of the idea.

Historically, myotonic dystrophy was the single disease most closely associated with anticipation. As we have seen, several other disorders, including Huntington's disease, which had been regularly associated with anticipation in the first third of the twentieth century, were no longer associated with this mode of heredity by 1970. Despite the discovery in the 1970s of the linkage between the paternal inheritance of Huntington's disease and the early onset of the disease, anticipation was not one of the explanatory models considered for it by researchers. In the 1980s, however, the form of X-linked mental retardation which had once been known as Martin-Bell syndrome was reclassified by the name "fragile X syndrome" in McKusick's *Mendelian Inheritance in Man*.⁹⁴ The inheritance pattern of X-linked disorders usually follows certain rules, but fragile X's odd mode of inheritance and the apparent worsening of its effects over succeeding generations baffled many researchers. Fragile X syndrome offered a new experimental case to researchers who sought explanations for such changes. The sequencing of the causative gene for fragile X in 1991 that finally identified the causative mechanism behind the appearance of anticipation in certain genetic diseases.

"A Clinical and Genetic Study in Myotonic Dystrophy" (1986)

Höweler continued his work on myotonic dystrophy in his dissertation "A Clinical and Genetic Study in Myotonic Dystrophy" which he defended in 1986. During the intervening time, he continued rereading Penrose and considering his ideas about anticipation. Höweler eventually concluded that "Penrose appeared to be convinced that anticipation did not exist even before he formulated the arguments. I then became so fascinated by this issue that I made it the main subject of my thesis."⁹⁵ On first reading, Penrose's arguments were very persuasive. Höweler states, "it took me four years of thinking and rereading Penrose's paper about fifteen times before I could identify them [problems with Penrose's approach to the study of anticipation.]"⁹⁶ Through careful analysis the 14 myotonic dystrophy families and a close examination of previous papers

⁹⁴ McKusick, *Mendelian Inheritance in Man*, 7th ed., (1986).

⁹⁵ Höweler, Correspondence with Judith Friedman, 18 March 2004.

⁹⁶ Höweler, Correspondence with Judith Friedman, 18 March 2004.

on myotonic dystrophy, Höweler was able to disprove several aspects of Penrose's 1948 hypothesis that anticipation was a product of ascertainment bias rather than a genuine biological phenomenon.⁹⁷

One of the major pillars of Penrose's argument concerning anticipation was his prediction of the existence of complementary parent-child pairs, in which children with a later age of onset than their affected parent would balance out the more easily ascertained children with an earlier age of onset than their affected parent. He argued that given the nature of the human life span and the working life of the scientist that the parent-child pairs with late-onset children could easily be missed, while those parent-child pairs in which the child developed the disease at an earlier age would be more easily seen.⁹⁸ Höweler was able to disprove the existence of these individuals through his careful study of several complete generations in 14 families. In the "61 parent-child pairs" studied within 14 families, Höweler observed a 98% incidence of anticipation—i.e. the children almost always developed the disease at an earlier age than their parents.⁹⁹ "The possibility of the future existence of complementary pairs was studied. The penetrance of the myotonic dystrophy gene appeared to be almost complete in the 14 families. It is unlikely, therefore, that sufficient complementary pairs will appear in the future to cancel out entirely the observed anticipation."¹⁰⁰ Thus, Höweler's dissertation was the first modern study that firmly disproved the existence of Penrose's posited complementary pairs—a major requirement of his hypothesis—and once more suggested that anticipation was a real, if, as yet, inexplicable biological phenomenon.¹⁰¹

Hóweler's dissertation committee was originally made up of two neurologists, Professor Dr. Arthur Staal and Professor Dr. Herman Busch. Because of the controversial subject matter involved, two geneticists were asked to join the examination committee, Professor Dr. Joep Geraedts and Professor Dr. Martinus Niermeyer. Höweler

⁹⁷ Christiaan Jacob Höweler, "A Clinical and Genetic Study in Myotonic Dystrophy," Erasmus University of Rotterdam: MD thesis, 1986.

⁹⁸ For a discussion of Penrose's hypothesis on anticipation, see chapter four. Lionel S. Penrose, "The problem of Anticipation in Pedigrees of Dystrophia Myotonica." *Annals of Eugenics* 14 (1948): 126-129.

⁹⁹ Höweler, "Clinical and Genetic Study," 70.

¹⁰⁰ Höweler, "Clinical and Genetic Study," 70.

¹⁰¹ Höweler, "Clinical and Genetic Study," 78.

says that they “both had the courage to approve with the thesis ‘because I [*sic*] presented good arguments against Penrose’s hypothesis, whether or not it was true.’”¹⁰²

“Anticipation in Myotonic Dystrophy: Fact or Fiction?” (1989)

Three years later a paper published in *Brain*, disseminated Höweler’s viewpoint much more widely.¹⁰³ Höweler and his colleagues argued there that “the hypothesis put forward by Penrose in 1948 that ‘anticipation’ is caused by bias of index case selection was based on theoretical arguments only and has not been supported by clinical observations.”¹⁰⁴ They re-examined 14 myotonic dystrophy families with a protocol designed to enable them to avoid the sources of bias that Penrose had identified.¹⁰⁵ They avoided index-patient bias by not including that individual when selecting parent-child pairs for analysis.¹⁰⁶ They looked for early onset parents with late onset children by asking late onset patients about the health of their parents: none were found.¹⁰⁷ Lastly, they examined patient fertility to see if low fertility was the cause of the missing complementary pairs postulated by Penrose but since fertility was reduced only in the most serious of cases, they concluded that this did not explain the absence of the late-onset side of the complementary pairs.¹⁰⁸ Since close examination of patients revealed that penetrance of the gene was nearly complete it was extremely unlikely that any such pairs would appear in the future.¹⁰⁹ In 98% of all cases an earlier age of onset was found in succeeding generations, more notably in cases of maternal than paternal transmission.¹¹⁰ They concluded that anticipation “appears to be inherent in the transmission of MD.”¹¹¹

¹⁰² Höweler, Correspondence with Judith Friedman, 18 March 2004.

¹⁰³ Christiaan J. Höweler, H. F. M. Busch, J. P. M. Geraedts, M. F. Niermeijrt, and A. Staal, “Anticipation in Myotonic Dystrophy: fact or fiction?” *Brain* 112 no. 3 (June 1989): 779-797.

¹⁰⁴ The first individual in a family that presents with a disease is called the index patient. When analyzing the heredity of the disease in a family counting the index patient can skew the results. As a result the researcher generally excludes the index patient from their analysis so as to avoid this type of selection bias. Höweler *et al.*, “Fact,” 779.

¹⁰⁵ Höweler *et al.*, “Fact,” 779, 781-782, 788-793.

¹⁰⁶ Höweler *et al.*, “Fact,” 779, 781-782.

¹⁰⁷ Höweler *et al.*, “Fact,” 779, 781-782.

¹⁰⁸ Höweler *et al.*, “Fact,” 779, 781-782.

¹⁰⁹ Höweler *et al.*, “Fact,” 779, 793.

¹¹⁰ Höweler *et al.*, “Fact,” 779, 793.

¹¹¹ Höweler *et al.*, “Fact,” 793.

Höweler relates that it was “rather difficult to get the paper published, but on rereading the discussion with the editor and reviewers I am impressed how straight and clean the British geneticists played the discussion.”¹¹² One of *Brain*’s referees was critical of the paper and one was in favour so a third reviewer was brought in who suggested publication with some revisions. Höweler responded to the first referee’s criticisms, and the paper was accepted with revisions. Dr. John Edwards, an Oxford geneticist, invited him to present his work at a seminar on the genetics of myotonic dystrophy a half a year before the publication of the article in *Brain*. His presentation persuaded two geneticists to change their thinking on anticipation but not another who visited Höweler in Maastricht shortly after the publication of the paper. Höweler reported that “apart from these warm responses I got surprisingly few reactions on the paper.”¹¹³ These observations are supported by an examination of the paper’s reception as indicated in the science citation index, which shows relatively few citations of the paper until after the sequencing of the causative genes for fragile X and myotonic dystrophy in 1991.¹¹⁴

Fragile X Syndrome: A New Experimental System

Fragile X mental retardation syndrome is second only to Down’s syndrome as the most common cause of mental retardation.¹¹⁵ The X-linked form of mental retardation that later became known as fragile X was first reported by J. P. Martin and Julia Bell in 1943.¹¹⁶ This form of sex-linked mental retardation was later referred to as “Martin-Bell

¹¹² Höweler, Correspondence with Judith Friedman, 18 March 2004.

¹¹³ Höweler, Correspondence with Judith Friedman, 18 March 2004.

¹¹⁴ Höweler *et al.*, “Fact,” was cited in the scientific literature 1 time in 1990, 7 times in 1991, 22 times in 1992, 26 times in 1993, 24 times in 1994, 18 times in 1995, 15 times in 1996, 14 times in 1997, 11 times in 1998, 10 times in 1999, and 4 times in 2000. Citations of this article increased dramatically with the discovery of expanding trinucleotide repeats in fragile X syndrome, myotonic dystrophy, and Huntington’s disease between 1991 and 1993 and then began to drop off as the idea became disseminated within the scientific community. For further discussion on the dissemination of the discovery of the genetic mechanism behind anticipation see chapter six.

¹¹⁵ François Rousseau, Patricia Rouillard, Marie-Lou Morel, Edward W. Khandjian, and Kenneth Morgan, “Prevalence of carriers of premutation-size alleles of the *FMRI* gene—and implications for the population genetics of the fragile X syndrome,” *American Journal of Human Genetics* 57 no. 5 (November 1995): 1006-1018.

¹¹⁶ J. P. Martin and Julia Bell, “A pedigree of mental defect showing sex linkage,” *Journal of Neurology and Psychiatry* 6 (1943): 154-157.

syndrome.”¹¹⁷ In 1969, the American geneticist Herbert Lubs examined a family with sex-linked mental retardation over three generations. His cytogenetic studies of the X chromosome showed a fragile site on the X chromosome under certain conditions. This observation later gave rise to the name “fragile X syndrome.”¹¹⁸ The linkage between Martin-Bell syndrome and fragile X syndrome was made in 1981 when Richards *et al.* demonstrated that the kinship grouping first documented by Martin and Bell did indeed show the same fragile site on the affected X chromosome.¹¹⁹

Researchers noted several peculiarities in the inheritance of fragile X syndrome. Usually female carriers of X-linked disorders, like colour-blindness, were free from signs of the mutation while all male carriers exhibited signs of the disorder. This was not the case in fragile X, for some of the male carriers (normal transmitting males or NTMs) appeared to be perfectly normal, while some of the female carriers were mentally impaired.¹²⁰ In 1984, some researchers suggested that an autosomal gene might be acting to suppress the effect of the mutated gene in cases of transmission by unaffected males.¹²¹ Other researchers suggested that the action of an autosomal gene or modifier might explain both the existence of normal males who transmitted fragile X and the fact that while approximately one-third of female carriers are mentally impaired, the mothers and daughters of normal transmitting males were only rarely affected by mental impairment.¹²² Three groups of researchers had postulated that genetic copying errors

¹¹⁷ John M. Opitz, Joan M. Westphal, and Art Daniel, “Discovery of a connective tissue dysplasia in the Martin-Bell syndrome,” *American Journal of Medical Genetics* 17 no. 1 (January 1984): 101-109.

¹¹⁸ Herbert A. Lubs, “A marker X chromosome,” *American Journal of Human Genetics* 21 (1969): 231-244. For a follow-up study see: Herbert A. Lubs, Michael Watson, Roy Breg, Enrique Lujan and John M. Opitz, “Restudy of the original marker X family,” *American Journal of Medical Genetics* 17 no. 1 (January 1984): 133-144.

¹¹⁹ B. W. Richards, P. E. Sylvester and Carol Booker, “Fragile X-linked mental retardation: the Martin-Bell syndrome,” *Journal of Mental Deficiency Research* 25 (1981): 253-256.

¹²⁰ M. V. Bell, M. C. Hirst, Y. Nakahori, R. N. MacKinnon, A. Roche, T. J. Flint, P. A. Jacobs, N. Tommerup, L. Tranebjaerg, U. Froster-Iskenius, B. Kerr, G. Turner, R. H. Lindenbaum, R. Winter, M. Pembrey, S. Thibodeau, and K. E. Davies, “Physical Mapping across the Fragile X: Hypermethylation and Clinical Expression of the Fragile X Syndrome,” *Cell* 64 (February 22, 1991): 861-866.

¹²¹ Ursula Froster-Iskenius, Annegret Schulze and E. Schwinger, “Transmission of the marker X syndrome trait by unaffected males: conclusions from studies of large families,” *Human Genetics* 67 no. 4 (September 1984): 419-427.

¹²² P. Steinbach, “Mental impairment in Martin-Bell syndrome is probably determined by the interaction of several genes: simple explanation of phenotypic differences between unaffected and affected males with the same X chromosome,” *Human Genetics* 72 (1986): 248-252; M. H. Israel, “Autosomal suppressor gene for fragile-X: an hypothesis,” *American Journal of Medical Genetics* 26 (1987): 19-31; S. L. Sherman, “A

occurring (or accumulating) during meiosis in egg formation might provide a mechanism with which to explain the finding that carrier females seemed to transmit a more severe form of the disease than the normal transmitting males.¹²³ Environmental factors like genomic imprinting and methylation were also known to affect the expression of the relevant genes and were therefore closely investigated in fragile X as methylation of the fragile site clearly affected the expression of the disease.¹²⁴ Finally, some researchers combined genetic and environmental hypotheses to suggest a two-stage mutation hypothesis in which a pre-mutation that occurred in an ancestor was later converted to a full mutation via recombination, amplification, imprinting, or methylation.¹²⁵ Nevertheless, as in Huntington's disease and myotonic dystrophy, researchers were far from agreeing on an explanation for hereditary transmission in fragile X prior to 1991.

RESISTING OR REASSESSING CONCEPTS OF ANTICIPATION: 1989-1991

The idea that the concept of anticipation might have a biological basis was gradually incorporated into textbooks after 1989. The work of Peter Harper was largely responsible for this change. In his chapter on myotonic dystrophy in the second edition of Emery's *Principles and Practice of Medical Genetics*, published in 1990, Harper discussed the history of the observation of anticipation in myotonic dystrophy and the biases that Penrose had pointed out as possible causes for these findings. However persuasive

new genetic model for the fragile X syndrome involving an autosomal suppressor gene—comments on the paper by M. H. Israel,” *American Journal of Medical Genetics* 26 (1987): 33-36.

¹²³ M. E. Pembrey, R. M. Winter, and K. E. Davies, “A premutation that generates a defect at crossing over explains the inheritance of fragile X mental retardation,” *American Journal of Medical Genetics* 21 no. 4 (August 1985): 709-717; David H. Ledbetter, Susan A. Ledbetter, Robert L. Nussbaum, “Implications of fragile X expression in normal males for the nature of the mutation,” *Nature* 324 (13 November 1996): 161-163; Höweler *et al.*, “Fact,” 795.

¹²⁴ During the 1980s scientists began to be aware of a range of epigenetic processes including genomic imprinting and methylation by which the expression of genes is effected (sometimes even from one generation to the next) but which does not actually involve a direct mutation of the gene itself. In recent years the study of the so-called epigenome has taken on an increased importance as scientists begin to tease out the effects of environment and behaviour on the expression of genes. Bell *et al.*, “Physical,” 861; Robin Holliday, “The inheritance of epigenetic defects,” *Science* 238 no. 4824 (9 October 1987): 163-170; Höweler *et al.*, “Fact,” 795. For a wider discussion of epigenetics see also, Eve Jablonka, *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioural, and Symbolic Variation in the History of Life*, (Cambridge MA: MIT Press, 2005).

¹²⁵ Bell *et al.*, “Physical,” 861; Peter S. Harper, *Myotonic Dystrophy*, 2nd ed. (London: W. B. Saunders, 1989) 312; Höweler *et al.*, “Fact,” 795; N. E. Morton and J. N. Macpherson, “Population genetics of the fragile-X syndrome: Multiallelic model for the *FMRI* locus,” *Proceedings of the National Academy of Sciences USA* 89 (1992): 4215-421. See also the 1940s work of Ravin and Waring discussed in chapter four.

Penrose's arguments, Harper noted, a number of clinicians continued to believe that anticipation was a biological phenomenon. Congenital myotonic dystrophy in particular reinforced this belief, he believed, since most of the mothers of affected children were themselves only mildly affected. He was unsure whether the combination of the intrauterine factor with the presence of the affected gene in mother and child would be sufficient to explain anticipation, but he cited Höweler's 1989 article as supporting the view that there was a true progression of the disease between generations. Several possible causes of anticipation were mentioned, and Harper made the intriguing and suggestive comment: "It would not surprise the author if some unexpected additional factor were to be operating, particularly in relation to the origin, mutational or otherwise, of the mildest cases."¹²⁶ Harper, then, was instrumental in helping to disseminate Höweler's ideas on anticipation to a more general audience.

Other authors were not so quick to update their ideas on anticipation. In the 1990 ninth edition of *Mendelian Inheritance in Man*, McKusick offered the same discussion of anticipation as in previous editions: perceptions of anticipation were likely caused by ascertainment bias, and congenital myotonic dystrophy seemed to be caused by some sort of maternal transmission effect that had been seen in disorders like neurofibromatosis.¹²⁷

Höweler's theory that anticipation was a biological reality was incorporated surprisingly quickly into the next generation of monographs on Huntington's disease and myotonic dystrophy due in large part to Peter Harper who incorporated these ideas into his new monographs on both subjects in 1989 and 1991. In 1989, Harper published the second edition of his monograph *Myotonic Dystrophy* in an expanded and up-to-date edition that covered new developments in the field. A number of questions remained concerning the inheritance of congenital myotonic dystrophy.¹²⁸ In Harper's opinion:

the evidence for the action of a maternal factor as well as the abnormal gene is overwhelming; the unsolved problem is, what is the nature of the factor? This remains as speculative now as it was 10 years ago; it may prove to be one of the numerous problems that will only be solved once the gene and its product are isolated.¹²⁹

¹²⁶ Harper, "Myotonic dystrophy and related disorders," 587-588.

¹²⁷ McKusick *et al.*, *Mendelian Inheritance in Man*, 9th ed., (1990), 639.

¹²⁸ Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 218.

¹²⁹ Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 220.

Several possible causes of this maternal effect were under consideration but most of the proposed mechanisms failed to explain all of the clinical findings.¹³⁰ Faced with the genetic and clinical evidence gathered over the previous ten years, the appearance of anticipation in myotonic dystrophy and perhaps in other disorders could no longer be set aside as merely a result of ascertainment bias. Once again, Harper laid out the disagreements between those who believed that anticipation might be a real phenomenon (clinicians, neurologists) and those who did not (geneticists). Harper stated that his “own views have over the years been intermediate between these polarized positions, but in the decade since the first edition of this book there seems to have been a genuine shift in the balance of evidence towards anticipation in myotonic dystrophy being a true biological phenomenon.”¹³¹ He credited the work of Höweler in 1986 and 1989 as well as recent findings in other disorders (particularly fragile X syndrome) for providing “the stimulus for this reassessment.”¹³²

While observations of anticipation in myotonic dystrophy dated back to 1918, Harper acknowledged that “the principal factor which turned most scientists against accepting the validity of anticipation was the authoritative paper of Penrose (1948)” adding that “Penrose’s stature in the field of genetics was immense, as was that of the Galton Laboratory where both he and Julia Bell were based, so it is hardly surprising that his views were generally accepted by geneticists.”¹³³ While Harper admitted that Penrose’s general arguments concerning the problems of ascertainment bias in hereditary disease were valid, he questioned if they actually applied to the case of myotonic dystrophy.¹³⁴ Work done by recent researchers, most notably Höweler, had shown that most of Penrose’s criticisms regarding study format had been met while his proposed “missing” individuals had been shown unlikely to exist.¹³⁵ While it was now clear to him that anticipation was a real biological phenomenon, the mechanism behind its function

¹³⁰ Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 221-223.

¹³¹ Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 309.

¹³² Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 310.

¹³³ Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 310.

¹³⁴ Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 310-311.

¹³⁵ Harper, *Myotonic Dystrophy*, 2nd ed., (1989), 311.

was still unknown and remained so until the gene for myotonic dystrophy was sequenced in the coming years.¹³⁶

Harper's 1991 monograph on Huntington's disease also helped to spread Höweler's ideas amongst this research community. In this text, Harper stated that since anticipation had been shown by Höweler as likely to be caused by a real biological phenomenon in the case of myotonic dystrophy that this might also be the case with Huntington's disease in which several extensive studies had shown that anticipation seemed to be taking place.¹³⁷ Both imprinting and mitochondrial inheritance, the current favourite hypotheses to explain the paternal transmission effect in Huntington's disease, had difficulties explaining all of the hereditary effects seen in the disease, while methylation had not been shown to affect the region containing the gene. Since the gene causing Huntington's disease had been localized and was well on its way to being isolated and sequenced, Harper hoped that this would at last provide an answer to the question of anticipation in Huntington's disease and explain the paternal inheritance effect.¹³⁸

Not all monographs were so quick to incorporate the new findings concerning anticipation. The second edition of Caughey and Myriantopoulos's *Dystrophia Myotonica* appeared in 1991.¹³⁹ Somewhat ironically perhaps, since Caughey had openly disagreed with Myriantopoulos on the subject in the 1963 edition of their work, this time he handed the issue to Dr. Joanne Dixon who wrote the section on genetics in myotonic dystrophy in Myriantopoulos' stead.¹⁴⁰ Like Myriantopoulos, Dixon followed Penrose's opinion on anticipation almost entirely. Anticipation in myotonic dystrophy, she stated, "is clearly recognised as a bias of ascertainment rather than a

¹³⁶ Harper reiterated these reasons during interviews with me in 2002. He also believed that Penrose's strong religious and moral beliefs were likely additional factors behind his antipathy towards anticipation. Peter S. Harper, Interviews with Judith Friedman., 27 June 2002, 23 July 2002. See also his interview with Jacqueline Donachie in 2004. Jacqueline Donachie and Darren G. Monckton, *Tomorrow Belongs to Me*, (Glasgow: University of Glasgow, 2006), 50-67.

¹³⁷ Harper, *Huntington's Disease*, (1991), 308-310.

¹³⁸ Harper, *Huntington's Disease*, (1991), 310-311.

¹³⁹ The preface, however, was dated 1988, predating both the general publication of Höweler's work and the 2nd edition of Harper's monograph, which may explain things. Caughey and Myriantopoulos, *Dystrophia Myotonica*, 2nd ed., (Springfield IL: Charles C. Thomas Publisher, 1991), vii.

¹⁴⁰ Caughey reported that Myriantopoulos was unable to contribute to the second edition so the chapter on genetics in myotonic dystrophy was written by Dr. Dixon instead. Despite the publication date of the monograph, the latest reference from this chapter dates from 1987. Caughey and Myriantopoulos, *Dystrophia Myotonica*, 2nd ed., (1991), 195-198.

genetic reality.”¹⁴¹ She did recognise the importance of the maternal transmission effect however, but in this case she followed Harper’s older argument that it was caused by a maternal or environmental factor that acted upon foetuses that carried the affected gene.¹⁴²

RE-CONCEPTUALIZING ANTICIPATION: 1970-1989

Around the time Lionel Penrose died in 1972, new findings suggested anticipation in both Huntington’s disease and myotonic dystrophy. A variety of explanations were advanced to explain or explain away these findings, but none were particularly successful. In the meantime, evidence grew that in the case of myotonic dystrophy maternal transmission led to the earlier onset of disease in the succeeding generation while in Huntington’s disease the male parent transmitted the early onset form of the disease to the next generation. While these new findings were being discussed in medical and scientific journals, medical genetics textbooks on the whole continued to be dismissive of anticipation as a factor in hereditary illness or simply ignored the concept altogether. Pure genetics works ignored it entirely.

This state of affairs remained the status quo until the work of the Dutch physician and researcher Christiaan Jacob Höweler came to the attention of myotonic dystrophy researchers.¹⁴³ In his multi-generational study of several Dutch families suffering from myotonic dystrophy Höweler made the surprising discovery that Penrose’s hypothesis explaining away anticipation as merely an experimental artefact was in fact incorrect on several key points. He concluded that anticipation must be an actual biological phenomenon, albeit one that had yet to be explained. Höweler’s theory became more widely accessible with the publication of a 1989 article in the journal *Brain* where he clearly laid out his ideas and the conclusion “that anticipation may be inherent in the transmission of myotonic dystrophy.”¹⁴⁴

¹⁴¹ Caughey and Myriantopoulos, *Dystrophia Myotonica*, 2nd ed., (1991), 185.

¹⁴² Caughey and Myriantopoulos, *Dystrophia Myotonica*, 2nd ed., (1991), 190.

¹⁴³ As seen in the previous section, there was significant overlap between the myotonic dystrophy and Huntington’s disease research communities. In this and future sections Peter Harper will become an important point of contact, spreading the news about discoveries concerning anticipation in myotonic dystrophy to other Huntington’s disease researchers.

¹⁴⁴ C. J. Höweler, H. F. M. Busch and J. P. M. Geraedts, “Anticipation in myotonic dystrophy: fact or fiction?” *Brain* 112 (1989): 779-797.

Höweler's work came to the attention of Peter Harper, an influential researcher in both myotonic dystrophy and Huntington's disease, and both the second edition of his monograph on myotonic dystrophy and the first edition of his monograph on Huntington's disease reflect his changing attitude towards the existence of anticipation. Researchers, utilising new discoveries made in the field of molecular biology in the 1980s and early 1990s proposed a variety of possible ways to explain the findings of anticipation in these diseases. While Höweler may have disproved Penrose's approach to anticipation, none of the other proposed explanatory models could immediately replace it successfully. Simply put, there seemed to be no way to account theoretically for the findings of anticipation in myotonic dystrophy and Huntington's disease within a framework of Mendelian inheritance. In the late 1980s, work on fragile X syndrome would provide a new experimental system in which to examine mechanisms by which diseases might worsen over succeeding generations. However, as in the case of Huntington's disease and myotonic dystrophy, researchers remained divided as to the actual causative mechanism. It would not be until the sequencing of the causative gene for fragile X syndrome in 1991 that the puzzle of anticipation would finally be solved in principle and the mechanism behind anticipation began to be described.

Chapter 6: Anticipation Redeemed – Discovering Expanding Trinucleotide Repeats (1991-1994)

A MOLECULAR MECHANISM AT LAST

One problem in the way of the scientific acceptance of anticipation as a real biological phenomenon was the lack of a sufficient and clear-cut causative mechanism—whether genetic, epigenetic, or biological. While many possible explanations for the phenomenon had been suggested—including methylation, genetic heterogeneity, maternal inheritance factors including cytoplasmic inheritance and mitochondrial mutations, and the possible influence of additional genes, as well as the more traditional objections of selection bias and incomplete ascertainment—none of these was sufficient to explain the findings which had been well established by the late 1980s, that anticipation seemed to be inherent in myotonic dystrophy and that something similar was involved in the cases of Huntington’s disease and Fragile X syndrome. Many agreed, however, that a final answer would need to wait on the location and analysis of the genes involved.

Locating, isolating, and understanding the mutant genes involved in disease had been a dream of human geneticists dating back to the 1930s and 1940s when the Rockefeller Foundation first began to fund linkage analysis studies in human beings. Unfortunately, linking human genes to screenable factors was a long-term and often frustrating project. By the late 1980s and early 1990s, the field of medical genetics was undergoing a series of scientific and technical breakthroughs that would shortly make possible the location and sequencing of genes associated with various diseases.¹ Researchers had high hopes that, by locating and sequencing the genes involved in disease, they would better understand the causes of each disease. Once the technical difficulties were surmounted, even if a cure was not immediately forthcoming, physicians

¹ Despite a call to arms by Daniel Kevles and Gerald Geison in 1995, a comprehensive history of the developments in the fields of genetics or human genetics in the last quarter of the twentieth century still remains to be written. Daniel Kevles and Geison, “The Experimental Life Sciences in the Twentieth Century,” *Osiris* 10 (1995): 97-121. A few scholars have examined particular developments in the field. For example, Paul Rabinow’s account of the creation of PCR which is perhaps the most important piece of technology driving the revolution in biology. Paul Rabinow, *Making PCR: A Story of Biotechnology*. Chicago: University of Chicago Press, 1996.

would at least be able to offer better genetic counselling to affected families. The sequencing of the genes in diseases associated with anticipation that finally led to the discovery of the genetic mechanism that accounted for this most puzzling form of heredity. The unequivocal identification of this mechanism—expanding trinucleotide repeats—allowed anticipation to be explained within a Mendelian framework. This in turn led to an astonishingly fast turnaround in the thinking of medical geneticists toward anticipation, moving it from the realm of speculation and supposition to that of accepted fact.

ANTICIPATORY SYNDROMES--

MYOTONIC DYSTROPHY, HUNTINGTON'S DISEASE AND FRAGILE X

In the late 1980s, aided by advancements in molecular biology, scientists began postulating mechanisms to explain anticipation. New parallels were noted at the time between myotonic dystrophy, Huntington's disease, and Fragile X syndrome, all of which exhibited similar patterns of inheritance. Myotonic dystrophy and Huntington's disease were both autosomal dominant progressive disorders that normally manifested symptoms only in adulthood. In the 1970s and 1980s, however, congenital and juvenile forms of these disorders were also recognized. Strangely, it seemed that these more severe forms of the disease which displayed early onset were almost exclusively found in the children of either affected mothers (in the case of myotonic dystrophy) or affected fathers (in the case of Huntington's disease).² Fragile X syndrome, the most common cause of inherited mental retardation after Down's syndrome, was found to be associated with a fragile site on the X chromosome.³ Unusually for an X-related disorder, some of the male carriers appear to be perfectly normal (normal transmitting males or NTMs) while up to one-third of the female carriers showed signs of mental impairment.⁴ By the early 1990s, several teams of researchers were speculating about mechanisms that might lie behind the manifestation of anticipation in these diseases. However, opinion was split as

² For a discussion of these discoveries, see chapter five.

³ M. V. Bell, M. C. Hirst, Y. Nakahori, R. N. MacKinnon, A. Roche, T. J. Flint, P. A. Jacobs, N. Tommerup, L. Tranebjaerg, U. Froster-Iskenius, B. Kerr, G. Turner, R. H. Lindenbaum, R. Winter, M. Pembrey, S. Thibodeau, and K. E. Davies, "Physical Mapping across the Fragile X: Hypermethylation and Clinical Expression of the Fragile X Syndrome," *Cell* 64 (February 22, 1991): 861.

⁴ Bell *et al.*, "Physical," 861.

to whether it was genetic or environmental factors that caused anticipation in these apparently unrelated disorders.⁵ At the same time, technological advances allowed researchers to begin to locate the actual genes causing genetic diseases and to sequence them with the hope that, by understanding what was going wrong with the relevant gene, the disease could be treated and perhaps even cured.

Hypotheses Explaining Anticipation

As earlier chapters have shown, some possible genetic causes for anticipation had been postulated as far back as 1938.⁶ Penrose addressed the most logical ones in his groundbreaking paper in 1948.⁷ Perhaps the most frequently offered explanation for the appearance of anticipation was that the variability in age of onset and symptoms was caused either by the normal allele that was paired with the disease gene or by some modifying effect exerted by an unrelated gene or genes.⁸ If confirmed, this mechanism could explain variations in the severity of the diseases associated with anticipation, although it would still not account for the progressive nature of these variations through the generations.⁹

In the cases of myotonic dystrophy and Huntington's disease researchers had considered, and largely discarded, several other possible mechanisms. Genetic heterogeneity—or the idea that the congenital or juvenile forms of the disease were caused by a different mutation than that responsible for the classical form of the disease—had been ruled out by linkage analysis and by the fact that both forms of the disease occurred in the same affected families. At the same time, careful experimental design and multi-generational studies had disproved the old standby objections that claims for anticipation were merely the result of selection bias and incomplete ascertainment of all affected individuals.¹⁰

⁵ See chapter five.

⁶ See chapter three.

⁷ See chapter four.

⁸ For an overview of views on anticipation in the clinical and medical genetic research communities in 1992 see, C. J. Höweler, H. F. M. Busch, J. P. M. Geraedts, M. F. Niermeijrt, and A. Staal, "Anticipation in Myotonic Dystrophy: fact or fiction?" *Brain* 112 no. 3 (June 1986): 795.

⁹ Höweler *et al.*, "Fact," 795; also chapter five.

¹⁰ See chapter five.

By the 1980s, several mechanisms were being explored to explain anticipation in myotonic dystrophy, Huntington's disease, and Fragile X syndrome. A variety of maternal factors figured among those being considered. In myotonic dystrophy, researchers were searching for a maternal factor that somehow acted to affect only the children of affected mothers who themselves carried the gene. In Huntington's disease, some researchers speculated that a maternal mitochondrial or cytoplasmic factor might be at play.¹¹ In Fragile X syndrome, a meiotic mechanism was postulated to explain why the children of carrier females tended to have a more severe form of the disease while the children of non-transmitting males did not.¹² A two-stage mutation hypothesis was consequently formulated in which a pre-mutation occurred first in one generation and later became converted to a full mutation via recombination, amplification, imprinting, or methylation.¹³

Animal studies in the previous decade had suggested that environmental factors like genomic imprinting and methylation could affect the production of the gene involved. This seemed a promising avenue for research in the case of Fragile X syndrome where methylation of the fragile site was clearly associated with expression of the disease.¹⁴ Nevertheless, methylation was apparently not involved in myotonic dystrophy or in Huntington's disease.¹⁵ Researchers therefore turned to genomic imprinting as the possible cause of anticipation, since in all three of these disorders either strictly paternal or maternal inheritance of the gene seemed to be involved in generating the most severe forms of the disease.¹⁶ However, imprinting did not seem to offer a full explanation for the progressive and irreversible generational changes.¹⁷

¹¹ See chapter five.

¹² Höweler *et al.*, "Fact," 795; also chapter five.

¹³ Bell *et al.*, "Physical," 861; Peter Harper, *Myotonic Dystrophy*, 2nd ed., (London: W. B. Saunders, 1989), Höweler *et al.*, "Fact," 795; N. E. Morton and J. N. Macpherson, "Population genetics of the fragile-X syndrome: Multiallelic model for the *FMRI* locus," *Proceedings of the National Academy of Sciences USA* 89 (1992): 4215. Similar hypotheses had been put forward in the 1930s and 1940s. See chapters three and four.

¹⁴ Methylation refers to the addition of methyl groups (-CH₃) to CG rich areas of DNA. Increased or decreased methylation can have a significant impact on the production of the protein coded for by the methylated region of DNA. Bell *et al.*, "Physical," 861; Höweler *et al.*, "Fact," 795.

¹⁵ Peter Harper, Helen G. Harley, William Reardon, and Duncan J. Shaw, "Review Article: Anticipation in Myotonic Dystrophy: New Light on an Old Problem," *American Journal of Human Genetics* 51 (1992): 13-14.

¹⁶ On imprinting in fragile X syndrome see: Harper *et al.*, "Anticipation," 13-14; Morton and Macpherson, "Population," 4215. On imprinting in Huntington's disease see: Peter S. Harper, "Genetic Aspects of

While researchers were weighing up the possible causes of anticipation, efforts continued to isolate, clone, and sequence the genes involved in these disorders. The researchers examining Fragile X syndrome were the first to reach this goal, and their discovery finally led to the modern understanding of the mechanism behind anticipation—namely, an expanding trinucleotide repeat area within the affected genes.

ANTICIPATION IN GENETICS AND MEDICAL GENETICS TEXTS CA. 1990

As discussed in chapter five, between 1989 and 1991 anticipation began to be reintegrated into specialist monographs regarding diseases with which the concept had been associated—notably Huntington’s disease and myotonic dystrophy. Yet, any discussion of anticipation remained absent—perhaps unsurprisingly—from introductory genetic textbooks.¹⁸ Nor had McKusick yet fully incorporated any of these new findings into the ninth edition of his compendium, *Mendelian Inheritance In Man* (1990).¹⁹ Clinical genetics textbooks incorporated the discoveries of the 1980s into their advice for genetic counselling—for example, warning women with mild myotonic dystrophy that they were at a 50% risk of having an affected child who would likely suffer from a more severe form of the disease.²⁰ Medical genetic textbooks—which had over the course of

Huntington’s Disease,” in *Huntington’s Disease*, Peter S. Harper ed., (London: W. B. Saunders Company Ltd, 1991), 281-311; Harper, *Myotonic Dystrophy* 2nd ed., (1989), 312; Höweler *et al.*, “Fact,” 795. On imprinting in Myotonic Dystrophy see: Harper, *Myotonic* 2nd ed., (1989), 312.

¹⁷ Harper *et al.*, “Anticipation,” 13-14.

¹⁸ See for example: William S. Klug and Michael R. Cummings, *Concepts of Genetics*, 2nd ed., (Glenview IL: Scott, Foreman and Company, 1986), The text by Klug and Cummings is included in this list because the 4th edition, published in 1994, was the first to incorporate the new material on anticipation and its biological cause); David Suzuki, Anthony J. F. Griffiths, Jeffrey H. Miller, and Richard C. Lewontin. *An Introduction to Genetic Analysis*, 4th ed., (New York: W. H. Freeman and Company, 1989); Benjamin Lewin, *Genes IV*, (Oxford: Oxford University Press, 1990).

¹⁹ The ninth edition of *Mendelian Inheritance in Man* contains a peculiar sentence in the entry on myotonic dystrophy: “With only rare exception it is the mother who transmits the disease.” This comment must have been intended to indicate the maternal transmission of the congenital form of the disease as myotonic dystrophy was a standard autosomal Mendelian disease, transmitted equally by males and females. Victor McKusick, *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*, 9th ed., (Baltimore and London: The Johns Hopkins Press, 1990), 639.

²⁰ See for example, Helen Kingston, *ABC of Clinical Genetics*, (London: British Medical Association, 1989), 13.

the last decade overwhelmed the human genetics texts of previous decades—were also incorporating the new discoveries made in the 1980s.²¹

***A SATISFACTORY ANSWER AT LAST: FINDING TRINUCLEOTIDE REPEATS
Fragile X Syndrome***

The breakthrough in understanding anticipation came shortly after the gene for Fragile X syndrome was sequenced. In May and June 1991, nine months before publication of the *New York Times* article quoted at the outset of this dissertation, several groups of researchers published papers reporting that insertions had been found in the Fragile X gene. I. Oberlé *et al.* isolated a 150-1400 base pair insertion in non-transmitting males that was passed essentially unchanged to their daughters, but that expanded greatly and with a good deal of variation among siblings in the following generation. In addition to the expansion of the gene, selective methylation seemed to be occurring at the site of insertion: the gene remained unmethylated in non-transmitting males, was methylated in their daughters only on the inactivated chromosome, and was completely methylated in most males suffering from Fragile X syndrome.²² Two weeks later, A. Verkerk *et al.* published a paper that indicated that the mutation was located in the coding region of the FMR-1 protein and that it actually coincided with the fragile site that gave the disease its name.²³ This region included an imperfect repeated DNA sequence of “28 CGG triplets interspersed with two AGG triplets.”²⁴ In June, a third group of researchers showed that

²¹ See for example, Peter Harper, “Myotonic dystrophy and related disorders,” In *Principles and Practice of Medical Genetics*, 2nd ed., Vol. 1., Alan E. H. Emery and David L. Rimoin, Eds., (Edinburgh: Churchill Livingstone, 1990), 579-597.

²² This means that the methylation of the gene is related to the finding of mental retardation in Fragile X carriers and sufferers. I. Oberlé, F. Rousseau, D. Heitz, C. Kretz, D. Devys, A. Hanauer, J. Boué, M. F. Bertheas, and J. L. Mandel, “Instability of a 550 bp DNA segment and abnormal methylation in Fragile X Syndrome,” *Science* 252 (24 May 1991): 1097.

²³ Martin and Bell first described the form of familial sex-linked mental retardation that would later be known as Fragile X in 1943. In 1969, the American Herbert Lubs developed a chromosomal test for the disease linking it to a fragile site at the tip of the X chromosome. J. Purdon Martin and Julia Bell, “A Pedigree of Mental Defect Showing Sex-Linkage,” *Journal of Neurology and Psychiatry* 6 (1943): 154-157; H. A. Lubs Jr., “A marker X chromosome,” *American Journal of Human Genetics* 21 (1969): 231-244; A. J. M. H. Verkerk, M. Pieretti, J. S. Sutcliffe, Y. Fu, D. P. A. Kuhl, A. Pizzuti, O. Reiner, S. Richard, M. F. Victoria, F. Zhang, B. E. Eussen, G. B. van Ommen, L. A. J. Blonden, G. J. Riggins, J. L. Chastain, C. B. Kunst, H. Galjaard, C. T. Caskey, D. L. Nelson, B. A. Oostra, and S. T. Warren, “Identification of a Gene (*FMR-1*) Containing a CGG Repeat Coincident with a Breakpoint Cluster Region Exhibiting Length Variation in Fragile X Syndrome,” *Cell* 65 (May 31, 1991): 905-906.

²⁴ Verkerk *et al.*, “Identification,” 910.

the region of instability and the fragile site coincided with the CGG triplet repeat region.²⁵ In normal chromosomes, this region formed a stable DNA polymorphism with a certain but varied number of copies of CGG. In the case of individuals with Fragile X syndrome, however, the number of copies of the CGG triplet repeat increased dramatically.²⁶ Although it was known that regions of DNA that are rich in cytosine and guanine have a tendency to be “sticky” and prone to mutation when copied during mitosis and meiosis, the mechanism behind the expansion of the repeat area and the role of methylation of the region on the expression of the gene remained unknown.²⁷

By the end of December 1991, Ying-Hui Fu *et al.* published a paper that outlined the genetic basis of Fragile X syndrome in essentially complete form, as the condition had been recognized as being caused by a mutation in a region where CGG was repeated in the FMR-1 gene. The number of CGG repeats varied between 6 and 54 within normal individuals. In Fragile X carriers who showed no sign of the disease, this region—now said to constitute a permutation—had become larger, ranging from 52 to over 200 repeats of CGG. Once the gene had more than 52 repeats, it became unstable during the process of meiosis and was subject to further expansion. Expansions to the full mutation were thought to occur during oogenesis (the development of the ovum), although in one case a contraction of the mutation to a normal size had been observed. In cases with the full expansion, mosaicism (the finding of a variety of mutations within one individual) was often observed, and was presumably caused by mitotic instability which led to a wide range of repeat sizes in various tissues of the body. Methylation of the site was clearly involved in some way, but the exact mechanism of its action remained unknown.²⁸

These findings were able to explain the previously noted Sherman paradox, which found that the risk of mental impairment in Fragile X families depended upon their position in the pedigree: “brothers of NTMs are at less (~9%) risk, while grandsons and

²⁵ E. J. Kremer, M. Pritchard, M. Lynch, S. Yu, K. Holman, E. Baker, S. T. Warren, D. Schlessinger, G. R. Sutherland, and R. I. Richards, “Mapping of DNA Instability at the Fragile X to a Trinucleotide Repeat Sequence p(CGG)*n*,” *Science* 252 (21 June 1991): 1711.

²⁶ Kremer *et al.*, “Mapping,” 1713.

²⁷ Kremer *et al.*, “Mapping,” 1714.

²⁸ Y. Fu, D. P. A. Kuhl, A. Piazzuti, M. Pieretti, J. Sutcliffe, S. Richards, A. Verkerk, J. J. A. Holden, R. G. Fenwick, S. T. Warren, B. A. Oostra, D. L. Nelson, and C. T. Caskey, “Variation of the CGG repeat at the Fragile X Site Results in Genetic Instability: Resolution of the Sherman Paradox,” *Cell* 67 (December 20, 1991): 1047-1058.

great grandsons have much higher risks (40% and 50%).”²⁹ Fu and his colleagues proposed that a slipped mispairing during DNA replication was responsible for the expansion of the unstable region, since the surrounding regions remained unchanged.³⁰ Over the next several months, other researchers fleshed out the details for establishing methods of pre-natal testing for the gene, determined how the mutation spread within family groups over generations, and specified the action of the gene and its expression.³¹

The broader importance of the discovery of expanding trinucleotide repeats as a genetic basis for anticipation was recognised soon after the first papers on the Fragile X CGG repeat were published. In May 1991, Keith Johnson, a member of a London-based group of researchers seeking to sequence the myotonic dystrophy gene, attended a meeting at Cold Spring Harbor where the findings of an expanding trinucleotide repeat in the fragile X gene were discussed. He reports that he “knew instantly that DM was going to be a repeat expansion. I told David Porteous, who was a co-organiser of the meeting and was [*sic*] sat next to me at the time.”³² In August 1991, G. R. Sutherland *et al.* postulated in print that:

such heritable unstable DNA sequences could be present in other parts of the genome and that these might explain a number of genetic events that are not well understood in terms of classical genetic mechanisms. Such poorly explained observations include anticipation, incomplete penetrance, and possibly imprinting, variegation, and multifactorial inheritance.³³

²⁹ Fu *et al.*, “Variation,” 1047.

³⁰ Fu *et al.*, “Variation,” 1056.

³¹ J. S. Sutcliffe, D. L. Nelson, F. Zhang, M. Pieretti, C. T. Caskey, D. Saxe, and S. T. Warren, “DNA methylation represses *FMR-1* transcription in fragile X syndrome,” *Human Molecular Genetics* 1 (1992): 397-400; R. I. Richards, K. Holman, K. Friend, E. Kremer, D. Hillen, A. Staples, W. T. Brown, P. Goonewardena, J. Tarleton, C. Schwartz, and G. R. Sutherland, “Evidence of founder chromosomes in fragile X syndrome,” *Nature Genetics* 1 (July 1992): 257-259; A. K. Gedeon, E. Baker, H. Robinson, M. W. Partington, B. Gross, A. Manca, B. Korn, A. Poustka, S. Yu, G. R. Sutherland and J. C. Mulley, “Fragile X syndrome without CCG amplification has an *FMRI* deletion,” *Nature Genetics* 1 (August 1992) 341-344; D. Wöhrle, D. Kotzot, M. C. Hirst, A. Manca, B. Korn, A. Schmidt, G. Barbi, H. Rott, A. Poustka, K. E. Davies, and P. Steinbach, “A Microdeletion of Less than 250 kb, Including the Proximal Part of the *FMR-1* Gene and the Fragile-X Site, in a Male with the Clinical Phenotype of Fragile-X Syndrome,” *American Journal of Human Genetics* 51 (1992): 299-305.

³² Keith J. Johnson, Correspondence with Judith Friedman, 5 July 2002. See also Jacqueline Donachie and Darren G. Monckton, *Tomorrow Belongs to Me*, (Glasgow: University of Glasgow, 2006), 163-170.

³³ G. R. Sutherland, E. A. Haan, E. Kremer, M. Lynch, M. Pritchard, S. Yu, and R. I. Richards, “Hereditary unstable DNA: a new explanation for some old genetic questions?” *The Lancet* 338 (August 3, 1991): 289.

The authors suggested that such an unstable DNA repeat could be the cause of anticipation within myotonic dystrophy too. In their views, the same mechanism might also eventually explain adult polycystic kidney disease, Waardenburg syndrome, cases of incomplete penetrance and variable expression, multifactorial inheritance and conditions related to other fragile sites on various chromosomes.³⁴

Myotonic Dystrophy

While expanding trinucleotide repeats were being discovered in Fragile X syndrome, research into myotonic dystrophy was also going forward in several loosely affiliated labs in Wales, England, the United States, Canada, and the Netherlands.³⁵ At least one of the scientists involved in the research at Cardiff believed that since the mutation in Fragile X syndrome was caused by an expanding trinucleotide repeat, that it was worthwhile looking for something similar in myotonic dystrophy.³⁶ On his return from the meeting at Cold Spring Harbor, Keith Johnson had set his lab looking for “an expanded repeat in the physically defined DM interval.”³⁷ C. Thomas Caskey—whose lab at Baylor College of Medicine in Texas had been involved in the sequencing of fragile X—joined the hunt for a trinucleotide expansion in myotonic dystrophy in 1991 after attending the myotonic

³⁴ Sutherland *et al.*, “Hereditary,” 290-291.

³⁵ The main research took place at the Institute of Medical Genetics, University of Wales, Cardiff, Wales; Charing Cross and Westminster Medical School, London, England; MIT Boston, USA; Lawrence Livermore National Laboratory (LLNL), California, USA; Ottawa, Canada; Nijmegen, the Netherlands; Baylor College of Medicine, Texas. These groups knew of each other and, from time to time, shared research personnel, information, etc. and would collaborate for publication. This, however, did not mean that these groups were not still in competition with one another. Sociologists have examined the interrelation of these groups and their behaviour as the discovery of the sequence of the gene for myotonic dystrophy neared and found that cooperation between the various groups decreased as they came closer to sequencing the gene. See C. Batchelor, E. Parsons, and P. Atkinson, “The Career of a Medical Discovery,” *Qualitative Health Research* 6 (May 1996): 225-226, 234-242.

³⁶ Batchelor *et al.*, did not identify the scientist, as this would have gone against their sociological methodology. Based upon statements in later papers and personal interviews I do know that Peter Harper of the Cardiff lab was looking in this direction and that he was familiar with Höweler’s work on anticipation in myotonic dystrophy. Höweler himself was collaborating with the Dutch research group in Nijmegen. Peter S. Harper, Interviews with Judith Friedman, 27 June 2002, 23 July 2002; Christiaan J. Höweler, Correspondence with Judith Friedman, 18 March 2004.

³⁷ Johnson had been aware of Höweler’s assertions that anticipation in myotonic dystrophy was a real biological phenomenon since Höweler had presented on his findings at a series of meetings on genetics and disease held by John Edwards at Oxford University. Johnson, Correspondence with Judith Friedman, 5 July 2002. Höweler, Correspondence with Judith Friedman, 19 March 2004, 10 June 2004, 20 January 2005

dystrophy panels at the International Congress of Human Genetics in Washington D.C.³⁸ Linkage analysis had already found the general location of the gene and shown that a significant number of British and French-Canadian cases of myotonic dystrophy were descended from the same ancestral mutation.³⁹

The final discovery of the location and sequence of the myotonic dystrophy gene was made almost simultaneously in several of the competing research groups. Several papers published in 1992, each describing some novel portion of the discovery and with overlapping authorship, appeared within a short period of one another in *Nature*, *Science*, and *Cell*.⁴⁰ This led to competition between the three journals to publish the results in as timely a fashion as possible in order to gain the most recognition for publishing this new and important research. For this purpose, *Science* broke its rule about releasing news of its upcoming publication because it was about to be scooped by a larger and more complete article on the same subject in *Cell*.⁴¹ This situation led John Maddox, *Nature*'s main editor, to comment acerbically on the goings-on:

Are we heading for a state of affairs in which what tends to be published is not the 'minimum publishable unit', a slice of salami, but a more substantial record of the discovery with something novel tagged onto the end? Those concerned cannot be accused of duplicate publication, because the overlapping parts have not yet appeared in print. Confusion is further aggravated by the overlapping membership of the author groups ... suggesting that apparently competing groups knew in advance of the overlapping parts. There is nothing wrong with that either, except the hint of a suspicion that people out to maximize the publicity attending discovery have taken to playing tricks on journals. There are two remedies: journals must watch out, especially for the quality of what they publish, and must be uniformly faster.⁴²

³⁸ In his interview with me Johnson speculated that it was after attending these panels that Caskey joined the race to sequence the myotonic dystrophy gene. Johnson, Correspondence with Judith Friedman, 5 July 2002, 9 July 2002. This was confirmed in an interview of Caskey by Donachie. Donachie and Monckton, *Tomorrow Belongs to Me*, 130-131.

³⁹ H. G. Harley, J. D. Brook, J. Floyd, S. A. Rundle, S. Crow, K. V. Walsh, M. Thibault, P. S. Harper, and D. J. Shaw, "Detection of Linkage Disequilibrium between the Myotonic Dystrophy Locus and a New Polymorphic DNA Marker," *American Journal of Human Genetics* 49 (1991): 68.

⁴⁰ The actual order of events regarding who made which discovery first remains somewhat contentious. Johnson, Interview with Judith Friedman, 5 July 2002; Batchelor *et al.*, 243-244.

⁴¹ J. Maddox, "Melodrama in research publication," *Nature* 355 (27 February 1992): 767.

⁴² Maddox, "Melodrama," 767.

These six papers laid out the discovery of the myotonic dystrophy gene and the role of expanding trinucleotide repeats in causing anticipation within it.

The first three papers, whose main authors were from the Cardiff, London, and American contingents respectively, appeared in *Nature* on 6 February 1992. The first outlined the discovery of an expanding fragment within the region of the myotonic dystrophy gene that was not apparently caused by recombination.⁴³ The second paper showed that the size of this region was larger in myotonic dystrophy patients than in normal individuals and that the severity of symptoms seemed to be correlated with the length of the fragment.⁴⁴ The final paper analysed the expanding segment, noted its similarities to the unstable segment in Fragile X syndrome, and concluded that the variable length of the region was probably involved in generating the complex array of symptoms in myotonic dystrophy.⁴⁵

The fourth paper was published in *Cell* on 21 February 1992, and its main authors were from the American labs and the London and Welsh groups. This paper identified the expanding region as a CTG triplet repeat located in the 3' untranslated region of an mRNA coding for an unknown protein kinase that was expressed in tissues affected by the disease. The length of the repeat varied within the population; normal individuals had between 5 and 27 copies of CTG, those mildly affected by myotonic dystrophy had at least 50 copies, and those with severe disease could have up to several kilobase pairs of the repeat.⁴⁶

⁴³ H. J. Harley, J. D. Brook, S. A. Rundle, S. Crow, W. Reardon, A. J. Buckler, P. S. Harper, D. E. Housman, and D. J. Shaw, "Expansion of an unstable DNA region in phenotypic variation in myotonic dystrophy," *Nature* 355 (6 February 1992): 545-546.

⁴⁴ J. Buxton, P. Shelbourne, J. Davies, C. Jones, T. Tongeren, C. Aslanidis, P. de Jong, G. Jansen, M. Anvret, B. Riley, R. Williamson and K. Johnson, "Detection of an unstable fragment of DNA specific to individuals with myotonic dystrophy," *Nature* 355 (6 February 1992): 547-548.

⁴⁵ C. Aslanidis, G. Jansen, C. Amemiya, G. Shutler, M. Mahadevan, C. Tsilfidis, C. Chen, J. Alleman, N. G. M. Wormskamp, M. Vooijs, J. Buxton, K. Johnson, H. J. M. Smeets, G. G. Lennon, A. V. Carrano, R. G. Korneluk, B. Wieringa, and P. de Jong, "Cloning of the essential myotonic dystrophy region and mapping of the putative defect," *Nature* 355 (6 February 1992): 548, 550.

⁴⁶ J. D. Brook, M. E. McCurrach, H. G. Harley, A. J. Buckler, D. Church, H. Aburatani, K. Hunter, V. P. Stanton, J. Thirion, T. Hudson, R. Sohn, B. Zemelman, R. G. Snell, S. A. Rundle, S. Crow, J. Davies, P. Shelbourne, J. Buxton, C. Jones, V. Juvonen, K. Johnson, P. S. Harper, D. J. Shaw, and D. E. Housman, "Molecular Basis of Myotonic Dystrophy: Expansion of a Trinucleotide (CTG) Repeat at the 3' End of a Transcript Encoding a Protein Kinase Family Member," *Cell* 68 (February 21, 1992): 799-807.

The final two papers appeared in *Science* on 6 March 1992 and the main authors were members of the American and Canadian research groups. The fifth paper repeated that the myotonic dystrophy gene coded for a protein kinase (myotonin protein kinase) and contained an unstable CTG repeat that was larger in individuals suffering from the disease. When inherited from the mother, this allele appeared to be considerably more unstable than when inherited from the father. This fact explained both anticipation in myotonic dystrophy and the observation that the most severe cases were seen in the offspring of female sufferers.⁴⁷ The final paper analysed the myotonic dystrophy gene in 258 individuals and found that in 98 percent of the cases the CTG region was larger than normal. This correlation suggested that the expansion of the CTG region was the primary cause of myotonic dystrophy.⁴⁸

THE DISSEMINATION OF THE IDEA: 1992-2005

The information in the 1992 papers moved swiftly into the scientific and medical mainstream. On 9 May 1992, an article in the prominent medical journal *The Lancet* provided a summary of the recent papers on myotonic dystrophy for a medical audience.⁴⁹ This article concentrated on the clinical implications of the discoveries for diagnosis and genetic counselling. The observations of anticipation and the variation of the symptoms of the disorder were explained as having been caused by expansion of the trinucleotide repeat within the relevant gene although the exact mechanism of the maternal transmission of the most severe forms of the disease could not yet be specified.⁵⁰ It was also noted that most cases of myotonic dystrophy seemed to be descended from the same ancestral mutation, likely an increase of the number of CTG

⁴⁷ Y. Fu, A. Pizzuti, R. G. Fenwick, J. King, S. Rajnarayan, P. W. Dunne, J. Dubel, G. A. Nasser, T. Ashizawa, P. de Jong, B. Wieringa, R. Korneluk, M. B. Perryman, H. F. Eptsein, and C. T. Caskey, "An Unstable Triplet Repeat in a Gene Related to Myotonic Muscular Dystrophy," *Science* 255 (6 March 1992): 1256-1258.

⁴⁸ M. Mahadevan, C. Tsilfidis, L. Sabourin, G. Shutler, C. Amemiya, G. Jansen, C. Neville, M. Narang, J. Barcelo, K. O'Hoy, S. Leblond, J. Earle-Macdonals, P. de Jong, B. Wieringa, and R. G. Korneluk, "Myotonic dystrophy mutation: an unstable CTG repeat in the 3' untranslated region of the gene," *Science* 255 (6 March 1992): 1253-1255.

⁴⁹ A similar review appeared in the November 1992 issue of the *Journal of Medical Genetics*. G. K. Suthers, S. M. Huson, and K. E. Davies, "Instability versus predictability: the molecular diagnosis of myotonic dystrophy," *Journal of Medical Genetics* 29 (1992): 761-765.

⁵⁰ H. G. Harley, S. A. Rundle, W. Reardon, J. Myring, S. Crow, J. D. Brook, P. S. Harper, D. J. Shaw, "Unstable DNA sequence in myotonic dystrophy," *Lancet* 339 no. 8802 (9 May 1992): 1125-1127.

repeats from 5-27 to about 50 copies. This would have caused little or no apparent effect, but the increased size of the repeat would make further enlargement of the gene over later generations considerably easier until the insert reached a size that caused noticeable clinical symptoms.⁵¹

A further review article also appeared in *The American Journal of Human Genetics* in July 1992. The authors, Peter Harper *et al.*, reviewed the controversial history of anticipation over the past century and outlined the developments that led to the discovery of the genetic mechanism responsible for anticipation, namely, expanding trinucleotide repeats.⁵² In their view, this discovery meant that “anticipation can now be considered as a genuine and proven phenomenon in myotonic dystrophy.” The discovery vindicated “the observations of a long series of clinicians working on myotonic dystrophy over a span of three-quarters of a century” and provided a warning for researchers to be more open-minded when dealing with observations that do not seem to fit in with recognised modes of inheritance.⁵³ Within a remarkably short period anticipation had gone from being considered an experimental artefact caused by selection bias and incomplete ascertainment to being deemed a real biological condition with a clearly delineated, although far from understood, underlying genetic cause.

Finding Expanding Trinucleotide Repeats in Other Syndromes

Once anticipation in myotonic dystrophy and Fragile X syndrome had been shown to be caused by expanding trinucleotide repeats, several research groups began to wonder whether this novel form of mutation might play a causative role in other genetic diseases. Over the next few years, expanding trinucleotide repeats were found in several other genes, as these were isolated and sequenced. Anticipation had been observed in most of these disorders, and the severity of the disease was generally linked to the size of the triplet repeat—the larger the repeat, the worse the symptoms. In several cases, the largest expansions were associated with inheritance of the mutation through either the male or the female line.

⁵¹ Harley *et al.*, “Unstable DNA,” 1127-1128.

⁵² Peter S. Harper, Helen G. Harley, William Reardon, and Duncan J. Shaw, “Review Article: Anticipation in Myotonic Dystrophy: New Light on an Old Problem,” *American Journal of Human Genetics* 51 (1992): 10-14.

⁵³ Harper *et al.*, “Anticipation,” 15.

X-linked spinal and bulbar muscular atrophy (SBMA) was the next disorder that was linked to expanding trinucleotide repeats. The expansion of a CAG repeat located within the first exon of the gene altered the function of the gene and led to progressive muscle weakness and atrophy as well as other symptoms.⁵⁴

Huntington's disease represents perhaps the most important and well-known disorder caused by expanding triplet repeats. As discussed earlier, Huntington's disease, an autosomal dominant disorder characterized by uncontrollable movement and mental deterioration, showed cases of juvenile onset only in the sons of male sufferers. Peter Harper, who had been involved in the sequencing of the myotonic dystrophy gene and who was well aware of the link between expanding trinucleotide repeats and anticipation, in 1992 suggested to his colleagues in the Huntington's Disease Collaborative Research Group that they concentrate their efforts in this direction.⁵⁵ The approach bore fruit in March 1993, when the Huntington's Disease Collaborative Research Group was able to report that an expanding CAG triplet repeat located within the first exon of the gene was the cause of the mutation responsible for the disease.⁵⁶

Triplet repeats were also found to play a role in several disorders caused by abnormalities on two additional fragile sites on the X chromosome: FRAXE (GCC)⁵⁷ and FRAXF (GCC).⁵⁸ Spinocerebellar ataxia type 1 (SCA1), an autosomal dominant neurodegenerative disorder, was found to be caused by an expanded CAG trinucleotide

⁵⁴ Nuclear DNA contains areas that code for protein (exons) and areas that do not code for protein (introns). In order for the information in a gene to be successfully translated into a protein product an RNA copy of the DNA sequence must be made. This RNA is then processed in the nucleus in order to remove the unnecessary portions of the DNA (the introns). The mature mRNA (made up of the exons) can then leave the nucleus and be translated into protein within the cell. Any mutation that effects and exon or coding region of the DNA will likely effect the end protein product, possibly rendering it damaged or useless. A. R. La Spada, E. M. Wilson, D. B. Lubahn, A. E. Harding, and K. H. Fischbeck, "Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy," *Nature* 352 (4 July 1991): 77-79.

⁵⁵ Harper, Interview with Judith Friedman, 27 June 2002, 23 July 2002.

⁵⁶ Huntington's Disease Collaborative Research Group, "A novel gene containing a trinucleotide repeat that is expanded and unstable of Huntington's disease chromosomes," *Cell* 72 (March 26 1993): 971-983.

⁵⁷ S. J. L. Knight, A. V. Flannery, M. C. Hirst, L. Campbell, Z. Christodoulou, S. R. Phelps, J. Pointon, H. R. Middleton-Price, A. Barnicoat, M. E. Pembrey, J. Holland, B. A. Oostra, M. Bobrow, and K. E. Davies, "Trinucleotide repeat amplification and hypermethylation of a CpG island in FRAXE mental retardation," *Cell* 74 (July 16 1993): 127-134.

⁵⁸ J. E. Parrish, B. A. Oostra, A. J. M. H. Verkerk, C. S. Richards, J. Reynolds, A. S. Spikes, L. G. Shaffer, and D. L. Nelson., "Isolation of a GCC repeat showing expansion in FRAXF, a fragile site distal to FRAXA and FRAXE," *Nature Genetics* 8 (8 November 1994): 229-235.

repeat within an exon.⁵⁹ Researchers then postulated that a similar mechanism might be behind the anticipation seen in spinocerebellar ataxia type 5 (SCA5).⁶⁰ Dentatorubral-pallidoluysian atrophy (DRPLA), also known as Haw River syndrome in the United States, was yet another rare autosomal dominant neurodegenerative disorder found to be caused by a CAG triplet repeat located in the 5' side of the coding region. Like Huntington's disease, those most severely affected by the disease, and those with the largest trinucleotide expansion, were the children of affected males.⁶¹ Spurred on by the discovery of the role of expanding trinucleotide repeats in these other autosomal dominant neurodegenerative disorders, researchers studying Machado-Joseph disease (MJD) looked for, and found, an expanding CAG repeat in the coding region of the gene for that condition.⁶²

As this series of discoveries makes apparent, the identification of triplet repeats opened up a significant new area of research. The disorders listed above include only those discovered by 1994. Researchers even developed a PCR based technique, repeat expansion detection (RED), which enabled scientists to take a shotgun approach to locating further trinucleotide repeats within the human genome.⁶³

⁵⁹ H. T. Orr, M. Chung, S. Banfi, T. J. Kwiatkowski, A. Servadio, A. L. Beaudet, A. E. McCall, L. A. Duvick, L. P. W. Ranum, and H. Y. Zoghbi, "Expansion of an unstable CAG repeat in spinocerebellar ataxia type 1," *Nature Genetics* 4 (July 1993): 221-226; M. Chung, L. P. W. Ranum, L. A. Duvick, A. Servadio, H. Y. Zoghbi, and H. T. Orr, "Evidence for a mechanism predisposing to intergenerational CAG repeat instability in spinocerebellar ataxia type I," *Nature Genetics* 5 (November 1993): 254-258.

⁶⁰ L. P. W. Ranum, L. J. Schut, J. K. Lundgren, H. T. Orr, and D. M. Livingston, "Spinocerebellar ataxia type 5 in a family descended from the grandparents of President Lincoln maps to chromosome 11," *Nature Genetics* 8 (November 1994): 280-284.

⁶¹ Shiro Miwa, "Triplet repeats strike again," *Nature Genetics* 6 (January 1994): 3-4; R. Koide, T. Ikeuchi, O. Onodera, H. Tanaka, S. Igarashi, K. Endo, H. Takahashi, R. Kondo, A. Ishikawa, T. Hayashi, M. Saito, A. Tomoda, T. Miike, H. Naito, F. Ikuta, and S. Tsuji, "Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA)," *Nature Genetics* 6 (January 1994): 9-13; S. Nagafuchi, H. Yanagisawa, K. Sato, T. Shirayama, E. Ohsaki, M. Bundo, T. Takeda, K. Tadokoro, I. Kondo, N. Murayama, Y. Tanaka, H. Kikushima, K. Umino, H. Kurosawa, T. Furukawa, K. Nihei, T. Inoue, A. Sano, O. Komure, M. Takahashi, T. Yoshizawa, I. Kanazawa, and M. Yamada, "Dentatorubral and pallidoluysian atrophy expansion of an unstable CAG trinucleotide on chromosome 12p," *Nature Genetics* 6 (January 1994): 14-18; J. R. Burke, M. S. Wingfield, K. E. Lewis, A. D. Roses, J. E. Lee, C. Hulette, M. A. Pericak-Vance, and J. M. Vance, "The Haw River Syndrome: Dentatorubropallidoluysian atrophy (DRPLA) in an African-American family," *Nature Genetics* 7 (August 1994): 521-524.

⁶² Y. T. Kawaguchi, Okamoto, M. Taniwaki, M. Aizawa, M. Inoue, S. Katayama, H. Kawakami, S. Nakamura, M. Nishimura, I. Akiguchi, J. Kimura, S. Narumiya, and A. Kakizuka, "CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1," *Nature Genetics* 8 (November 1994): 221-228.

⁶³ M. Schalling, T. J. Hudson, K. H. Buetow, and D. E. Housman, "Direct detection of novel expanded trinucleotide repeats in the human genome," *Nature Genetics* 4 (June 1993): 135-139.

Anticipation in Genetics and Human and Medical Genetics Texts 1991-2005

In the period following the discovery of the genetic mechanism underlying anticipation, the concept has been incorporated into the specialist literature involving the diseases with which such expanding trinucleotide repeats are associated.⁶⁴ However, in spite of the discovery of a molecular mechanism underlying anticipation, the concept has not consistently been discussed in general genetics literature, perhaps because the idea that GC-rich regions of DNA have been known for some time to be reproductively unstable and authors do not feel that they need to address anticipation specifically.⁶⁵ This may change as some researchers began speculating late in 1994 that such regions might allow for rapid evolutionary changes, particularly during time of stress.⁶⁶ On the other hand, medical genetics textbooks published the new information of the genetic basis of

⁶⁴ See for example, Russell J. M. Lane, Peggy Shelbourne and Keith J. Johnson, "Myotonic Dystrophy," In *Handbook of Muscle Disease*, Russell J. M. Lane ed., (New York: Marcel Dekker, Inc., 1996), 311-328; Alan E. H. Emery, "Molecular Genetics of Neuromuscular Disorders: Applications in Clinical Medicine," In *Neuromuscular Disorders: Clinical and Molecular Genetics*, (Alan E. H. Emery Ed. Chichester: John Wiley and Sons, 1998), 1-20; Barry Brewster, Patricia Groenen and Bé Wieringa, "Myotonic Dystrophy: Clinical and Molecular Aspects," In *Neuromuscular Disorders: Clinical and Molecular Genetics*, Alan E. H. Emery Ed., (Chichester: John Wiley and Sons, 1998), 323-364.

⁶⁵ Cold Spring Harbor Press dedicated an entire volume of their Genome Analysis series to the question of genomic rearrangement and stability, including expanding trinucleotide repeats. Kay E. Davies and Stephen T. Warren, Eds., *Genome Analysis Volume 7: Genome Rearrangement and Stability*, (Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 1993); Klug and Cummings were the first to incorporate anticipation into the 4th edition of their text published in 1994. William S. Klug and Michael R. Cummings, *Concepts of Genetics*, 4th ed., (Engelwood Cliffs, NJ: Prentice Hall, 1991), 213-214. In 1995 an article on trinucleotide repeat expansions appeared in the *Annual Review of Genetics*. Claude T. Ashley Jr. and Stephen T. Warren, "Trinucleotide Repeat Expansion and Human Disease," *Annual Review of Genetics* 29 (1995): 703-728. Some texts have, however, not yet incorporated anticipation. See for example: Robert H. Tamarin, *Principles of Genetics*, 5th ed., (Dubuque IA: Wm. C. Brown Publishers, 1996); Benjamin Lewin, *Genes VIII*, (Upper Saddle River NJ: Pearson Prentice Hall, 2004). The eighth edition of *Introduction to Genetic Analysis* discusses anticipation as a special case of errors in DNA replication found in humans. Anthony J. F. Griffiths, Susan R. Wessler, Richard C. Lewontin, William M. Gelbart, David T. Suzuki, Jeffrey H. Miller, *Introduction to Genetic Analysis*, 8th ed., (New York: W. H. Freeman and Company, 2005), 464-468.

⁶⁶ This line of research has led to some fascinating work on how the change in repeat number in certain genes has led to the wide variation in breeds of dogs. John W. Fondon III and Harold R. Garner, "Molecular origins or rapid and continuous morphological evolution," *PNAS* 101 no. 52 (28 December 2004): 18058-18063; Elizabeth Pennisi, "Genetics: A Ruff Theory of Evolution: Gene Stutters Drive Dog Shape," *Science* 306 no. 5705 (24 December 2004): 2172; Douglas M. Ruden, Mark D. Garfinkel, Li Xiao and Xiangyi Li, "Epigenetic Regulation of Trinucleotide Repeat Expansions and Contractions and the 'Biased Embryo' Hypothesis for Rapid Morphological Evolution," *Current Genomics* 6 no. 3 (May 2005): 145-155; John W. Fondon III and Harold R. Garner, "Detection of length-dependant effects of tandem repeat alleles by 3-D geometric decomposition of craniofacial variation," *Development Genes and Evolution* 217 no. 1 (January 2007): 79-85.

anticipation as it was found, first in Fragile X,⁶⁷ and, from 1993 to 2005 in an increasing number of human diseases.⁶⁸ The rapidly increasing number of texts and the frequent publication of new editions are indicative of the rapid rate of change and advancement in the field of medical genetics over the last two decades.

EXPLANATIONS REVISITED: ACCOUNTING FOR TRINUCLEOTIDE REPEATS

Accounting For Trinucleotide Repeats: Explaining the Explanation

Yet despite all the research into identifying expanding trinucleotide repeats, the actual mechanism responsible for the expansion process remained unknown. Indeed, scientists have discovered that the replication of simple repeat DNA is far from simple.⁶⁹ The term “dynamic mutation” has been used to describe trinucleotide repeat instability because it has been observed that the larger the number of copies within the repeat, the greater the likelihood that it will mutate.⁷⁰ Although observations of the expansion of

⁶⁷ The 8th edition of Emery’s *Elements of Medical Genetics* included a description of the peculiar mode of heredity in Fragile X and myotonic dystrophy, but did not include any of the post-1990 papers in which the genetic mechanism was elucidated. It is worth noting that Emery, who in previous editions was very critical of anticipation, noted in this edition that “despite these reservations, however, recent carefully designed studies now indicate that, at least in the case of myotonic dystrophy, anticipation is in fact a true biological phenomenon” but one without any explanation (although Emery thought that it might be due to imprinting). Alan E. H. Emery and Robert F. Mueller, *Elements of Medical Genetics*, 8th ed., (Edinburgh: Churchill Livingstone, 1992), 137-138, 149, 117, 283.

⁶⁸ See for example: D. J. H. Brock, *Molecular genetics for the clinician*, (Cambridge: Cambridge University Press, 1993); R. J. Trent, *Molecular Medicine: An Introductory Text for Students*, (Edinburgh: Churchill Livingstone, 1993); Lynne B. Jorde, John C. Carey, and Raymond L. White, *Medical Genetics*, (St Louis: Mosby, 1995); R. J. Trent, *Molecular Medicine: An Introductory Text for Students*, 2nd ed., (New York: Churchill Livingstone, 1996); Thomas D. Gelehrter, Francis S. Collins and David Ginsburg, *Principles of Medical Genetics*, 2nd ed., (Baltimore: William & Wilkins, 1998); George H. Sack, *Medical Genetics*, (New York: McGraw-Hill, 1999); A. Gardner, R. T. Howell, and T. Davies, *Human Genetics*, (London: Arnold, 2000); Lynne B. Jorde, John C. Carey, Michael J. Bamshad and Raymond L. White, *Medical Genetics*, 2nd ed., (St Louis: Mosby, 2000); Bruce R. Korf, *Human Genetics: A Problem-Based Approach*, (Malden MA: Blackwell Science, 2000); Robert L. Nussbaum, Roderick R. McInnes, and Huntington F. Willard, *Thompson & Thompson: Genetics in Medicine*, 6th ed., (Philadelphia: W. B. Saunders Company, 2001); Lynne B. Jorde, John C. Carey, Michael J. Bamshad and Raymond L. White, *Medical Genetics*, 3rd ed., (St Louis: Mosby, 2003); Robert L. Nussbaum, Roderick R. McInnes, and Huntington F. Willard, *Thompson & Thompson: Genetics in Medicine*, 6th ed., Revised Reprint, (Philadelphia: Saunders, 2004); R. J. Trent, *Molecular Medicine: An Introductory Text for Students*, 3rd ed. (Amsterdam: Elsevier Academic Press, 2005); Ian D. Young, *Medical Genetics*, (Oxford: Oxford University Press, 2005).

⁶⁹ R. I. Richards and G. R. Sutherland, “Simple repeat DNA is not replicated simply,” *Nature Genetics* 6 (February 1994): 114-116.

⁷⁰ Richards and Sutherland, “Simple,” 115.

these trinucleotide regions have been common, only rarely has the opposite effect—the deletion of expanded regions of DNA down to a normal size range—been seen.⁷¹

Several mechanisms of mutation leading to expanding trinucleotide repeats have been suggested. Founder effects and linkage disequilibrium in many cases of trinucleotide repeat disorders suggest that an original mutation occurred some time in the past that predisposed daughter chromosomes to further mutational events.⁷² It seems likely that this original mutation caused intervening sequences in an imperfect—and therefore replication-stable—repeat to be lost, thereby creating a perfect repeat that was then more susceptible to future mutations.⁷³ Expansion of the perfect repeat might then be caused by slippage during DNA replication.⁷⁴ Examinations of mutations within human minisatellites suggest that unequal sister chromatid exchange or some other complex conversion-like events might be responsible for more mutational events than

⁷¹ Y. Fu, D. P. A. Kuhl, A. Piazzuti, M. Pieretti, J. Sutcliffe, S. Richards, A. Verkerk, J. J. A. Holden, R. G. Fenwick, S. T. Warren, B. A. Oostra, D. L. Nelson, and C. T. Caskey, "Variation of the CGG repeat at the Fragile X Site Results in Genetic Instability: Resolution of the Sherman Paradox," *Cell* 67 no. 6 (20 December 1991): 1047-1058; Hans G. Brunner, G. J. Jansen, W. Nillesen, M. R. Nelen, C. E. M. de Die, C. J. Höweler, B. A. van Oost, B. Wieringa, H. Ropers, and H. J. M. Smeets, "Brief Report: Reverse Mutation in Myotonic Dystrophy," *New England Journal of Medicine* 328 (18 February 1993): 476-480. For an editorial discussing questions raised by these and other findings in the study of diseases caused by trinucleotide repeats see, Jean-Louis Mandel, "Trinucleotide diseases on the rise," *Nature Genetics* 7 (August 1994): 453-455.

⁷² In a paper written in 1994 C. E. M. Die-Smulders *et al.* remarked that some ancestral mutation in the myotonic dystrophy gene seemed to be at work in the family that they studied—and likely in the population as a whole. This ancestral mutation appeared to be reasonably stable allowing it to spread within the population. However, some unknown factor could trigger a "cascade" of anticipation in succeeding generations and the descendants of asymptomatic carriers would develop increasingly severe manifestations of the disease as the trinucleotide repeat region expanded. It appeared, however, that after a number of generations the myotonic gene would find itself naturally eliminated from the family through a combination of childlessness among those with moderate and severe forms of the disease and with infant mortality in the most severe manifestation of the disease. Their unaffected siblings do not serve as a reservoir for the mutation. C. E. M. Die-Smulders, C. J. Höweler, J. F. Mirandolle, H. G. Brunner, V. Hovers, H. Brüggewirth, H. J. M. Smeets, and J. P. M. Geraedts, "Anticipation resulting in elimination of the myotonic dystrophy gene: a follow up study of one extended family," *Journal of Medical Genetics* 31 (1994): 595-601.

⁷³ Regions of DNA composed of long runs of repeated nucleotide sequences are particularly prone to errors during DNA replication. For this reason, there are usually naturally occurring short intervening segments of DNA made up of a different sequence of nucleotides breaking up such long runs of repeated sequences. These intervening sequences make the long stretch of DNA with the repeated sequence "imperfect" but allow it to be replicated in a stable fashion. Richards and Sutherland, "Simple," 115.

⁷⁴ Although the exact sequences vary from disease to disease, the trinucleotide repeat disorders contain long runs of CG rich regions of DNA. Such regions are particularly prone to errors during replication, including slippage errors which can result in the addition of extra segments of DNA in the daughter chromosome. Richards and Sutherland, "Simple," 115-116

would be caused by slippage during DNA replication.⁷⁵ In the case of myotonic dystrophy, meiotic drive has also been suggested, as there appears to be a preferential transmission of somewhat larger numbers of trinucleotide repeats.⁷⁶ If this were to be the case, then the larger the repeat number, the more unstable the repeat, and the likelier it would be to expand to the point at which it caused symptoms. This would account for how such an apparently undesirable mutation had been maintained within the population.⁷⁷ However, mutational bias rather than meiotic drive has been suggested as the cause of the expansion of CAG repeats in Huntington's disease.⁷⁸ Researchers in this field suggest that the number of human CAG repeats has increased since the ancestral state, but they see no preferential replication of longer repeat lengths. Rather, they believe that a mutational bias towards expansion of the CAG repeat leads to increasing instability in the region—i.e. the longer the repeat gets, the likelier it is to undergo further expansion. Unfortunately, if this model holds true, it would mean that Huntington's disease can be expected to become more common over time as the CAG repeat continues to expand within the human population. Nor will natural selection be effective at stopping its slow and apparently inexorable process since, except in its most extreme manifestations, Huntington's disease does not manifest itself until after individuals have entered their reproductive years and it very rarely effects fertility.⁷⁹ This bears a striking

⁷⁵ Minisatellites are short sections of repeated segments of DNA (generally CG-rich) which occur regularly within a genome and appear to encourage crossing over—i.e. the swapping of DNA between sister chromosomes during meiosis—which adds to genetic variation. A. J. Jeffreys *et al.* suggested that these events were more likely to cause mutations than slippage of during DNA replication. A. J. Jeffreys, K. Tamaki, A. MacLeod, D. G. Monckton, D. L. Neil, and J. A. L. Armour, "Complex gene conversion events in germline mutation at human satellites," *Nature Genetics* 6 (February 1994): 136, 144.

⁷⁶ According to normal patterns of Mendelian segregation, during gamete formation half of an organism's offspring should receive one allele of a gene and half should receive the other. In the case of meiotic drive one of the alleles is represented disproportionately in the population—i.e. the gene in question was passed on to more than 50% of the offspring. N. Carey, K. Johnson, P. Nokelainen, L. Peltonen, M. Sacontaus, V. Juvonen, M. Anvret, U. Grandell, K. Chotai, E. Robertson, H. Middleton-Price, and S. Malcom, "Meiotic drive at the myotonic dystrophy locus?" *Nature Genetics* (February 1994): 117-118.

⁷⁷ Carey *et al.*, "Meiotic drive at the myotonic dystrophy locus?" *Nature Genetics* (February 1994): 117-118.

⁷⁸ D. C. Rubinsztein *et al.* suggest that there is a tendency for repeat length to gradually increase over time through continuous mutation (mutational bias) rather than having certain alleles of the gene be preferentially selected during gamete formation (meiotic drive). D. C. Rubinsztein, W. Amos, J. Leggo, S. Goodburn, R. S. Ramesar, J. Old, R. Bontrop, R. McMahon, D. E. Barton, and M. A. Ferguson-Smith, "Mutational bias provides a model for the evolution of Huntington disease and predicts a general increase in disease prevalence," *Nature Genetics* 7 (August 1994): 525-530.

⁷⁹ The research group ran computer simulations of their model that appeared to verify their hypothesis. Rubinsztein *et al.*, "Mutational bias.

similarity to another (still largely) discredited biological phenomenon—orthogenesis—which posited directional evolution.⁸⁰ Nevertheless, more research is clearly required before the mechanism leading to the expansion of trinucleotide repeats is understood.

NEW PROBLEM AREAS: ANTICIPATION IN SCHIZOPHRENIA AND BPD?

Anticipation has been associated with psychiatric illness ever since the work of Morel in 1857.⁸¹ In his later research into insanity and genetics, Mott too, thought he noticed clear signs of anticipation. In fact, he claimed that up to 50% of the offspring of the insane would themselves suffer from insanity, and likely at an earlier age.⁸² In 1916, the German physician, psychiatrist, eugenicist (and later Nazi) Ernst Rüdin argued that anticipation was at work in families suffering from dementia praecox (schizophrenia).⁸³ The view that anticipation was involved in mental illness fell out of favour after the Second World War as noted in chapter four.⁸⁴ However, since the validation of anticipation by the discovery of expanding trinucleotide repeats in the early 1990s, several researchers have been seeking to rehabilitate the idea that anticipation is operative in certain mental illnesses, particularly bipolar disorders.

The role of genetics in psychiatric illness is itself controversial. Several times researchers have claimed that they had found evidence supporting a genetic cause for these illnesses, but for the most part the search for specific genes responsible for particular disorders has been unsuccessful.⁸⁵ Yet, even in the absence of a causative

⁸⁰ Orthogenesis was a term coined in the late nineteenth century to describe the concept of a force or drive that encouraged mutations to occur in one direction. This kind of evolution was traditionally used to explain traits which had developed beyond the point of evolutionary advantage—such as the canine teeth in “saber-toothed” cats and the outsized antlers of the Irish elk. However, this kind of directional evolution was unacceptable to the neo-Darwinian synthesis that developed in the second half of the twentieth century and orthogenesis was discarded. The biologist Robert Reid argues that orthogenesis should never have been discarded and that it provides a useful way of looking at evolution and the emergence of new characters. Moreover, molecular mechanisms—including anticipation—now provide a biological basis to explain these amplifications and duplications that allow the creation of genetic diversity. See, Robert Reid, *Biological Emergences: Evolution by Natural Experiment*, (Cambridge MA: The MIT Press, 2007), 267-287.

⁸¹ Joel Gelernter, “Genetics of Bipolar Affective Disorder: Time for Another Reinvention?” *American Journal of Human Genetics* 56 (1995): 1263.

⁸² F. W. Mott, “A Lecture on Heredity and Insanity,” *Lancet* 177 no. 4576 (May 13, 1911): 1251-1259.

⁸³ Ernst Rüdin, *Studien Über Vererbung und Entstehung Geistiger Störungen. I. Zur Vererbung und Neuentstehung Der Dementia Praecox*, (Berlin: Julian Springer, 1916), 123-138. In the 1920s and 1930s the German school repudiated the notion of anticipation altogether. See chapter two and three.

⁸⁴ Gelernter, “Genetics,” 1263.

⁸⁵ Gelernter, “Genetics,” 1262.

gene, some researchers believe that the discovery of trinucleotide repeat disorders has provided a mechanism to account for observations of anticipation within certain families suffering from bipolar disorder. From 1990 onwards, researchers have again looked for and claimed to find evidence of earlier onset in successive generation in bipolar disorder.⁸⁶ The finding of this pattern has been taken to suggest that expanding trinucleotide repeats are involved, even though no gene has yet been located.⁸⁷ Researchers have also found that in some families the children of women suffering from bipolar disorder seem to have more severe disease. Although this effect could be caused by imprinting or mitochondrial inheritance, it has also been seen as a sign that expanding repeats might be involved.⁸⁸ Advocates of this mode of inheritance in bipolar disorder respond to criticisms that no gene for the disorder has yet been located by pointing out that anticipation was associated with myotonic dystrophy and Fragile X syndrome long before the genes causing them were located.⁸⁹

Researchers who were involved in sequencing the gene for myotonic dystrophy are divided on this issue regarding anticipation in mental conditions. Peter Harper believes that, in the absence of a gene containing an expanding trinucleotide repeat, claims of anticipation in schizophrenia and bipolar disorder should be treated sceptically.⁹⁰ However, Keith Johnson, who also worked on the myotonic dystrophy project, believes that researchers should keep an open mind on the subject since anticipation was shown to be a real phenomenon in myotonic dystrophy and other disorders.⁹¹ The arguments at play concerning anticipation in diseases whose genes have not yet been located and sequenced bear a striking similarity to arguments made about anticipation in the 1930s and 1940s.

⁸⁶ Gelernter, "Genetics," 1263.

⁸⁷ Gelernter, "Genetics," 1264.

⁸⁸ F. J. McMahon, O. C. Stine, D. A. Meyers, S. G. Simpson, and J. R. DePaulo, "Patterns of Maternal Transmission in Bipolar Affective Disorder," *American Journal of Human Genetics* 56 (1995): 1284.

⁸⁹ Gelernter, "Genetics," 1262-1265.

⁹⁰ Harper, Interview with Judith Friedman, 27 June 2002, 23 July 2002.

⁹¹ Johnson, Correspondence with Judith Friedman, 5 July 2002, 9 July 2002.

Conclusion

In some respects, the debate on anticipation and hereditary disease has come full circle in the last century, but in other respects thinking has shifted enormously. Prosper Lucas first developed his concept of hereditary degeneration in certain families in the context of mid-nineteenth century French social degeneration theory. His basic idea was reiterated by Charles Darwin and developed by Francis Galton into the idea of the intensification of hereditary traits, both positive and negative. Converging with late nineteenth and early twentieth century social anxieties, this idea became an accepted part of the social Darwinist framework of degeneration within “weak breeding stock.” Psychiatrists, first Bénédict Augustin Morel and then Henry Maudsley, popularised the idea that affected families underwent mental degeneration within a short span of generations. This idea was applied most widely to families suffering from a perceived “constitutional diathesis” in which migraine or epilepsy in one generation predicted insanity, imbecility, and early death in later generations.

The work of British ophthalmologist Edward Nettleship brought together the hereditarian and psychiatric streams of thought on the subject in 1905. He was the one who first constructed the idea of anticipation as a condition in which hereditary disease appeared earlier in succeeding generations, and he placed it within the evolving—but still very fluid—early field of genetics. A well-respected researcher who was able to straddle the divide between the then prominent schools of biometricians and Mendelians, Nettleship used the concept of anticipation to underpin his pedigree analyses of hereditary eye-diseases, and he sought to encourage other researchers to take up the subject.

The most important of his contemporaries to do so was the British psychiatrist Frederick Walker Mott. Mott applied anticipation to his already existing theories of degeneration within families suffering from a variety of mental illnesses. He took an active role popularising the idea of anticipation as a means by which mental illness intensified over generations within a family until the most badly affected members would not be able to reproduce. Within a few years, Mott developed the opinion, controversial to most eugenicists, that if a member of an affected family reached a certain age (twenty-

five) they were likely free of hereditary taint and could thus marry without concern of passing along the tendency to mental illness to their children. For this reason, he opposed the policy of legalizing sterilization which he also feared would be applied unevenly to members of different social classes. Mott's opinions angered the biometrical eugenicists who stressed that his arguments suffered from statistical failings and who feared that the acceptance of "Mott's law" could undermine eugenicists' efforts to carry out a programme of discouraging members—even apparently normal members—of affected families from breeding.

Between 1915 and 1930, theoretical development of the concept of anticipation seems to have ceased, but it remained a topic of interest for psychiatrists and for physicians studying diseases with which it came to be associated, most notably myotonic dystrophy and Huntington's disease. The British Eugenics Society's attempt to revive the topic of eugenic sterilization legislation in 1929, as the Depression unfolded, revived interest in anticipation. This time around, the theoretical discussion of anticipation largely centred on its potential to support arguments against sterilization legislation. Anticipation, argued the anti-sterilization advocates, was Nature's way of seeing to the extinction of bad genes within an affected stock. Curiously, both eugenicists (such as Karl Pearson and Arthur Paterson) and the new generation of left-leaning mathematically trained Mendelian geneticists (such as Lionel Penrose) opposed the notion of anticipation at this time, although for different reasons. Angered that anti-sterilization activists were using the idea of anticipation to their advantage, the eugenicists Pearson and Paterson levelled early arguments of statistical fallacy against the idea. On the other hand, Penrose, an ardent anti-eugenicist, opposed both anticipation—on the grounds that it was bad science—and the proposed sterilization legislation—on the grounds that it was immoral as well as futile from a genetic standpoint. At the same time, researchers examining evidence of anticipation in various specific disorders previously linked to the idea began to try to explain their own findings within the new mathematical Mendelian framework of the 1930s.

With the development of modern neo-Mendelian genetics during this period, the idea of anticipation as a biological entity was increasingly questioned, and a rift developed between researchers who were geneticists by training and those who were

physicians working with inherited diseases. The geneticists tried, and generally failed, to find Mendelian explanations against anticipation (or in the case of Goldschmidt alone, for it), while physicians continued to report findings of anticipation within their patient populations. Lionel Penrose came on the scene with new studies related to anticipation (among other issues of heredity) during the 1930s, and in 1948 published the long-standing definitive paper dismissing anticipation. Penrose's work employed mathematical and modelling methodologies that represented the best that the developing field of genetics had to offer at that time. A scrupulously moral, liberal-minded individual, his views on anticipation were shaped by an adherence to Mendelian genetics, were based on systematic research carried out by himself and his colleagues, and were backed by an enviable mathematical and statistical apparatus. Yet they were also based on a series of assumption that later turned out to be false. Penrose's influence was so pervasive within the small but rapidly expanding field of human genetics, that his ideas remained essentially unchallenged for over 30 years. During this time, no matter what their clinical colleagues may have seen or believed, geneticists would only consider anticipation to be a product of experimental bias.

Not until the discovery of juvenile or congenital onset varieties of Huntington's disease and myotonic dystrophy in the late 1960s and early 1970s, together with the linkage of these conditions respectively to paternal and maternal inheritance, did human geneticists again examine anticipation, though dismissively at first. Slowly, however it became apparent that these modes of inheritance were in fact the expressions of an identifiable biological condition and were not merely, as Penrose had suggested, the results of selection bias and faulty ascertainment. The work of the Dutch physician and researcher Christiaan J. Höweler proved pivotal to the reintroduction of the concept of anticipation as a real biological phenomenon. In his 1986 dissertation and in a widely circulated 1989 article in *Brain*, Höweler showed several key flaws in Penrose's argument against the notion of anticipation. While Höweler convinced some influential human geneticists (most notably Peter Harper) of the merits of his argument, many continued to remain sceptical.

The strong decades-long resistance to the idea of anticipation among the human and medical genetics communities makes especially interesting their almost

instantaneous acceptance of anticipation after the discovery by some of their members of a causative molecular mechanism. The discovery of expanding trinucleotide repeats within the genes of diseases long associated with anticipation (fragile-X, myotonic dystrophy, and Huntington's disease) led to a remarkable reversal in thinking about anticipation in the early 1990s. Even though the underlying cause of these expanding trinucleotide repeats remained unknown, the fact that the idea of anticipation could now be placed within a theoretical and methodological framework congenial to them, allowed it to gain a wide degree of acceptance.

This acceptance in explaining a limited set of disease conditions does not mean, however, that the idea has now become orthodox in all realms of medical research. In the case of schizophrenia and other diseases still lacking clear evidence of a genetic cause, claims of anticipation remain as controversial now as they were seventy years ago, and for many of the same reasons (although thankfully state-mandated sterilization is no longer under discussion). Arguments for anticipation being at work in schizophrenia and certain other diseases might currently be discussed as speculation, but unless and until clearly related genes with expanding trinucleotide repeats have been discovered as the cause of these conditions, its actual presence must remain questionable.

Bibliography

PRIMARY SOURCES

Manuscript Collections and Archives

Penrose, Lionel S. Papers. University College London Archive, University College London Library, London, England.

Rockefeller Foundation Archives, Rockefeller Archive Center, Sleepy Hollow, New York, USA.

Royal Society of London Library and Archives, Royal Society of London, London, England.

Stern, Curt. Papers. American Philosophical Society Archive, Philadelphia, Pennsylvania, USA.

Correspondence and Interviews

Harper, Peter S. Interviews with Judith Friedman. 27 June 2002, 23 July 2002.

Höweler, Christiaan Jacob. Correspondence with Judith Friedman, 18 March 2004, 19 March 2004, 10 June 2004, 20 January 2005, 20 June 2007.

Johnson, Keith J. Correspondence with Judith Friedman, 5 July 2002, 9 July 2002.

McKusick, Victor. Oral History Interview. 10-11 December 2001 (Ms. Coll. no. 316), Oral History of Human Genetics Collection, History & Special Collections Division, Louise M. Darling Biomedical Library, University of California, Los Angeles.

Unpublished Materials Including Dissertations

Harper, Peter S. "Genetic studies in myotonic dystrophy." Oxford: DM thesis, 1972.

Hayden, M. R. "Huntington's chorea in South Africa." PhD Thesis, University of Cape Town, 1979.

Höweler, Christiaan Jacob. "A Clinical and Genetic Study in Myotonic Dystrophy." Erasmus University of Rotterdam: MD thesis, 1986.

Stevens, D. L. "Huntington's chorea: a demographic genetic and clinical study." University of London: MD thesis, 1976.

Newspaper Articles

- Haldane, J. B. S. "Eugenics: We need to know a great deal more about human heredity." *Daily Worker*, Tuesday, June 4, 1946, page 2.
- Kolata, Gina. "Geneticists find defect worsens over generations." *New York Times*, February 6, 1992, page A1.
- Scott, Leslie. A. F. Tredgold, H. B. Brackenbury, Evelyn Fox, "Mental Deficiency. Case For Institutional Treatment." *The Times* (London), 20 January 1926, pg. 8, Issue 44174, col. D.

Articles and Books

- Abitol, M., C. Menini, A. Delezoide, T. Rhyner, M. Vekemans, and J. Mallet. "Nucleus basalis magnocellularis and hippocampus are the major sites of *FMR-1* expression in the human fetal brain." *Nature Genetics* 4 (June 1993): 147-153.
- Adami, John George. "A Study in Eugenics: Unto the Third Generation." *Lancet* 180 no. 4653 (2 November 1912): 1199-1204.
- Addie, W. J. and J. G. Greenfield. "Dystrophia Myotonica (Myotonia Atrophica)." *Brain* 46 no. 1 (1923): 73-127.
- Aicardi, J., D. Conti, and F. Goutières. "Les formes néo-natales de la dystrophie myotonique de Steinert." *Journal of the Neurological Sciences* 22 (1974): 149-164.
- Allen, Robert M., Arnold D. Cortazzo, and Richard P. Toister. eds. *The Role of Genetics in Mental Retardation*. Coral Gables, Florida: University of Miami Press, 1971.
- Anonymous. "Anticipating myotonic dystrophy." *Lancet* 339 no. 8802 (9 May 1992): 1124.
- Anonymous. "Bibliography of Human Genetics." *American Journal of Human Genetics* Vol. 1 no. 1 (September 1949): 105-112.
- Anonymous. "Eugenic Sterilisation in the United States." *Nature* 132 (August 12, 1933): 234.
- Anonymous. "Eugenics and Marriage Laws." *Nature* 131 (April 15, 1933): 540.
- Anonymous. "Eugenics and Society." *Nature* 137 (April 11, 1936): 593.
- Anonymous. "Frederick Mott, K.B.E., M.D., F.R.C.P. Lond., LL.D. Edin., F.R.S.," *Lancet* 207 no. 5364 (19 June 1926): 1228-1230.

- Anonymous. "General Discussion." *British Medical Journal* 2 (31 October 1925), 784-788.
- Anonymous. "Genetics and Race." *Nature* 138 (December 12, 1936): 988-989.
- Anonymous. "Huntington's Chorea." *Nature* 137 (January 11, 1936): 73.
- Anonymous. "Medical Societies: Royal Society of Medicine." *Lancet* 181 no. 4667 (8 February 1913): 387-389.
- Anonymous. "Medicine and Eugenics." *Nature* 141 (February 26, 1938): 382.
- Anonymous. "Medicine and Eugenics." *Nature* 142 (July 9, 1938): 68.
- Anonymous. "Mental Deficiency." *Nature* 129 (February 20, 1932): 287-288.
- Anonymous. "Notes of the Quarter." *Eugenics Review* 22 (1931): 235-238.
- Anonymous. "Notes of the Quarter." *Eugenics Review* 38 no. 3 (October 1946): 111-117.
- Anonymous. "Notes of the Quarter." *Eugenics Review* 38 no. 4 (January 1947): 163-167.
- Anonymous. "Notes of the Quarter." *Eugenics Review* 40 no. 1 (April 1948): 4-11.
- Anonymous. "Notes of the Quarter." *Eugenics Review* 40 no. 2 (July 1948): 55-61.
- Anonymous. "Notes of the Quarter." *Eugenics Review* 42 no. 2 (July 1950): 69-74.
- Anonymous. "Obituary: A. F. Tredgold, M.D., F.R.C.P." *British Medical Journal* 2 (27 September 1952): 726-727.
- Anonymous. "Problems of Human Nutrition." *Nature* 135 (March 2, 1935): 321-322.
- Anonymous. *Semi-Centennial of The Biological Laboratory*. Cold Spring Harbour, New York: Long Island Biological Association, 1940.
- Anonymous. "Sir Frederick Mott." *Lancet* 207 no 5363 (12 June 1926): 1156.
- Anonymous. "Social Selection of Human Fertility." *Nature* 129 (June 18, 1932): 896-897.
- Anonymous. "Societies and Academies." *Nature* 129 (June 18, 1932): 914.

- Anonymous. "State Policies of Eugenic Sterilization." *Nature* 132 (August 12, 1933): 221-222.
- Anonymous. "The Eugenic Problem in Great Britain." *Nature* 132 (October 7, 1933): 540.
- Anonymous. "The Seventh International Congress of Genetics." *Nature* 144 (November 11, 1939): 813.
- Anonymous. "The Society's Further Projects." *Eugenics Review* 14 (1932): 12-13.
- Anonymous. "The Value of Heredity." *Lancet* 176 no. 4531 (July 2, 1910): 38-39.
- Ashby, Eric, F. A. E. Crew, C. D. Darlington, E. B. Ford, J. B. S. Haldane, E. J. Salisbury, W. B. Turrill, and C. H. Waddington. "Genetics in the Universities." *Nature* 138 (December 5, 1936): 972-973.
- Ashizawa, T., M. Anvret, M. Baiget, J. M. Barceló, H. Brunner, A. M. Cobo, B. Dallapiccola, R. G. Fenwick, W. Grandell, H. Harley, C. Junien, M. C. Koch, R. G. Korneluk, C. Lavedan, T. Miki, J. C. Mulley, A. L. de Munian, G. Novelli, A. D. Roses, W. K. Seltzer, D. J. Shaw, H. Smeets, G. R. Sutherland, H. Yamagata, and P. S. Harper. "Characteristics of Intergenerational Contractions of the CTG Repeat in Myotonic Dystrophy." *American Journal of Human Genetics* 54 (1994): 414-423.
- Ashley, C. T., J. S. Sutcliffe, C. B. Kunst, H. A. Leiner, E. E. Eichler, D. L. Nelson, and S. T. Warren. "Human and murine *FMR-1*: alternative splicing and translational initiation downstream of the CGG-repeat." *Nature Genetics* 4 (July 1993): 244-251.
- Ashley, C. T., K. D. Wilkinson, D. Reines, and S. T. Warren. "*FMR 1* protein: conserved RNP family domains and selective RNA binding." *Science* 262 (22 October 1993): 563-568.
- Aslanidis, C., G. Jansen, C. Amemiya, G. Shutler, M. Mahadevan, C. Tsilfidis, C. Chen, J. Alleman, N. G. M. Wormskamp, M. Vooijs, J. Buxton, K. Johnson, H. J. M. Smeets, G. G. Lennon, A. V. Carrano, R. G. Korneluk, B. Wieringa, and P. de Jong. "Cloning of the essential myotonic dystrophy region and mapping of the putative defect." *Nature* 355 (6 February 1992): 548-551.
- Avery, O. T., C. M. Macleod and M. McCarty. "Studies on the Chemical Transformation of Pneumococcal Types." *Journal of Experimental Medicine* 79 (1944): 137-158.

- Bächner, D., A. Manca, P. Steinbach, D. Wöhrle, W. Just, W. Vogel, H Hameister, A. Poustka. "Enhanced expression of the murine FMR1 gene during germ cell poliferation suggests a special function in both the male and female gonad." *Human Molecular Genetics* 2 (1993): 2043-2050.
- Bakker, Cathy E., Coleta Verheij, Rob Willemsen, Robert van der Helm, Frank Oerlemans, Marcel Vermey, Anne Bygrave, André T. Hoogeveen, Ben A. Oostra, Erwin Ryniers, Kristel De Boule, Rudi D'Hooge, Patrick Cras, Désiré van Velzen, Guy Nagels, Jean-Jacques Martin, Peter P. De Deyn, John K. Darby, Patrick J. Willems. "*Fmr1* knockout mice: A model to study fragile X mental retardation." *Cell* 78 no. 1 (15 July 1994): 23-33.
- Baraister, Michael and Robin M. Winter. *A Colour Atlas of Clinical Genetics*, London: Wolfe Medical Publications Ltd., 1983.
- Barbeau, André. "Parental ascent in the juvenile form of Huntington's chorea." *Lancet* 296 no. 7679 (31 October 1970): 937.
- Batten, F. E. and H. P. Gibb. "Myotonia atrophica." *Brain* 32 no. 2 (1909): 187-205.
- Baur, Erwin, Eugen Fisher, and Fritz Lenz. *Grundriß der menschlichen Erblichkeitslehre und Rassenhygiene. Band 1, Menschliche Erblehre*. Munich: J. F. Lehmanns Verlag, 1923.
- Baur, Erwin, Eugen Fisher, and Fritz Lenz. *Grundriß der menschlichen Erblichkeitslehre und Rassenhygiene. Band 2, Menschliche Auslese und Rassenhygiene*. Munich: J. F. Lehmanns Verlag, 1923.
- Baur, Erwin, Eugen Fisher, and Fritz Lenz. *Human Heredity*. Translated by Eden Paul and Cedar Paul. London: George Allen & Unwin Ltd., 1931.
- Baur, Erwin, Eugen Fisher, and Fritz Lenz. *Menschliche Erblerhre und Rassenhygiene. Band 1, Menschliche Erblehre*. Munich: J. F. Lehmanns Verlag, 1936.
- Bell, D. B. and D. W. Smith. "Myotonic dystrophy in the neonate." *Journal of Pediatrics* 81 (1972): 83-86.
- Bell, Julia. "On the age of onset and the age of death in hereditary muscular dystrophy with some observations bearing on the question of antedating." *Annals of Eugenics* 10 (1940): 272-289.
- Bell, Julia. "The Age of Onset in Hereditary Optic Atrophy." *Annals of Eugenics* 3 (1928): 269-276.

- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye. Nettleship Memorial Volume, Part 1: Retinitis Pigmentosa and Allied Diseases Congenital Stationary Night-Blindness Glioma Retinae*, with a memoir of Edward Nettleship by J. B. Lawford, ed., Karl Pearson, Cambridge: Cambridge University Press, 1922.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye. Nettleship Memorial Volume, Part 2: Colour-Blindness*, ed., Karl Pearson, Cambridge: Cambridge University Press, 1926
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye. Nettleship Memorial Volume, Part 3: Blue Sclerotics and Fragility of Bone*, ed., Karl Pearson, Cambridge: Cambridge University Press, 1928.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye, Part 4: Hereditary Optic Atrophy (Leber's disease)*, ed., Karl Pearson. Cambridge: Cambridge University Press, 1931.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 2, *Anomalies and Diseases of the Eye. Nettleship Memorial Volume, Part 5: On Some Hereditary Structural Anomalies of the Eye and on the Inheritance of Glaucoma*, ed., Karl Pearson, Cambridge: Cambridge University Press, 1932.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Disorders, Part 1: Huntington's Chorea*, ed. R. A. Fisher. Cambridge: Cambridge University Press, 1934.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Disorders, Part 2: On the Peroneal Type of Progressive Muscular Atrophy*, ed., R. A. Fisher. Cambridge: Cambridge University Press, 1935.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 3: On Hereditary Ataxia and Spastic Paraplegia*, assisted by E. Arnold Carmichael, ed., R. A. Fisher. Cambridge: Cambridge University Press, 1939.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 4: On Pseudohypertrophic and Allied Types of Progressive Muscular Dystrophy*, ed., R. A. Fisher. Cambridge: Cambridge University Press, 1943.
- Bell, Julia. *The Treasury of Human Inheritance*. Vol. 4, *Nervous Diseases and Muscular Dystrophies, Part 5: Dystrophia Myotonica and Allied Diseases*, with clinical notes by J. Purdon Martin, ed., L. S. Penrose. Cambridge: Cambridge University Press, 1947.

- Bell, M. V., M. C. Hirst, Y. Nakahori, R. N. MacKinnon, A. Roche, T. J. Flint, P. A. Jacobs, N. Tommerup, L. Tranebjaerg, U. Froster-Iskenius, B. Kerr, G. Turner, R. H. Lindenbaum, R. Winter, M. Pembrey, S. Thibodeau, and K. E. Davies. "Physical Mapping across the Fragile X: Hypermethylation and Clinical Expression of the Fragile X Syndrome." *Cell* 64 (February 22, 1991): 861-866.
- Bennett, J. H. ed. *Natural Selection, Heredity, and Eugenics: Including selected correspondence of R.A. Fisher with Leonard Darwin and others*. Oxford: Clarendon Press, 1983.
- Bickford, J. A. R. and R. M. Ellison. "The high incidence of Huntington's chorea in the duchy of Cornwall." *Journal of Mental Science* 99 (1953): 291-294.
- Binney, Cecil. "Eugenic Aspects of the English Criminal Law." *Eugenics Review* 37 no. 3 (October 1945): 105-115.
- Bird, Adrian P. "CpG-rich islands and the function of DNA methylation" *Nature* 321 (15 May 1986): 209-213.
- Bird, E. D., A. J. Caro, and J. B. Pilling, "A sex related factor in the inheritance of Huntington's chorea." *Annals of Human Genetics* 37 (1974): 255-260.
- Blacker, C. P. *A Social Problem Group?* London: Oxford University Press, 1937.
- Blacker, C. P. *Eugenics in Retrospect and Prospect: The Galton Lecture, 1945*. 2d ed. London: The Eugenics Society and Cassell and Company Ltd., 1950.
- Blacker, C. P. "Food, Health and Income." *Eugenics Review* 28 no. 3 (1936): 228-229.
- Blacker, C. P. "Mental Defect." *Eugenics Review* 25 (1933): 267-269.
- Blacker, C. P. "Notes of the Quarter." *Eugenics Review* 38 no. 3 (October 1946): 115-117.
- Blacker, C. P. "Positive Eugenics: A Proposal." *Eugenics Review* 38 no. 1 (April 1946): 25-26.
- Blacker, C. P. "The Press and Eugenics: A Review of Reviews." *Eugenics Review* 26 (1934): 207-212.
- Blacker, C. P. "The Sterilization Proposals: A History of their Developments." *Eugenics Review* 22 no. 4 (January 1931): 239-247.
- Bodmer, W. R. and L. L. Cavilli-Sforza. *Genetics, Evolution, and Man*. San Francisco: W. H. Freeman and Company, 1976.

- Boehnke, M., P. M. Colleally, and K. Lange. "Two models for a maternal factor in the inheritance of Huntington's Disease." *American Journal of Human Genetics* 35 (1983): 845-860.
- Brackenridge, C. J. "A genetic and statistical study of some sex-related factors in Huntington's disease." *Clinical Genetics* 2 no. 5 (September 1971): 267-286.
- Brackenridge, C. J. "The relation of type of initial symptoms and line of transmission to ages at onset and death in Huntington's disease." *Clinical Genetics* 2 no. 5 (1971): 287-297.
- Brewster, Barry., Patricia Groenen and Bé Wieringa. "Myotonic Dystrophy: Clinical and Molecular Aspects." In *Neuromuscular Disorders: Clinical and Molecular Genetics*. Alan E. H. Emery Ed. Chichester: John Wiley and Sons, 1998, 323-364.
- Bristowe, John Syer. *A Treatise on the Theory and Practice of Medicine*. 7th ed. London: Smith, Elder, 1890.
- Brook, David J., Mila E. McCurrach, Helen G. Harley, Alan J. Buckler, Deanna Church, Hiroyuki Aburatani, Kent Hunter, Vincent P. Stanton, Jean-Paul Thirion, Thomas Hudson, Robert Sohn, Boris Zemelman, Russell G. Snell, Shelley A. Flundle, Steve Crow, June Davies, Peggy Shelbourne, Jessica Buxton, Clare Jones, Vesa Juvonen, Keith Johnson, Peter S. Harper, Duncan J. Shaw, and David E. Housman. "Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member." *Cell* 68 (February 21, 1992): 799-808.
- Brown, Sanger. "On Hereditary Ataxy, with a Series of Twenty-One Cases." *Brain* 15 no. 2 (1892): 250-268.
- Brown, Sanger. "The Morbid Anatomy of a Case of Hereditary Ataxy." *Brain* 20 (1897): 276-289.
- Brunner, Han G., B. C. J. Hamel, P. Rieu, C. J. Höweler, and F. T. M. Peters. "Intestinal pseudo-obstruction in myotonic dystrophy." *Journal of Medical Genetics* 29 (1992): 791-793.
- Brunner, H. G., G. J. Jansen, W. Nillesen, M. R. Nelen, C. E. M. de Die, C. J. Höweler, B. A. van Oost, B. Wieringa, H. Ropers, and H. J. M. Smeets. "Brief Report: Reverse Mutation in Myotonic Dystrophy." *New England Journal of Medicine* 328 (18 February 1993): 476-480.
- Brunner, H. G., W. Nillesen, B. A. van Oost, G. Jansen, B. Wieringa, H. Ropers, and H. J. M. Smeets. "Presymptomatic diagnosis of myotonic dystrophy." *Journal of Medical Genetics* 29 (1992): 780-784.

- Bruyn, G. W. "Huntington's Chorea—Historical, Clinical and Laboratory Synopsis." In *Handbook of Clinical Neurology*. Vol. 6. Eds., P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland Publishing Company, 1968, 298-378.
- Budney, Sarah and C. O. Carter. "Early recognition of heterozygotes for the gene for dystrophia myotonica." *Journal of Neurology, Neurosurgery, and Psychiatry* 33 no. 3 (1970): 279-293.
- Budney, Sarah and C. O. Carter. "Genetic heterogeneity for dystrophia myotonica." *Journal of Medical Genetics* 9 (1972): 311-315.
- Burke, J. R., M. S. Wingfield, K. E. Lewis, A. D. Roses, J. E. Lee, C. Hulette, M. A. Pericak-Vance, and J. M. Vance. "The Haw River Syndrome: Dentatorubropallidoluysian atrophy (DRPLA) in an African-American family." *Nature Genetics* 7 (August 1994): 521-524.
- Busch, H. F. M. and C. J. Höweler, "Dystrophia Myotonica." *Early diagnosis and prevention of genetic diseases*. L. N. Went, C. Vermeij-Keers and A. G. J. M. van der Linden Eds. Leiden: Leiden University Press, 1975, 26-32.
- Buxton, J., P. Shelbourne, J. Davies, C. Jones, T. Tongeren, C. Aslanidis, P. de Jong, G. Jansen, M. Anvret, B. Riley, R. Williamson and K. Johnson. "Detection of an unstable fragment of DNA specific to individuals with myotonic dystrophy." *Nature* 355 (6 February 1992): 547-548.
- Buyle, S., E. Reyniers, L. Vits, K. De Boule, I. Handig, F. L. E. Wuyts, W. Deelen, D. J. Halley, B. A. Oostra, and P. J. Willems. "Founder effect in a Belgian-Dutch fragile X population." *Human Genetics* 92 (1993): 269-272.
- Byers, Randolph K. and John A. Dodge. "Huntington's chorea in children: Report of four cases." *Neurology* 17 no. 6 (1 June 1967): 587-596.
- Calderon, R. "Myotonic dystrophy: a neglected cause of mental retardation." *Journal of Pediatrics* 68 (1966): 423-431.
- Campbell, A. M. G., Beryl Corner, R. M. Norman, and H. Urich. "The Rigid Form of Huntington's Disease." *Journal of Neurology Neurosurgery and Psychiatry* 24 (1961): 71-77.
- Cannon, Gertrude L. and A. J. Rosanoff. "Preliminary Report of a Study of Heredity in Insanity in the Light of the Mendelian Laws." *Eugenics Record Office Bulletin* 3 (1911): 1-11.

- Carey, N., K. Johnson, P. Nokelainen, L. Peltonen, M. Sacontaus, V. Juvonen, M. Anvret, U. Grandell, K. Chotai, E. Robertson, H. Middleton-Price, and S. Malcom. "Meiotic drive at the myotonic dystrophy locus?" *Nature Genetics* (February 1994): 117-118.
- Carter, C. O. *An ABC of Medical Genetics*. Reprinted from "The Lancet", May 17 to June 28 1969, with two additional chapters. London: The Lancet Ltd., 1969.
- Caspersson, T. and Jack Schultz. "Nucleic Acid Metabolism of the Chromosomes in Relation to Gene Reproduction." *Nature* 142 (August 13, 1938): 294-295.
- Cattenach, B. M. and M. Kirk. "Differential activity of maternally and paternally derived chromosome regions in mice." *Nature* 315 (1985): 496-498.
- Caughey, J. E. "Cataract in dystrophia myotonica." *Transactions of the Ophthalmological Society of the United Kingdom* 53 (1933): 60-72.
- Caughey, J. E. "Congenital Mental and Physical Defects in Dystrophia Myotoica." in J. E. Caughey and N. C. Myriantopoulos. *Dystrophia Myotonica and Related Disorders*. Springfield IL: Charles C. Thomas Publisher, 1963. 124-137.
- Caughey, J. E. and J. Barclay. "Dystrophia myotonica and the occurrence of congenital physical defect in affected families." *Australasian Annals of Medicine* 3 no. 3 (August 1954): 165-170.
- Caughey, J. E. and N. C. Myriantopoulos. *Dystrophia Myotonica and Related Disorders*. Springfield IL: Charles C. Thomas Publisher, 1963.
- Caughey, J. E. and N. C. Myriantopoulos. *Dystrophia Myotonica and Related Disorders*. 2nd ed. Springfield IL: Charles C. Thomas Publisher, 1991.
- Chase, G. A., L. E. Markson, R. Brookmeyer, and S. E. Folstein. "Covariate-dependent genetic counseling in Huntington's disease." *Journal of Neurogenetics* 3 (1986): 215-223.
- Chesterton, G. K. *Eugenics and Other Evils*. London: Cassell and Company, Ltd., 1922.
- Chung, M., L. P. W. Ranum, L. A. Duvick, A. Servadio, H. Y. Zoghbi, and H. T. Orr. "Evidence for a mechanism predisposing to intergenerational CAG repeat instability in spinocerebellar ataxia type I." *Nature Genetics* 5 (November 1993): 254-258.
- Clark, David P. *Molecular Biology: Understanding the Genetic Revolution*. Amsterdam: Elsevier, 2005.

- Clarke, A. "Genetic imprinting in clinical genetics." In *Genomic Imprinting*. eds. M. Monk and A. Surani, Cambridge: Cambridge University Press, 1990. pp. 131-139.
- Clarke, Cyril A. *Genetics for the Clinician*. Oxford: Blackwell Scientific Publications, 1962.
- Clarke, Cyril A. *Genetics for the Clinician*. 2nd ed. Oxford: Blackwell Scientific Publications, 1964.
- Clarke, Cyril A. *Selected Topics in Medical Genetics: A Review from the Nuffield Unit of Medical Genetics, Liverpool University*. London: Oxford University Press, 1969.
- Clarke, Cyril A., D. A. Price Evans, R. Harris, R. B. McConnell, and J. C. Woodrow. "Genetics in Medicine: A Review." *Quarterly Journal of Medicine* 37 no. 145 (January 1968):1-61.
- Clouston, Thomas Smith. *Clinical Lectures on Mental Diseases*. London: J. & A. Churchill, 1883.
- Coghlan, A. "Vital research caught in patent crossfire." *New Scientist* 137 (23 January 1993): 4.
- Cohen, J. I. "Intelligence and Birth-Rate." *Nature* 143 (March 18, 1939): 484-485.
- Cole, Leon J. "Recent Eugenics Legislation in the United States." *Eugenics Review* 5 (1913): 354.
- Colin, Edward C. *Elements of Genetics: Mendel's Laws of Heredity with Special Application to Man*. 3rd ed. New York: McGraw-Hill Book Company, Inc., 1956.
- Concar, D. "Rush to patent human genes 'will hinder research'." *New Scientist* 133 (18 January 1992): 12.
- Conneally P. M. "Huntington's disease: genetics and epidemiology." *American Journal of Human Genetics* 36 (1984): 506-526.
- Cotton, Henry A. "Some Problems in the Study of Heredity in Mental Diseases." *Eugenics Record Office Bulletin* 8 (August 1912): 1-59.
- Crew, F. A. E. *Genetics in Relation to Clinical Medicine*. Edinburgh: Oliver and Boyd, 1947.
- Crick, F. H. C. "On Protein Synthesis." *The Symposia for the Society of Experimental Biology* 12 (1958): 138-163.

- Cummings, J. N. and O. Maas. "Blood Changes in Dystrophia Myotonica." *Brain* 62 (1939): 422-425
- Curschmann, Hans. "Eine neue Chorea-Huntington-Familie." *Deutsche Zeitschrift für Nervenheilkunde* 35 (1908): 293-305.
- Darwin, Charles. *The Descent of Man, and Selection in Relation to Sex*. 2 Vols. London: John Murray, 1871.
- Darwin, Charles. *The Descent of Man, and Selection in Relation to Sex*. 2nd ed. revised. New York: D. Appleton and Company, 1883.
- Darwin, Charles. *The Descent of Man and Selection in Relation to Sex*. 2nd ed. revised. New York: A. L. Fowle, 1888plus.
- Darwin, Charles. *The Descent of Man and Selection in Relation to Sex*. 2nd ed. revised. London: John Murray, 1890.
- Darwin, Charles. *The Origin of Species by Means of Natural Selection*. (1859) Edited with an introduction by J. W. Burrow. London: Penguin Books, 1985.
- Darwin, Charles. *The Variation of Animals and Plants Under Domestication*. 2 vols. New York: D. Appleton and Company, 1896.
- Davenport, Charles B. "A Discussion of the Methods and Results of Dr. Heron's Critique." *Eugenics Record Office Bulletin* 11 (1914): 3-24.
- Davenport, C. B. *Heredity in Relation to Eugenics*. London: Williams and Norgate, 1912.
- Davenport, C. B. *Heredity in Relation to Eugenics*. New York: Henry Holt and Company, 1913.
- Davenport, C. B. "Heredity of Constitutional Mental Disorders." *Eugenics Record Office Bulletin* 20 (1920): 300-310.
- Davenport, C. B. "Huntington's Chorea in Relation to Heredity and Eugenics." *Proceedings of the National Academy of Sciences of the United States of America* 1 no. 5 (15 May 1915): 283-285.
- Davenport, C. B. and Elizabeth B. Muncey. "Huntington's Chorea in Relation to Heredity and Eugenics." *American Journal of Insanity* 73 (1916): 195-222.
- Davenport, C. B. and Elizabeth B. Muncey. "Huntington's Chorea in Relation to Heredity and Eugenics." *Eugenics Record Office Bulletin* 17 (1916): 195-222.

- Davenport, C. B., H. H. Laughlin, D. F. Weeks, E. R. Johnstone, and H. H. Goddard. "The Study of Human Heredity: Methods of Collecting, Charting and Analyzing Data." *Eugenics Record Office Bulletin* 2 (1911): 1-17.
- Davies, J., H. Yamagata, P. Shelbourne, J. Buxton, T. Ogihara, P. Nokelainen, M. Nakagawa, R. Williamson, K. Johnson, and T. Miki. "Comparison of the myotonic dystrophy associated CTG repeat in European and Japanese populations." *Journal of Medical Genetics* 29 (1992) 766-769.
- Davies, Kay E. and Stephen T. Warren Eds. *Genome Rearrangement and Stability*. Cold Spring Harbour, NY: Cold Spring Harbour Laboratory Press, 1993.
- De Boulle, Kristel, Annemieke J.M.H. Verkerk, Edwin Reyniers, Lieve Vits, Jan Hendrickx, Bernadette Van Roy, Feikje Van Den Bos, Esther de Graaff, Ben A. Oostra and Patrick J. Willems. "A Point Mutation in the *FMR-1* gene associated with fragile X mental retardation." *Nature Genetics* 3 no. 1 (January 1993): 31-33.
- De Graaff, E., R. Willemsen, N. Zhong, C. E. M. de Die-Smulders, W. T. Brown, G. Freling, and B. Oostra. "Instability of the CGG repeat and expression of the *FMR1* protein in a male fragile X patient with a lung tumor." *American Journal of Human Genetics* 57 (1995): 609-618.
- De Jong, Johannes Gerardus Ype. "Dystrophia Myotonica, Paramyotonia, and Myotonia Congenita." *Acta Genetica et Statistica Medica* 7 (1957): 310-314.
- De Jong, Johannes Gerardus Ype. *Dystrophia Myotonica Paramyotonia and Myotonia Congenita*. Translation by Sister M. Lidwina van Weers and Sister M. Luke Gray. Assen: Von Gorcum, 1956.
- De Vries, B. B. A., A. M. Wiegers, E. de Graaff, A. J. M. H. Verkerk, J. O. Van Hemel, D. J. J. Halley, P. Fryns, L. M. G. Curfs, M. F. Niermeier, B. A. Oostra. "Mental status and fragile X expression in relation to FMR-1 gene mutation." *European Journal of Human Genetics* 1 (1993): 72-79.
- Delmas-Marsalet, P., M. Bourgeois, Cl. Vital, and X. Fontages. "Formes rigide de la maladie de Huntington (etude d'une famille avec un cas anatomo-clinique)." *Revue Neurologique* 118 (1968): 273-383.
- Demerec, M. *Annual Report of the Biological Laboratory: Fifty-Second Year*. Cold Spring Harbor, New York: Long Island Biological Association, 1941.
- Devys, D., Y. Lutz, N. Rouyer, J. Bellocq, and J. Mandel. "The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutations." *Nature Genetics* 4 (August 1993): 335-340.

- Die-Smulders, C. E. M., C. J. Höweler, J. F. Mirandolle, H. G. Brunner, V. Hovers, H. Brüggewirth, H. J. M. Smeets, and J. P. M. Geraedts. "Anticipation resulting in elimination of the myotonic dystrophy gene: a follow up study of one extended family." *Journal of Medical Genetics* 31 (1994): 595-601.
- Dodge, P. R., I. Gamstorp, R. K. Byers, and P. Russell. "Myotonic dystrophy in infancy and childhood." *Pediatrics* 35 (1966): 3-19.
- Donachie, Jacqueline. and Darren G. Monckton. *Tomorrow Belongs to Me*. Glasgow: University of Glasgow, 2006.
- Drew, H. T. B. "Cultivation of the Unfit." *Nature* 137 (February 15, 1936): 276.
- Dunlop, B. "Cultivation of the Unfit." *Nature* 137 (February 1, 1936): 188.
- Dutch-Belgian Fragile X Consortium. "*Fmr1* Knockout Mice: A Model to Study Fragile X Mental Retardation." *Cell* 78 (July 15 1994): 23-33.
- Dyken, Paul R. "The changing syndromes of dystrophia myotonica." *Neurology* 19 no. 3 (March 1969): 292.
- Dyken, Paul R. and Peter S. Harper. "Congenital dystrophia myotonica." *Neurology* 23 no. 5 (May 1973): 465-473.
- Editor. "Editorial Notes." *Eugenics Review* 2 (1910): 1-2.
- Editor. "Notes of the Quarter." *Eugenics Review* 22 (1931): 235-238.
- Eichler, Evan E., Stephen Richards, Richard A. Gibbs, and David L. Nelson. "Fine Structure of the Human FMR1 Gene." *Human Molecular Genetics* 2 no. 8 (1993): 1147-1153.
- Eichler, Evan E., Jeanette J. A. Holdon, Bradley W. Popovich, Allan L. Reiss, Karen Snow, Stephen N. Thibideau, C. Sue Richards, Patricia A. Ward, and David L. Nelson. "Length of uninterrupted CGG repeats determines instability in the *FMR1* gene." *Nature Genetics* 8 (September 1994): 88-94.
- Emery, Alan E. H. *Elements of Medical Genetics*, 5th ed. Edinburgh: Churchill Livingstone, 1979.
- Emery, Alan E. H. *Elements of Medical Genetics*, 6th ed. Edinburgh: Churchill Livingstone, 1983.
- Emery, Alan E. H. *Heredity, Disease, and Man: Genetics in Medicine*. Berkeley CA: University of California Press, 1968.

- Emery, Alan E. H. *Modern Trends in Human Genetics 1*. London: Butterworths, 1970.
- Emery, Alan E. H. "Molecular Genetics of Neuromuscular Disorders: Applications in Clinical Medicine." In *Neuromuscular Disorders: Clinical and Molecular Genetics*. Alan E. H. Emery Ed. Chichester: John Wiley and Sons, 1998, 1-20.
- Emery, Alan E. H. Ed. *Neuromuscular Disorders: Clinical and Molecular Genetics*. Chichester: John Wiley and Sons, 1998.
- Emery, Alan E. H. and Robert F. Mueller. *Elements of Medical Genetics*. 7th ed. Edinburgh: Churchill Livingstone, 1988.
- Emery, Alan E. H. and Robert F. Mueller. *Elements of Medical Genetics*. 8th ed. Edinburgh: Churchill Livingstone, 1992.
- Emery, Alan E. H. and D. L. Rimoin eds. *Principles and Practice of Medical Genetics*. Vol. 1 Edinburgh: Churchill Livingstone, 1983.
- Emery, Alan E. H. and D. L. Rimoin eds. *Principles and Practice of Medical Genetics*. 2nd ed.. Vol. 1 Edinburgh: Churchill Livingstone, 1990.
- Entres, J. L. *Zur Klinik und Vererbung der Huntingtonschen Chorea. Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie*. Heft 37. Berlin: Springer Verlag, 1921.
- Erikson, R. P. "Chromosomal imprinting and the parent transmission specific variation in Huntington's Disease." *American Journal of Human Genetics* 37 (1985): 827-829.
- Farrer, L. A. and P. M. Conneally. "A genetic model for age at onset in Huntington's disease." *American Journal of Human Genetics* 37 (1985): 350-357.
- Farrer, L. A., and P. M. Conneally. "Predictability of phenotype in Huntington's disease." *Archives of Neurology* 44 (1987): 109-113.
- Farrer, L. A., P. M. Conneally, and P. I. Yu. "The natural history of Huntington's disease: Possible roles of 'aging genes.'" *American Journal of Medical Genetics* 18 (1984): 115-123.
- Feng, Y., R. Zhang, L. K. Lokey, J. L. Chastain, L. Lakkis, D. Eberhart, S. T. Warren. "Translation suppression by trinucleotide repeat expansion at *FMRI*." *Science* 268 (5 May 1995): 731-734.
- Fisher, R. A. "The Correlation between Relatives on the Supposition of Mendelian Inheritance." *Transactions of the Royal Society of Edinburgh* 52 (1918): 399-433.

- Fisher, R. A. "The Effect of Methods of Ascertainment Upon the Estimation of Frequencies." *Annals of Eugenics* 6 (1934): 13-25.
- Fisher, R. A. "The Elimination of Mental Defect." *Eugenics Review* 16 (1924): 114-116.
- Fleischer, Bruno. "Über Myotonia atrophicans und Kataract Bericht." *Versammlung der Heidelberger Ophthalmologisten Gesellschaft* 40 (1916): 441-447
- Fleischer, Bruno. "Über myotonische Dystrophie mit Katarakt: Eine hereditäre, familiäre Degeneration." *Albrecht Von Graefe's Archiv für Ophthalmologie* 96 (1918): 91-133.
- Fleischer, Bruno. "Untersuchung von sechs Generationen eines Geschlechtes auf das Vorkommen von myotonischer Dystrophie und anderer degenerativer Merkmale." *Archiv für Rassen und Gesellschafts Biologie* 14 (1922): 13-39.
- Fleischer, Bruno. "Zur Verebung nervöser Degenerationen." *Zeitschrift für die gesamte Neurologie und Psychiatrie* 84 (1923): 418-425.
- Fleischer, Bruno and W. Josenhans, "Ein Beitrag zur Frage der familiären Sehnervenatrophie (Leberscher Krankheit)." *Archiv für Rassen und Gesellschafts Biologie* 13 (1920): 129-163.
- Folstein, Susan E. *Huntington's Disease: A Disorder of Families*. Baltimore: The Johns Hopkins University Press, 1989.
- Folstein, Susan E., G. A. Chase, W. E. Wahl, A. M. McDonnell, and M. F. Folstein. "Huntington's disease in Maryland: Clinical aspects of racial variation." *American Journal of Human Genetics* 41 (1987): 168-179.
- Fondon III, John W. and Harold R. Garner. "Detection of length-dependant effects of tandem repeat alleles by 3-D geometric decomposition of craniofacial variation." *Development Genes and Evolution* 217 no. 1 (January 2007): 79-85.
- Fondon III, John W. and Harold R. Garner. "Molecular origins of rapid and continuous morphological evolution." *PNAS* 101 no. 52 (28 December 2004): 18058-18063.
- Ford, E. B. *Genetics for Medical Students*. London: Methuen & Co. Ltd., 1942.
- Foster, Nellis B. "Consanguineal Diabetes Mellitus." *Bulletin of the Johns Hopkins Hospital* 23 no. 252 (1912): 54-55.
- Franceschetti, Adolphe. "Die Vererbung von Augenleiden." In *Kurzes Handbuch der Ophthalmologie*, ed. P. Eislser, A. Franceschetti, R. A. Pfeifer, R. Seefelder, Berlin: Verlag von Julius Springer, 1930, 631-674.

- Franceschetti, Adolphe, and David Klein. "Über einen Stammbaum von myotonischer Dystrophie mit Anteponition und Potenzierung." *Archiv der Julius Klaus-Stiftung für Vererbungsforschung Sozialanthropologie und Rassenhygiene* 21 (1946): 315-322.
- Franceschetti, Adolphe., David Klein, and K. M. Walthard. "Klinisch-genealogische Untersuchungen über drei Fälle von Myotonia congenital (Thomsen) und acht neue Fälle von Dystrophia myotonica (Steinert-Batten) unter besonder Berücksichtigung der Diddifferentialdiagnose der beiden Krankheitsformen." *Schweizer Archiv für Neurologie und Psychiatrie* 60 (1947): 48-79.
- Franceschetti, Adolphe, David Klein, and K. M. Walthard. "Klinisch-genealogische Untersuchungen über drei Fälle von Myotonia congenital (Thomsen) und acht neue Fälle von Dystrophia myotonica (Steinert-Batten) unter besonder Berücksichtigung der Diddifferentialdiagnose der beiden Krankheitsformen." *Schweizer Archiv für Neurologie und Psychiatrie* 61 (1948): 152-207.
- Fraser, G. R. and O. Mayo, eds. *Textbook of Human Genetics*. Oxford: Blackwell Scientific Publications, 1975.
- Frey, Hans C. "Beitrag zur myotonischen Dystrophie." *Archiv für Rassen und Gesellschafts Biologie* 17 (1925): 1-46.
- Froster-Iskenius, Ursula., Annegret Schulze, and E. Schwinger. "Transmission of the marker X syndrome trait by unaffected males: conclusions from studies of large families." *Human Genetics* 67 no. 4 (September 1984): 419-427.
- Fu, Y., A. Pizzuti, R. G. Fenwick, J. King, S. Rajnarayan, P. W. Dunne, J. Dubel, G. A. Nasser, T. Ashizawa, P. de Jong, B. Wieringa, R. Korneluk, M. B. Perryman, H. F. Eptsein, and C. T. Caskey. "An Unstable Triplet Repeat in a Gene Related to Myotonic Muscular Dystrophy." *Science* 255 (6 March 1992): 1256-1258.
- Fu, Y., D. P. A. Kuhl, A. Piazzuti, M. Pieretti, J. Sutcliffe, S. Richards, A. Verkerk, J. J. A. Holden, R. G. Fenwick, S. T. Warren, B. A. Oostra, D. L. Nelson, and C. T. Caskey. "Variation of the CGG repeat at the Fragile X Site Results in Genetic Instability: Resolution of the Sherman Paradox." *Cell* 67 no. 6 (20 December 1991): 1047-1058.
- Galezowski, Xavier. "De l'étiologie de la cataract." *Recueil d'Ophthalmologie* 4 (1882): 730-731.
- Galton, Francis. "Hereditary Talent and Character." *Macmillan's Magazine* 12 no. 68 (1865): 157-166, 318-327.
- Galton, Francis. *Hereditary Genius: An Inquiry into its Laws and Consequences*. 2nd ed. reprinted. London: Macmillan and Co., Ltd., 1914.

- Garver, K. and S. Marchese, *Genetic Counseling For Clinicians*, Chicago: Year Book Medical Publishers, Inc., 1986, 103.
- Garrod, Archibald E. *The Inborn Factors in Disease: An Essay*. Oxford: Clarendon Press, 1931.
- Gates, Reginald Ruggles. "Human Genetics." *Nature* 144 (November 11, 1939): 821-822.
- Gates, Reginald Ruggles. *Human Genetics*. Vols. 1 and 2. New York: The Macmillan Company, 1946.
- Gates, Reginald Ruggles. "Mendelian Inheritance of Mental Deficiency." *Eugenics Review* 25 (1933): 207.
- Gaule, Alice. "Das Auftreten der Chorea Huntington in einer Familie der Nordostschweiz." *Schweizer Archiv für Neurologie und Psychiatrie* 29 (1932): 90-112.
- Gedda, L., D. Casa, and G. Brenci. "Chronon and the Problem of Anticipation (On two family cases of diabetes)." *Acta Geneticae Medicae et Gemellologiae* 16 no. 3 (July 1967): 217-228.
- Gedda, L., D. Casa, and G. Brenci. "Sulla Genetica del Diabete: Analisi di nove casi famigliari." *Acta Geneticae Medicae et Gemellologiae* 19 no. 3 (July 1970): 385-398.
- Gedeon, A. K., E. Baker, H. Robinson, M. W. Partington, B. Gross, A. Manca, B. Korn, A. Poustka, S. Yu, G. R. Sutherland and J. C. Mulley. "Fragile X syndrome without CCG amplification has an *FMRI* deletion." *Nature Genetics* 1 (August 1992) 341-344.
- Gelernter, Joel. "Genetics of Bipolar Affective Disorder: Time for Another Reinvention?" *American Journal of Human Genetics* 56 (1995): 1262-1266.
- Gibson, Robert. "Dystrophia Myotonica in Association with Mental Defect." *Canadian Medical Association Journal* 84 no. 22 (3 June 1961): 1234-1237.
- Goddard, Henry H. "Heredity of Feeble-Mindedness." *American Breeders Magazine* 1 no. 3 (1910): 165-178.
- Goddard, Henry H. "Heredity of Feeble-Mindedness." *Eugenics Record Office Bulletin* 1 (1911): 1-14.

- Goddard, Henry H. "Heredity of Feeble-Mindedness." *Eugenics Review* 3 (1911): 46-60.
- Goldschmidt, Richard. *In and Out of the Ivory Tower: The Autobiography of Richard B. Goldschmidt*. Seattle: University of Washington Press, 1960.
- Goldschmidt, Richard. *Physiological Genetics*. New York: McGraw-Hill Book Company, 1938.
- Goldschmidt, Richard. "'Progressive Heredity' and 'Anticipation': The Possibility of a Genetic Explanation of Certain Odd Hereditary Phenomena Observed in Man." *Journal of Heredity* 29 (1938): 140-142.
- Goldschmidt, Richard. "The Gene." *The Quarterly Review of Biology* 3 no. 3 (September 1928): 307-324.
- Goldschmidt, Richard. *The Material Basis of Evolution*. New Haven, CT: Yale University Press, 1940. Reprinted. New Jersey: Pageant Books, Inc., 1960.
- Goldschmidt, Richard. *Theoretical Genetics*. Berkeley: University of California Press, 1955. Second Printing 1958.
- Goldschmidt, Richard. *Understanding Heredity: An Introduction to Genetics*. New York: John Wiley & Sons, 1952.
- Goodman, Richard M. Ed., *Genetic Disorders of Man*. Boston: Little, Brown and Company, 1970.
- Gosney, E. A. and Paul Popenoe. *Sterilization for Human Betterment: A Summary of Results of 6,000 Operations in California, 1909-1929*. New York: The Macmillan Company, 1929.
- Greenfield, J. Godwin. "Notes on a Family of 'Myotonia Atrophica' and Early Cataract, with a Report of an Additional Case of 'Myotonia Atrophica.'" *Review of Neurology and Psychiatry* 9 (1911): 169-181.
- Greenwood Jr., M. "Heron, David, D.Sc. *Mendelism and the Problem of Mental Defect. Questions of the Day and of the Fray*. No. vii. London. Dulau and Co.; 1913." *Eugenics Review* 5 (1913): 367.
- Hagerman, Randi Jenssen and Amy C. Silverman. *Fragile X Syndrome: Diagnosis, Treatment and Research*. Baltimore: Johns Hopkins University Press, 1991.

- Hagerman, Randi J., C. E. Hull, J. F. Safanda, I. Carpenter, L. W. Staley, R. A. O'Connor, C. Seydel, M. M. M. Mazzocco, K. Snow, S. N. Thibodeau, D. Kuhl, D. L. Nelson, C. T. Caskey, and A. K. Taylor. "High Functioning Fragile X Males: Demonstration of an Unmethylated Fully Expanded FMR-1 Mutation Associated With Protein Expression." *American Journal of Medical Genetics* 51 (1994): 298-308.
- Haldane, J. B. S. *Heredity and Politics*. London: George Allen & Unwin Ltd., 1938.
- Haldane, J. B. S. "Mental Defect." *Nature* 141 (April 2, 1938): 575-576.
- Haldane, J. B. S. "Principles of Human Genetics." *Annals of Eugenics* 15 (1950): 282-283.
- Haldane, J. B. S. "The Hereditary Transmission of Acquired Characters." *Nature* 129 (June 11, 1932): 856-858.
- Haldane, J. B. S. "The Relative Importance of Principal and Modifying Genes in Determining Some Human Diseases." *Journal of Genetics* 41 (1941): 149-157.
- Hall, J. G. "How imprinting is relevant to human disease." In *Genomic Imprinting*. eds. M. Monk and A. Surani, Cambridge: Cambridge University Press, 1990. pp. 141-148.
- Hansen, Scott R., Stanley M. Gartler, C. Ronald Scott, Shi-Han Chen, and Charles D. Laird. "Methylation analysis of CGG sites in the CpG island of the human *FMR1* gene." *Human Molecular Genetics* 1 no. 8 (October 1992): 571-578.
- Hansen, R. S., T. K. Canfield, M. M. Lamb, A. M. Gartler, and C. D. Laird. "Association of Fragile X Syndrome with Delayed Replication of the *FMR1* Gene." *Cell* 73 (July 2 1993): 1403-1409.
- Hanzlik, A. J., M. M. Osemlak-Hanzlik, M. A. Hauser, and D. M. Kurnit. "A recombination-based assay demonstrates that the fragile X sequence is transcribed widely during development." *Nature Genetics* 3 (January 1993): 44-48.
- Harley, H. G., J. D. Brook, J. Floyd, S. A. Rundle, S. Crow, K. V. Walsh, M. Thibault, P. S. Harper, and D. J. Shaw. "Detection of Linkage Disequilibrium between the Myotonic Dystrophy Locus and a New Polymorphic DNA Marker." *American Journal of Human Genetics* 49 (1991): 68-75.
- Harley H. G., J. D. Brook, S. A. Rundle, S. Crow, W. Reardon, A. J. Buckler, P. S. Harper, D. E. Housman, and D. J. Shaw. "Expansion of an unstable DNA region in phenotypic variation in myotonic dystrophy." *Nature* 355 (6 February 1992): 545-546.

- Harley, H. G., S. A. Rundle, W. Reardon, J. Myring, S. Crow, J. D. Brook, P. S. Harper, D. J. Shaw. "Unstable DNA sequence in myotonic dystrophy." *Lancet* 339 no. 8802 (9 May 1992): 1125-1128.
- Harper, Peter S. "Congenital myotonic dystrophy in Britain. 1. Clinical aspects." *Archives of Disease in Childhood* 50 (1975): 505-513.
- Harper, Peter S. "Congenital myotonic dystrophy in Britain. 2. Genetic basis." *Archives of Disease in Childhood* 50 (1975): 514-521.
- Harper, Peter S. "Genetic Aspects of Huntington's Disease." In *Huntington's Disease*. Peter S. Harper ed. London: W. B. Saunders Company Ltd, 1991, 281-336.
- Harper, Peter S. ed., *Huntington's Disease*. London: W. B. Saunders, 1991.
- Harper, Peter S. ed., *Huntington's Disease*. 2nd ed. London: W. B. Saunders, 1996.
- Harper, Peter S. *Myotonic Dystrophy*. London: W. B. Saunders, 1979.
- Harper, Peter S. *Myotonic Dystrophy*. 2nd ed. London: W. B. Saunders, 1989.
- Harper, Peter S. "Myotonic dystrophy and related disorders." In *Principles and Practice of Medical Genetics*, Vol. 1, A. E. H. Emery and D. L. Rimoin eds., Edinburgh: Churchill Livingstone, 1983, 426-441.
- Harper, Peter S. "Myotonic dystrophy and related disorders." In *Principles and Practice of Medical Genetics*. Vol. 1, A. E. H. Emery, and D. L. Rimon eds. 2nd ed. Edinburgh: Churchill Livingstone, 1990, 579-597.
- Harper, Peter S. and Paul R. Dyken. "Early onset dystrophia myotonica—evidence supporting a maternal environmental factor." *Lancet* 300 no. 7767 (8 July 1972): 53-55.
- Harper, Peter S., Helen G. Harley, and D. J. Shaw. "Detection of minimum mutation carriers in myotonic dystrophy." *Lancet* 340 no. 8813 (July 25, 1992): 238-239.
- Harper, Peter S. Helen G. Harley, William Reardon, and Duncan J. Shaw. "Review Article: Anticipation in Myotonic Dystrophy: New Light on an Old Problem." *American Journal of Human Genetics* 51 (1992): 10-16.
- Hecht, Frederick. "Correspondence: Genetic Defect." *New England Journal of Medicine* 266 no. 1 (4 January 1962): 54.
- Heilbronner, E. "Über eine Art progressiver Heredität bei Huntingtonscher Chorea." *Archiv für Psychiatrie un Nervenkrankheiten* 36 (1903): 889-894.

- Heitz, D. and D. Devys, G. Imbert, C. Kretz, and J. Mandel. "Inheritance of the fragile X syndrome: size of the fragile X premutation is a major determinant of the transition to full mutation." *Journal of Medical Genetics* 29 (1992): 794-801.
- Henke, Karl and Siegfried Seeger. "Über die Vererbung der myotonischen Dystrophie. Genetischer Beitrag zum Problem der Degeneration." *Zeitschrift für Konstitutionslehre* 12 (1927): 371-415.
- Herbert, S. *The First Principles of Heredity*. London: Adam and Charles Black, 1910.
- Hergersberg, M, K. Matsuo, M Gassmann, W. Schaffner, B. Lüscher, T. Rüllicke and A. Aguzzi. "Tissue-specific expression of a *FMRI*/β-galactosidase fusion gene in transgenic mice." *Human Molecular Genetics* 4 (1995): 359-366.
- Heron, David. "An Examination of some Recent Studies of the Inheritance Factor in Insanity." *Biometrika* 10 (1914): 356-383.
- Heron, David. *Mendelism and the Problem of Mental Defect: I. A Criticism of Recent American Work*. London: Dulau and Co., Ltd., 1913.
- Hershey, A. D. and M. Chase. "Independent Functions of Viral Proteins and Nucleic Acid in Growth of Bacteriophage." *Journal of General Physiology* 36 (1952): 39-56.
- Hillard, L. T. and Brian H. Kirman. *Mental Deficiency*. London: J. & A. Churchill, 1957.
- Hillard, L. T. and Brian H. Kirman. *Mental Deficiency*. 2nd ed. London: J. & A. Churchill Ltd., 1965.
- Hinds, H. L., C. T. Ashley, J. S. Sutcliffe, D. L. Nelson, S. T. Warren, D. E. Housman, and M. Schalling. "Tissue specific expression of *FMR-1* provides evidence for a functional role in fragile X syndrome." *Nature Genetics* 5 (January 1993): 36-43.
- Hirst, M. C., P. K. Grewal, and K. E. Davies. "Precursor arrays for triplet repeat expansion at the fragile X locus." *Human Molecular Genetics* 3 (1994): 1553-1560.
- Hirst, M. C., S. J. L. Knight, Z. Christodoulou, P. K. Grewal, J. P. Fryns, and K. E. Davies. "Origins of the fragile X syndrome mutation." *Journal of Medical Genetics* 30 (1993): 647-650.
- Hodson, Cora B. S. *Human Sterilization To-Day: A Survey of the Present Position*. London: Watts & Co., 1934.
- Hogben, Lancelot. "Human Heredity." *Economica* 34 (November 1931): 463-469.

- Hogben, Lancelot. *Dangerous Thoughts*. London: George Allen & Unwin Ltd., 1939.
- Holliday, Robin. "The inheritance of epigenetic defects." *Science* 238 no. 4824 (9 October 1987): 163-170.
- Hopkinson, G. and P. Ley. "The Age of Onset in Manic-depressive Families." *Psychiatria et Neurologia* 152 no. 4 (1966): 217-221.
- Hornstra, Ian K., David L. Nelson, Stephen T. Warren and Thomas P. Yang. "High resolution methylation analysis of the FMR1 gene trinucleotide repeat region in fragile X syndrome." *Human Molecular Genetics* 2 no. 10 (1993): 1659-1665.
- Howe, Lucien. "A Bibliography of Hereditary Eye Defects." *Eugenics Record Office Bulletin* 21 (1921): 3-45.
- Höweler, Christiaan J., H. F. M. Busch, J. P. M. Geraedts, M. F. Niermeijrt, and A. Staal. "Anticipation in Myotonic Dystrophy: fact or fiction?" *Brain* 112 no. 3 (June 1989): 779-797.
- Hsia, David Yi-Yung., ed., *Lectures in Medical Genetics: A Course for Medical Students*. Chicago: Year Book Medical Publishers, Inc., 1966.
- Hunter, A., C. Tsilfidis, G. Mettler, P. Jacob, M. Mahadevan, L. Surh, and R. Korneluk. "The correlation of age of onset with CTG trinucleotide repeat amplification in myotonic dystrophy." *Journal of Medical Genetics* 29 (1992): 774-779.
- Huntingdon's Disease Collaborative Research Group. "A novel gene containing a trinucleotide repeat that is expanded and unstable of Huntington's disease chromosomes." *Cell* 72 (March 26 1993): 971-983.
- Huxley, J. S. "Natural Selection and Evolutionary Progress." *Nature* 138 (October 10, 1936): 603-605.
- Inge, William Ralph. *Outspoken Essays (Second Series)*. Second Impression. London: Longmans, Green and Co., 1922.
- Israel, M. H. "Autosomal suppressor gene for fragile-X: an hypothesis." *American Journal of Medical Genetics* 26 (1987): 19-31.
- Jackson, L. G. and R. N. Schimke, *Clinical Genetics: A Source Book for Physicians*, New York: John Wiley & Sons, 1979, 20.

- Jansen, G., M. Mahadevan, C. Amemiya, N. Wormskamp, B. Segers, W. Hendriks, K. O'Hoy, S. Baird, L. Sabourin, G. Lennon, P. L. Jap, D. Iles, M. Coerwinkel, M. Hofler, A. V. Carrano, P. J. de Jong, R. G. Korneluk, and B. Wieringa. "Characterization of the myotonic dystrophy region predicts multiple protein isoform-encoding mRNAs." *Nature Genetics* 1 (July 1992): 261-266.
- Jeffreys, A. J., K. Tamaki, A. MacLeod, D. G. Monckton, D. L. Neil, and J. A. L. Armour. "Complex gene conversion events in germline mutation at human satellites." *Nature Genetics* 6 (February 1994): 136-145.
- Jervis, George A. "Huntington's Chorea in Childhood." *Archives of Neurology* 9 no 3 (1963): 244-257.
- Jones, Henry Bence. "Lectures on Chemical and Mechanical Diseases and their Relationship." *Medical Times and Gazette* I (1865): 55-58.
- Jones, M. B. and Phillips, C. R. "Affected parent and age of onset in Huntington's chorea." *Journal of Medical Genetics* 7 (1970): 20-21.
- Junge, J. "Ocular Changes in Dystrophia myotonica, Paramyotonia and Myotonia congenital." In *Documenta Ophthalmologica: Advances in Ophthalmology*. Vol. 12. G. von Bahr, G. B. Bietti, J. ten Doesschate, H. Fischer-von Bünau, J. François, H. Goldmann, K. Müller, Jean Nordmann, A. J. Schaefer, and Arnold Sorsby, Eds., The Hague: Dr. W. Junk, 1966, 1-115.
- Kahndjian, E. O., A. Fortin, A. Thibodeau, S. Tremblay, F. Côté, D. Devys, J. Mandel, and F. Rousseau. "A heterogenous set of FMR1 proteins is widely distributed in mouse tissues and is modulated in cell culture." *Human Molecular Genetics* 4 (1995): 783-790.
- Kawaguchi, Y., T. Okamoto, M. Taniwaki, M. Aizawa, M. Inoue, S. Katayama, H. Kawakami, S. Nakamura, M. Nishimura, I. Akiguchi, J. Kimura, S. Narumiya, and A. Kakizuka. "CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1." *Nature Genetics* 8 (1 November 1994): 221-228.
- Kehrer, F. A. *Erblichkeit und Nervenleiden. Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie*. Heft 50. Berlin: Springer-Verlag, 1928.
- Kemp, Tage. *Genetics and Disease*. Edinburgh: Oliver and Boyd, 1951.
- Kingston, H. M. *ABC of Clinical Genetics*. London: British Medical Association, 1989.
- Klein, David. "La dystrophie myotonique (Steinert) et la myotonie congénitale (Thomsen) en Suisse." *Journal de Génétique Humaine* (Supplement) 7 (1958): 1-328.

- Klein, David. "Manifestations progressives et extensives d'une dystrophie myotonique dans une famille argovienne." *Confina Neurologica* 14 (1954): 169-175.
- Knight, S. J. L., A. V. Flannery, M. C. Hirst, L. Campbell, Z. Christodoulou, S. R. Phelps, J. Pointon, H. R. Middleton-Price, A. Barnicoat, M. E. Pembrey, J. Holland, B. A. Oostra, M. Bobrow, and K. E. Davies. "Trinucleotide repeat amplification and hypermethylation of a CpG island in *FRAXE* mental retardation." *Cell* 74 (July 16 1993): 127-134.
- Koide, R., T. Ikeuchi, O. Onodera, H. Tanaka, S. Igarashi, K. Endo, H. Takahashi, R. Kondo, A. Ishikawa, T. Hayashi, M. Saito, A. Tomoda, T. Miike, H. Naito, F. Ikuta, and S. Tsuji. "Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA)." *Nature Genetics* 6 (1 January 1994): 9-13.
- Kremer, E. J., M. Pritchard, M. Lynch, S. Yu, K. Holman, E. Baker, S. T. Warren, D. Schlessinger, G. R. Sutherland, and R. I. Richards. "Mapping of DNA Instability at the Fragile X to a Trinucleotide Repeat Sequence p(CGG)*n*." *Science* 252 (21 June 1991): 1711-1714.
- Kruyer, H., M. Milà, G. Glover, P. Carbonell, F. Ballesta, and X. Estevill. "Fragile X Syndrome and the (CGG)*n* Mutation: Two Families with Discordant MZ Twins." *American Journal of Human Genetics* 54 (1994): 437-442.
- Kryshowa, N and H. Bajevskaja. "Ein familiärer Fall der atrophischen Myotonie." *Zeitschrift für die gesamte Neurologie und Psychiatrie* 150 (1934): 505-514.
- Kunst, C. B., and S. T. Warren. "Cryptic and Polar Variation of the Fragile X Repeat Could Result in Predisposing Normal Alleles." *Cell* 77 (June 17 1994): 853-861.
- Kwakami, R. "Beitrage zur Vererbung der Familiären Sehnervenatrophie." *Albrecht von Graefes Archiv für Ophthalmologie*, 116 (March 1926): 568-595.
- La Spada, A. R., E. M. Wilson, D. B. Lubahn, A. E. Harding, and K. H. Fischbeck. "Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy." *Nature* 352 (4 July 1991): 77-79.
- Laird, C. "Huntington's disease: proposed mechanism of mutation, inheritance and expression." *Trends in Genetics* 6 (1990): 242-247.
- Lanari, Alfredo. *Miotonias*. Buenos Aires: El Ateneo, 1942.
- Landman, J. H. *Human Sterilization: The History of the Sexual Sterilization Movement*. New York: The Macmillan Company, 1932.

- Lane, Russell J. M., Peggy Shelbourne and Keith J. Johnson. "Myotonic Dystrophy." In *Handbook of Muscle Disease*. Russell J. M. Lane ed. New York: Marcel Dekker, Inc., 1996, 311-328.
- Lange, F. "Ueber chronische progressive Chorea (Huntington) im jugendlichen Alter." *Berliner Klinische Wochenschrift* 43 no. 6 (5 February 1906): 153-156.
- Lange, Johannes, Fritz Lenz, Otmar von Verschuer, and Wilhelm Weitz. *Menschliche Erblere und Rassenhygiene*. Band 1: 2. Hälfte, *Erbpathologie*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz. Munich-Berlin: J. F. Lehmanns Verlag, 1940.
- Laughlin, Harry H. "Report of the Committee to Study and to Report on the Best Practical Means of Cutting Off the Defective Germ-Plasm in the American Population. 1. The Scope of the Committee's Work." *Eugenics Record Office Bulletin* 10A (1914): 5-64.
- Lawford, J. B. "Examples of Hereditary Primary Glaucoma." *Royal London Ophthalmic Hospital Records* 17 (1907): 57-68.
- Leese, Stephanie M. "A Pedigree of Huntington's Chorea: With a note on linkage data by R. R. Race." *Annals of Eugenics* 17 (1952): 92-112.
- Lenz, Fritz. *Menschliche Erblere und Rassenhygiene*. Band 2, *Grundriß der menschlichen Erblichkeitslehre und Rassenhygiene*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz. Munich: J. F. Lehmanns Verlag, 1923.
- Lenz, Fritz. *Menschliche Erblere und Rassenhygiene*. Band 2, *Menschliche Auslese und Rassenhygiene*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz. Munich: J. F. Lehmanns Verlag, 1923.
- Lenz, Fritz. *Menschliche Erblere und Rassenhygiene*. Band 2, *Menschliche Auslese und Rassenhygiene (Eugenik)*, eds., Erwin Bauer, Eugen Fisher, and Fritz Lenz. Munich: J. F. Lehmanns Verlag, 1932.
- Lenz, Widukind. "Living History—Biography: Nature and Nurture." *American Journal of Medical Genetics* 37 no. 3 (November 1990): 356-361.
- Lenz, Widukind. *Medical Genetics*. Translated by Elizabeth F. Lanzel. Chicago: University of Chicago Press, 1963. Originally published as *Medizinische Genetik: Eine Einführung in ihre Grundlagen und Probleme* (Stuttgart: Thieme Verlag, 1961).
- Levitan, Max and Ashley Montagu. *Textbook of Human Genetics*. New York: Oxford University Press, 1971.

- Lidbetter, Ernest James. *Heredity and the Social Problem Group*. Vol. 1. London: Edward Arnold & Co., 1933.
- Lidbetter, E. J. "Nature and Nurture—A Study in Conditions." *Eugenics Review* 4 (1912): 54-73.
- Lidbetter, E. J. "The Social Problem Group: As Illustrated by a Series of East London Pedigrees." *Eugenics Review* 14 (1932): 7-12.
- Lidbetter, Ernest James and Edward Nettleship. "On a Pedigree Showing Both Insanity and Complicated Eye Disease: Anticipation of the Mental Disease in Successive Generations." *Brain* 35 no. 3 (February 1913): 195-221.
- Ledbetter, David H., Susan A. Ledbetter, Robert L. Nussbaum. "Implications of fragile X expression in normal males for the nature of the mutation." *Nature* 324 (13 November 1996): 161-163.
- Loch, C. S. "Eugenics and the Poor Law: The Majority Report." *Eugenics Review* 2 no. 3 (October 1910): 229-232.
- Lubs, Herbert A. "A marker X chromosome." *American Journal of Human Genetics* 21 (1969): 231-244.
- Lubs, Herbert A., Michael Watson, Roy Breg, Enrique Lujan and John M. Opitz. "Restudy of the original marker X family." *American Journal of Medical Genetics* 17 no. 1 (January 1984): 133-144.
- Lucas, Prosper. *Prosper Lucas's "On the Heredity of Mental Illness" [1850]*. Edited and with an introduction by Charles David Mellon. Translated by Linda Forge Mellon. New Mexico: Genetics Heritage Press, 1996.
- Lucas, Prosper. *Traité philosophique et physiologique de l'hérédité naturelle dans les état de santé et de maladie du système nerveux*. 2 vols. Paris: J. B. Ballière, 1847-1850.
- Lynas, Margaret A. "Dystrophia Myotonica with Special Reference to Northern Ireland." *Annals of Human Genetics* 21 (1957): 318-351.
- Lynch, Henry T. *Dynamic Genetic Counseling for Clinicians*. Springfield IL: Charles C. Thomas, 1969.
- M, E. W. "Cultivation of the Unfit." *Nature* 137 (February 1, 1936): 188-189.
- M, E. W. "Cultivation of the Unfit." *Nature* 137 (February 15, 1936): 276.
- M, E. W. "The Cultivation of the Unfit." *Nature* 137 (January 11, 1936): 44-45

- Maas, Otto. "Observations on Dystrophia Myotonica." *Brain* 60 (December 1937): 498-524.
- Maas, Otto and A. S. Paterson. "Dystrophia myotonica as a generalised disease." *Monatsschrift für Psychiatrie und Neurologie* 113 (1947): 79-99.
- Maas, Otto and A. S. Paterson. "Genetic and Familial Aspects of Dystrophia Myotonica." *Brain* 66 no. 1 (March 1943): 55-86.
- Maas, Otto and A. S. Paterson. "Mental Changes in Families Affected by Dystrophia Myotonica." *Lancet* 229 no. 5914 (2 January 1937): 21-23
- Maas, Otto and A. S. Paterson. "Myotonia congenita and dystrophia myotonica; further considerations indicating identity." *Monatsschrift für Psychiatrie und Neurologie* 126 no. 1 (July 1953): 27-33.
- Maas, Otto and A. S. Paterson. "Myotonia congenita, dystrophia myotonica and paramyotonia; reaffirmation of their identity." *Brain* 73 no. 3 (1950): 318-336.
- Maas, Otto and A. S. Paterson. "The Identity of Myotonia Congenita (Thomsen's Disease), Dystrophia Myotonica (Myotonia Atrophica) and Paramyotonia." *Brain* 62 (1939): 198-212.
- Macklin, Madge Thurlow. "Comparison of the Number of Breast-Cancer Deaths Observed in Relatives of Breast-Cancer Patients and the Number Expected on the Basis of Mortality Rates." *Journal of the National Cancer Institute* 22 (1959): 927-951.
- Macklin, M. T. "Education and Research in the Field of Inheritance of Disease." *The Canadian Medical Association Journal* 32 no. 1 (1935): 80-82.
- Macklin, M. T. "Genetical Aspects of Sterilization of the Mentally Unfit." *The Canadian Medical Association Journal* 30 no. 2 (1934): 190-195.
- Macklin, M. T. "Heredity and the Social Problem Group: A Review." *The Canadian Medical Association Journal* 30 no. 3 (1934): 309-310.
- Macklin, M. T. "Heredity as an Aid to Modern Therapy." *The Canadian Medical Association Journal* 28 no. 4 (1933): 394-397.
- Macklin, M. T. "Inheritance and Human Cancer." *Ohio State Medical Journal* 43 (August 1947): 836-840.
- Macklin, M. T. "Inherited Anomalies of Metabolism: 1. Diabetes Mellitus." *Journal of Heredity* 24 no. 9 (1933): 349-356.

- Macklin, Madge Thurlow. "Medical Genetics' A Necessity in the Up-to-date Medical Curriculum." *Journal of Heredity* 23 no. 12 (1932): 485-486.
- Macklin, M. T. "Medical Genetics." *Journal of the Association of American Medical Colleges* 8 (September 1933): 291-304.
- Macklin, M. T. "Should the teaching of genetics as applied to medicine have a place in the medical curriculum." *Journal of the Association of American Medical Colleges* 7 (November 1932): 368-373.
- Macklin, M. T. "Teaching human inheritance to medical students." *Medical Journal and Record* 136 (September 1932): 215-217.
- Macklin, M. T. "The Hereditary Factor in Human Neoplasms." *Quarterly Review of Biology* 7 no. 3 (September 1932): 255-281.
- Macklin, M. T. "The Need of a Course in Medical Genetics in the Medical Curriculum: A Pivotal Point in the Eugenic Program." In *A Decade of Progress in Eugenics: Scientific Papers of the Third International Congress of Eugenics held at American Museum of Natural History, New York, August 21-23, 1932*, Baltimore: The Williams & Wilkins Company, 1934, 157-158.
- Macklin, M. T. "The need of a course of medical genetics in the medical curriculum as the pivotal point in the eugenic program." *Edinburgh Medical Journal* 40 (1933): 20-30.
- Macklin, M. T. "The Relation of the Mode of Inheritance to the Severity of an Inherited Disease." *Human Biology* 4 (1932): 69-79.
- Macklin, M. T. "The Role of Heredity in Disease." *Medicine* 14 no. 1 (1935): 1-75.
- Macklin, M. T. "The teaching of inheritance of disease to medical students." *Annals of Internal Medicine* 6 (1933): 1335-1343.
- Macklin, M. T. "The Value of Accurate Statistics in the Study of Cancer." *The Canadian Journal of Public Health* 25 (1934): 369-373.
- Macpherson, J. N., D. L. Nelson, and P. A. Jacobs. "Frequent small amplifications in the FMR-1 gene in fra(X) families: limits to the diagnosis of 'premutations'." *Journal of Medical Genetics* 29 (1992): 802-806.
- Maddox, J. "Competition and the death of science." *Nature* 363 (24 June 1993): 667.
- Maddox, J. "Melodrama in research publication." *Nature* 355 (27 February 1992): 767.

- Mahadevan, M., C. Tsilfidis, L. Sbourin, G. Shutler, C. Amemiya, G. Jansen, C. Neville, M. Narang, J. Barcleó, K. O'Hoy, S. Leblond, J. Earle-Macdonals, P. de Jong, B. Wieringa, and R. G. Korneluk. "Myotonic Dystrophy Mutation: An Unstable CTG Repeat in the 3' Untranslated Region of the Gene." *Science* 255 no. 5049 (6 March 1992): 1253-1255.
- Marshall, William C. "Mr. Edward Nettleship, F.R.S. Born, 1845; Died, 1913." *Eugenics Review* 5 (1913): 353-354.
- Marshall, William. "Mr. Edward Nettleship, F.R.S." *Eugenics Review* 5 (April 1913): 353.
- Martin, J. Purdon and Julia Bell. "A Pedigree of Mental Defect Showing Sex-Linkage." *Journal of Neurology and Psychiatry* 6 (1943): 154-157.
- Mass, Otto. "Observations on Dystrophia Myotonica." *Brain* 60 (1937): 498-524.
- Mathieu, Jean., Marc De Breakeleer, and Claude Prevost. "Genealogical reconstruction of myotonic dystrophy in the Saguenay-Lac-Saint-Jean area (Quebec, Canada)." *Neurology* 40 no. 5 (May 1990): 839-842.
- Maudsley, Henry. *The Pathology of Mind. Being the third edition of the second part of the "Physiology & Pathology of Mind." Recast, Enlarged, and Rewritten.* London: Macmillan and Co., 1879.
- Maudsley, Henry. *The Pathology of Mind: A Study of its Distempers, Deformities, and Disorders.* London, Macmillan and Co., 1895.
- McConkie-Rosell, A., A. M. Lachiewucz, G. A. Spiridigliozzi, J. Tarleton, S. Schoenwald, M. C. Phelan, P. Goonewardena, X. Ding, and W. T. Brown. "Evidence that methylation of the FMR-1 locus is responsible for variable phenotypic expression of the fragile X syndrome." *American Journal of Human Genetics* 53 (1993):800-809.
- McKusick, Victor. *Human Genetics.* Englewood Cliffs NJ: Prentice-Hall Inc., 1964.
- McKusick, V. *Human Genetics.* 2nd ed. Englewood Cliffs NJ: Prentice-Hall Inc., 1969.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes.* 1st ed. Baltimore: The Johns Hopkins Press, 1966.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes.* London: William Heinemann Medical Books, Ltd., 1966.

- McKusick, Victor. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 2nd ed. Baltimore: The Johns Hopkins Press, 1968.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 3rd ed. Baltimore and London: The Johns Hopkins Press, 1971.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 4th ed. Baltimore and London: The Johns Hopkins Press, 1975.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 5th ed. Baltimore and London: The Johns Hopkins Press, 1978.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 6th ed. Baltimore and London: The Johns Hopkins Press, 1983.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 7th ed. Baltimore and London: The Johns Hopkins Press, 1986.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 8th ed. Baltimore and London: The Johns Hopkins Press, 1988.
- McKusick, V. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 9th ed. Baltimore and London: The Johns Hopkins Press, 1990.
- McMahon, F. J., O. C. Stine, D. A. Meyers, S. G. Simpson, and J. R. DePaulo. "Patterns of Maternal Transmission in Bipolar Affective Disorder." *American Journal of Human Genetics* 56 (1995): 1277-1286.
- Meehan, Richard R., Joe D. Lewis, Stewart McKay, Elke L. Kleiner, and Adrian P. Bird. "Identification of a Mammalian Protein That Binds Specifically to DNA Containing Methylated CpGs." *Cell* 58 (1989): 499-507.
- Meijer, H., E. De Graaff, D. M. L. Merckx, R. J. E. Jongbloed, C. E. M. de Die-Smulders, J. J. M. Engelen, J. Fryns, P. M. G. Curfs, and B. A. Oostra. "A deletion of 1.6 kb proximal to the CGG repeat of the FMR1 gene causes the clinical phenotype of the fragile X syndrome." *Human Molecular Genetics* 3 (1994): 615-620.

- Melchionda, S., A. Cobo, M. Gennarelli, L. Martorell, C. Farroeni, M. Baiget, A. L. De Munain, K. Johnson, P. Shelbourne, G. Novelli, B. Dallapiccola. "Expansion of the myotonic dystrophy gene I Italian and Spanish patients." *Journal of Medical Genetics* 29 (1992): 789-790.
- Merrit, A. Donald, P. M. Conneally, N. F. Rahman and A. L. Drew. "Juvenile Huntington's Chorea." in *Progress in Neurogenetics. Proceedings of the Second International Congress of Neuro-Genetics and Neuro-Ophthalmology of the World Federation of Neurology*. Vol. 1. Eds., André Barbeau and Jean-Réal Brunette. Amsterdam: Excerpta Medica Foundation, 1969, 645-650.
- Merritt, A. D., P. M. Conneally, N. F. Rahman, and A. L. Drew. "Juvenile Huntington's chorea." In *Progress in Neurogenetics*, ed., A. Barbeau and T. R. Brunette. Pp. 645-50. Amsterdam: Excerpta Medica Foundation, 1969.
- Merritt, H. Houston. *A Textbook of Neurology*. 4th ed. Philadelphia: Lea & Febiger, 1967.
- Merritt, H. Houston. *A Textbook of Neurology*. 5th ed. Philadelphia: Lea & Febiger, 1973.
- Miwa, Shiro. "Triplet repeats strike again." *Nature Genetics* 6 (January 1994): 3-4.
- Mohr, Otto L. "On the potency of mutant genes and wild-type allelomorphs." in *Proceedings of the Sixth International Congress of Genetics, Ithaca, New York, 1932*, Vol. 1, ed., Donald Jones, (Menasha WI: Brooklyn Botanic Garden, 1932), 190-212.
- Monk, M. and A. Surani, eds. *Genomic Imprinting*. Cambridge: Cambridge University Press, 1990.
- Montagu, Ashley. *Human Heredity*. Cleveland OH: The World Publishing Company, 1959.
- Morel, Bénédict Augustin. *Traité des dégénérescences: physiques, intellectuelles et morales de l'espèce humaine et des causes qui produisent ces variétés malades*. Paris: J. B. Baillière, 1857. Reprint edition 1976 by Arno Press.
- Morel, B. A. *Traité des maladies mentales*. Paris: Librairie Victor Masson, 1860.
- Morton N. E. and J. N. Macpherson. "Population genetics of the fragile-X syndrome: Multiallelic model for the *FMRI* locus." *Proceedings of the National Academy of Sciences USA* 89 (1992): 4215-4217.
- Mott, Frederick Walker. "A Lecture on Heredity and Insanity." *Lancet* 177 no. 4576 (May 13, 1911): 1251-1259.

- Mott, Frederick Walker. "A Lecture on The Causes of Insanity." *Lancet* 184 no. 4741 (11 July 1914): 75-81.
- Mott, F. W. "A Study of the Neuropathic Inheritance." *American Journal of Insanity* 64 no. 4 (1913): 907-938.
- Mott, F. W. "A Study of the Neuropathic Inheritance especially in Relation to Insanity." *Archives of Neurology and Psychiatry (London)* 6 (1914): 79-98.
- Mott, F. W. "Hereditary aspects of nervous and mental diseases." *The British Medical Journal* 2 (1910): 1013-1020.
- Mott, F. W. "Hereditary Transmission of Disease Especially in Relation to Anticipation." *Medical Chronicle* 22 (1911): 63-92.
- Mott, F. W. "Heredity and Eugenics in Relation to Insanity." In *Problems in Eugenics: Papers communicated to the First International Eugenics Congress*. London: Eugenics Society, 1912, 400-428.
- Mott, F. W. *Heredity and Eugenics in Relation to Insanity*. London: Eugenics Education Society, 1912.
- Mott, F. W. "Heredity and Insanity." *Eugenics Review* 2 (January 1911): 257-281.
- Mott, F. W. "Heredity in Relation to Mental Disease and Mental Deficiency." *British Medical Journal* 1 (19 June 1926): 1023-1026.
- Mott, F. W. "Maudsley Lecture." *Archives of Neurology and Psychiatry (London)* 8 (1922): 41-61.
- Mott, F. W. "Sanity and Insanity. A Lecture Delivered to the Royal Sanitary Institute on Wednesday, April 24th, 1912." *Journal of the Royal Sanitary Institute* 33 (1912): 228-251.
- Mott, F. W. "The Harveian Oration on Heredity in Relation to Mental Disease." *British Medical Journal* 2 (24 October 1925): 727-731.
- Mott, F. W. "The Huxley Lecture on Hereditary Aspects of Nervous and Mental Diseases." *The British Medical Journal* 2 (1910):1013-1020
- Mott, F. W. "The Huxley Lecture on The Hereditary Aspects of Nervous and Mental Diseases." *Lancet* 176 no. 4545 (8 October 1910): 1057-1064
- Mott, F. W. "The Inborn Factors of Nervous and Mental Disease." *Brain* 34 no. 1 (1911): 73-101.

- Mott, Frederick Walker. "The Pathology of Dementia Praecox." *British Medical Journal* 2 (20 November 1920): 781-782.
- Mott, F. W. "The Pathology of Syphilis of the Nervous System in the Light of Modern Research (Morison Lectures, 1909)." *Archives of Neurology and Psychiatry* 4 (1909): 13-57.
- Muller, H. J. "Our Load of Mutations." *American Journal of Human Genetics* 2 (1950): 111-176.
- Muller, H. J. "Progress and Prospects in Human Genetics." *American Journal of Human Genetics* 1 no. 1 (September 1949): 1-18.
- Muller, H. J., C. C. Little, and Laurence H. Snyder. *Genetics, Medicine, and Man*. Ithaca NY: Cornell University Press, 1947.
- Myers, R. H., D. Goldman, and E. D. Bird. "Maternal transmission in Huntington's disease." *Lancet* 321 no. 8318 (29 January 1983): 208-210.
- Myers, R. H., D. S. Sax, and M. Schoenfeld. "Late onset of Huntington's disease." *Journal of Neurology, Neurosurgery and Psychiatry* 48 (1985): 530-534.
- Myers, R. H., J. J. Madden, J. L. Teague, and A. Falek. "Factors related to onset of Huntington's disease." *American Journal of Human Genetics* 34 (1982): 481-488.
- Myerson, Abraham. "Certain Medical and Legal Phases of Eugenic Sterilization." *The Yale Law Journal* 52 no. 3 (1943): 618-633.
- Myriantopoulos, Ntinos C. "Disorders of Muscle." in *Clinical Genetics*, 2nd ed. 232.
- Myriantopoulos, Ntinos C. "Huntington's Chorea." *Journal of Medical Genetics* 3 (1966): 298-314.
- Myring, J., A. L. Meredith, H. G. Harley, G. Kohn, G. Norbury, P. S. and D. J. Shaw. "Specific molecular prenatal diagnosis for the CTG mutation in myotonic dystrophy." *Journal of Medical Genetics* 29 (1992): 785-788.
- Nagafuchi, S., H. Yanagisawa, K. Sato, T. Shirayama, E. Ohsaki, M. Bundo, T. Takeda, K. Tadokoro, I. Kondo, N. Murayama, Y. Tanaka, H. Kikushima, K. Umino, H. Kurosawa, T. Furukawa, K. Nihei, T. Inoue, A. Sano, O. Komure, M. Takahashi, T. Yoshizawa, I. Kanazawa, and M. Yamada. "Dentatorubral and pallidolusian atrophy expansion of an unstable CAG trinucleotide on chromosome 12p." *Nature Genetics* 6 (January 1994): 14-18.

- Nancarrow, J. K., E. Kremer, K. Holma, H. Eyre, N. A. Doggett, D. Le Paslier, D. F. Callen, G. R. Sutherland, R. I. Richards. "Implications of *FRA 16A* Structure for the Mechanism of Chromosomal Fragile Site Genesis." *Science* 264 (24 June 1994): 1938-1941.
- Needham, Joseph. "Cultivation of the Unfit." *Nature* 137 (February 1, 1936): 188.
- Neel, James V. and William J. Schull. *Human Heredity*. Chicago: University of Chicago Press, 1954.
- Neilson Jones, W. "Genetics in the University." *Nature* 138 (December 19, 1936): 1058.
- Nettleship, Edward. "On Heredity in the Various forms of Cataract." *The Royal London Ophthalmic Hospital Reports* 16 (October 1905): 179-246.
- Nettleship, E. "On Some Hereditary Diseases of the Eye. Being the Bowman Lecture, Delivered on Thursday, June 10th, 1909." *Transactions of the Ophthalmological Societies of the United Kingdom* 29 (1909): 52-198.
- Nettleship, Edward. "Some Points in Relation to the Heredity of Disease." *St. Thomas's Hospital Gazette* 20 (March 1910): 37-65.
- Nettleship, E. *The Bowman Lecture on Some Hereditary Diseases of the Eye*. London: Adelard and Son, 1909.
- Newcombe, R. G., D. A. Walker, and P. S. Harper. "Factors influencing age of onset and duration of survival in Huntington's chorea." *Annals of Human Genetics* 45 (1981): 387-396.
- Nordau, Max. *Degeneration*. Translated from the Second Edition of the German Work (1895) with an Introduction by George L. Mosse. New York: Howard Fertig, 1968.
- O'Brien, T. and P. S. Harper. "Course, prognosis and complications of childhood-onset myotonic dystrophy." *Developmental Medicine and Child Neurology* 26 (1984): 62-67.
- Oberel , I., F. Rousseau, D. Heitz, C. Kretz, D. Devys, A. Hanauer, J. Bou , M. F. Bertheas, and J. L. Mandel. "Instability of a 550 bp DNA segment and abnormal methylation in Fragile X Syndrome." *Science* 252 (24 May 1991): 1097-1102.
- Oliver, J. E. "Huntington's chorea in Northamptonshire." *British Journal of Psychiatry* 116 (1970): 241.
- Oostra, B. A. and P. J. Willems. "A fragile gene." *Bioessays* 17 (1995): 941-947.

- Opitz, John M., Joan M. Westphal, and Art Daniel. "Discovery of a connective tissue dysplasia in the Martin-Bell syndrome." *American Journal of Medical Genetics* 17 no. 1 (January 1984): 101-109.
- Ormerod and Bernhardt. "Remarks on Dr. Sanger Brown's Cases." *Brain* 15 no. 2 (1892): 268-282.
- Orr, H. T., M. Chung, S. Banfi, T. J. Kwiatkowski, A. Servadio, A. L. Beaudet, A. E. McCall, L. A. Duvick, L. P. W. Ranum, and H. Y. Zoghbi. "Expansion of an unstable CAG repeat in spinocerebellata ataxia type 1." *Nature Genetics* 4 (July 1993): 221-226.
- Orr, John Boyd. *Food Health and Income: Report on A Survey of Adequacy of Diet in Relation to Income*. London: Macmillan and Co., Ltd., 1936.
- Oudet, C., E. Mornet, J. L. Serre, F. Thomas, S. Lentes-Zengerling, C. Kretz, C. Deluchat, I. Tajada, J. Boué, A. Boué, and J. L. Mandel. "Linkage Disequilibrium between the Fragile X Mutation and Two Closely Linked CA Repeats Suggests That Fragile X Chromosomes Are Derived from a Small Number of Founder Chromosomes." *American Journal of Human Genetics* 52 (1993): 297-304.
- Parker, Neville. "Dystrophia myotonica presenting as congenital facial diplegia." *Medical Journal of Australia* 2 no. 23 (7 November 1963): 939-944.
- Parrish, J. E., B. A. Oostra, A. J. M. H. Verkerk, C. S. Richards, J. Reynolds, A. S. Spikes, L. G. Shaffer, and D. L. Nelson. "Isolation of a GCC repeat showing expansion in FRAXF, a fragile site distal to FRAXA and FRAXE." *Nature Genetics* 8 (8 November 1994): 229-235.
- Paterson, Arthur S. "'Anticipation' in Mental Disease." *Eugenics Review* 24 no. 3 (1932): 191-193.
- Paterson, Arthur S. "The Socalled Law of Anticipation in Mental Disease." *The Journal of Neurology and Psychopathology* 13 no. 51 (January 1933): 193-210.
- Pavy, Frederick W. *Researches on the Nature and Treatment of Diabetes*. 2nd ed. London: John Churchill & Sons, 1869.
- Pearson, Karl. "Darwinism, Biometry, and Some Recent Biology." *Biometrika* 7 (1910): 368-385.
- Pearson, Karl. *Drapers' Company Research Memoirs: Studies in National Deterioration 11. A First Study of the Statistics of Pulmonary Tuberculosis*. London: Dulau and Co., 1907.

- Pearson, Karl. "On an Apparent Fallacy in the Statistical Treatment of "Antedating" in the Inheritance of Pathological Conditions." *Nature* 90 (1912): 334-335.
- Pearson, Karl. "On the Inheritance of Mental Disease." *Annals of Eugenics* 4 (1931): 362-380.
- Pearson, Karl. "Prefatory Note." In Julia Bell. *The Treasury of Human Inheritance*. Vol. 2. *Anomalies and Diseases of the Eye: Nettleship Memorial Volume. Part 1: Retinitis Pigmentosa and Allied Diseases Congenital Stationary Night-Blindness Glioma Retinae*. With a Memoir of Edward Nettleship by J. B. Lawford. Cambridge: Cambridge University Press, 1922.
- Pearson, Karl. *The Problem of Practical Eugenics*. 2nd ed. London: Cambridge University Press, 1912.
- Pearson, Karl and Ethel Elderton. "Forward." *Annals of Eugenics* 1 (1925): 1-4.
- Pearson, Karl and Gustav A. Jaederholm. *Mendelism and the Problem of Mental Defect: II. On the Continuity of Mental Defect*. London: Cambridge University Press, 1914.
- Pembrey, M. E., R. M. Winter, and K. E. Davies. "A premutation that generates a defect at crossing over explains the inheritance of fragile X mental retardation." *American Journal of Medical Genetics* 21 no. 4 (August 1985): 709-717.
- Penrose, Lionel Sharples. *A Clinical and Genetic Study of 1280 Cases of Mental Defect*. London: His Majesty's Stationary Office, 1938.
- Penrose, L. S. "A Contribution to the Genetic Study of Mental Deficiency." *British Medical Journal* 1 (1934): 10-11.
- Penrose, L. S. "Autosomal mutation and modification in man, with special reference to mental defect." *Annals of Eugenics* 7 (1936): 1-16.
- Penrose, L. S. "Eugenic Prognosis with Respect to Mental Deficiency." *Eugenics Review* 31 (1939): 35-37.
- Penrose, L. S. "Introduction." In *Biological Aspects of Social Problems: A Symposium held by the Eugenics Society in October 1964*. J. E. Meade and A. S. Parkes, eds., Edinburgh: Oliver & Boyd, 1965, 111-113.
- Penrose, L. S. "Les Applications de la Génétique à la Médecine." *Annals of Eugenics* 13 (1947): 291.
- Penrose, L. S. *Mental defect*. London: Sidgwick & Jackson, 1933.

- Penrose, Lionel Sharples. *Mental Defect*. New York: Farrar & Rinehart, 1934.
- Penrose, L. S. "Mental Deficiency—II The Sub-Cultural Group." *Eugenics Review* 24 (1932): 289-291.
- Penrose, L. S. *Outline of Human Genetics*. London: Heinemann, 1959.
- Penrose, L. S. *Outline of Human Genetics*. London: Heinemann, 1959, Reprinted 1960.
- Penrose, L. S. *Outline of Human Genetics*. 2nd ed. London: Heinemann, 1963.
- Penrose, L. S. *Outline of Human Genetics*. 3rd ed. London: Heinemann Educational Books, 1973.
- Penrose, L. S. "Phenylketonuria: A Problem in Eugenics." *Lancet* 247 no. 6409 (29 June 1946): 949-953.
- Penrose, L. S. ed., *Recent Advances in Human Genetics*. With the assistance of Helen Lang Brown, London: J. & A. Churchill Ltd., 1961.
- Penrose, L. S. "Social Aspects of Psychiatry: The Importance of Statistics." *Journal of Mental Science* 92 no. 389 (October 1946): 713-718.
- Penrose, L. S. "Some Notes on Discrimination." *Annals of Eugenics* 13 no. 4 (1947): 228-237.
- Penrose, L. S. *The Biology of Mental Defect*. With a preface by J. B. S. Haldane. London: Sidgwick and Jackson Limited, 1949.
- Penrose, L. S. *The Biology of Mental Defect*. With a preface by J. B. S. Haldane. Second (revised) edition. London: Sidgwick and Jackson Limited, 1954.
- Penrose, L. S. *The Biology of Mental Defect*. With a preface by J. B. S. Haldane. Completely revised with the assistance of J. M. Berg and Helen Lang-Brown. Third edition. London: Sidgwick and Jackson Limited, 1963.
- Penrose, L. S. *The Biology of Mental Defect*. With a preface by J. B. S. Haldane. Completely revised with the assistance of J. M. Berg and Helen Lang-Brown. Fourth edition. London: Sidgwick and Jackson Limited, 1972.
- Penrose, L. S. "The Complex Determinants of Amentia." *Eugenics Review* 26 no. 2 (July 1934): 121-126.
- Penrose, L. S. "The Galton Laboratory: Its Work and Aims." *Eugenics Review* 41 no. 1 (1949): 17-27.

- Penrose, Lionel Sharples. "The Importance of Statistics in Psychiatry." *Proceedings of the Royal Society of Medicine* 40 no. 14 (1947): 863-870.
- Penrose, L. S. *The Influence of Heredity of Disease: Buckston Browne Prize Essay, 1933*. London: H. K. Lewis & Co. Ltd., 1934.
- Penrose, L. S. "The problem of Anticipation in Pedigrees of Dystrophia Myotonica." *Annals of Eugenics* 14 (1948): 125-132.
- Penrose, Lionel S. "Mental Deficiency—II: The Sub-Cultural Group." *Eugenics Review* 24 no. 4 (January 1933): 289-291.
- Penrose, L. S. "Some Notes on Discrimination." *Annals of Eugenics* 13 no. 4 (1947): 228-237.
- Penrose, Lionel S. and Curt Stern. "Reconsideration of the Lambert pedigree (ichthyosis hystrix gravior)." *Annals of Human Genetics* 22 no. 3 (1958): 258-283.
- Penrose, Lionel S. and J. B. S. Haldane. "Mutation Rates in Man." *Nature* 135 (June 1, 1935): 907-908.
- Pieretti, Maura., Fuping Zhiang, Ying-Hui Fu, Stephen T. Warren, Ben A. Oostra, C. Thomas Caskey, and David L. Nelson. "Absence of expression of the *FMR-1* gene in fragile X syndrome." *Cell* 66 no. 4 (23 August 1991): 817-822.
- Pierraccini, A. "On the Priority of the Biological Hereditary Law of 'Anticipation'." *Human Biology* 4 no. 4 (December 1932): 554-557
- Pollock, James and James Chisholm. *Medical Handbook of Life Assurance*. 2nd ed. London: Cassell & Company, Limited, 1889.
- Pratt, R. T. C. *The Genetics of Neurological Disorders*. London: Oxford University Press, 1967.
- Pridmore, S. A. "Age of onset of Huntington's disease in Tasmania." *Medical Journal of Australia* 153 (1990): 135-137.
- Pritchard, C. A., D. R. Cox, and R. M. Myers. "Methylation at the Huntington disease-linked D4S95 locus." *American Journal of Human Genetics* 45 (1989): 335-336.
- Pryse-Phillips, W., G. J. Johnson, and B. Larsen. "Incomplete manifestations of myotonic dystrophy in a large kinship in Labrador." *Annals of Neurology* 11 (1982): 582-591.

- Ranum, L. P. W., L. J. Schut, J. K. Lundgren, H. T. Orr, and D. M. Livingston. "Spinocerebellar ataxia type 5 in a family descended from the grandparents of President Lincoln maps to chromosome 11." *Nature Genetics* 8 (November 1994): 280-284.
- Ravin, Abe and James J. Waring. "Studies in Dystrophia Myotonica. I. Hereditary Aspects." *American Journal of the Medical Sciences* 197 (1939): 593-609.
- Read, Andrew P. "Huntington's disease: testing the test." *Nature Genetics* (August 1993): 329-330.
- Reardon, W., H. G. Harley, J. D. Brook, S. A. Rundle, S. Crow, P. S. Harper, and D. J. Shaw. "Minimal expression of myotonic dystrophy: a clinical and molecular analysis." *Journal of Medical Genetics* 29 (1992): 770-773.
- Reed, Sheldon C. *Counseling in Medical Genetics*. Philadelphia: W. B. Saunders Company, 1955.
- Reik, W. "Genomic imprinting: a possible mechanism for the parental origin effect in Huntington's chorea." *Journal of Medical Genetics* 25 (1988): 805-808.
- Reyniers, E., L. Vits, K. De Boulle, B. Van Roy, D. Van Velzen, E. de Graaff, A. J. M. H. Verkerk, H. Z. J. Jorens, J. K. Darby, B. Oostra, and P. J. Willems. "The full mutation in the FMR-1 gene of male fragile X patients is absent in their sperm." *Nature Genetics* 4 (June 1993): 143-146.
- Richards, R. I. and G. R. Sutherland. "Simple repeat DNA is not replicated simply." *Nature Genetics* 6 (February 1994): 114-116.
- Richards, R. I., K. Holman, K. Friend, E. Kremer, D. Hillen, A. Staples, W. T. Brown, P. Goonewardena, J. Tarleton, C. Schwartz, and G. R. Sutherland. "Evidence of founder chromosomes in fragile X syndrome." *Nature Genetics* 1 (July 1992): 257-260.
- Richards, R. I., K. Holman, S. Yu, and G. R. Sutherland. "Fragile X syndrome unstable element, p(CCG)_n, and other simple tandem repeat sequences are binding sites for specific nuclear proteins." *Human Molecular Genetics* 2 no. 9 (September 1993): 1429-1435.
- Richards, B. W., P. E. Sylvester and Carol Booker. "Fragile X-linked mental retardation: the Martin-Bell syndrome." *Journal of Mental Deficiency Research* 25 (1981): 253-256.
- Ride, Lindsay. *Genetics and the Clinician*. Bristol: John Wright & Sons Ltd., 1938.

- Ridley, R. M., C. D. Firth, T. J. Crow, and P. M. Conneally. "Anticipation in Huntington's disease is inherited through the male line but may originate in the female." *Journal of Medical Genetics* 25 no. 9 (September 1988): 589-595.
- Ridley, R. M., C. D. Frith, L. A. Farrer and P. M. Conneally. "Patterns of inheritance of the symptoms of Huntington's disease suggestive of an effect of genomic imprinting." *Journal of Medical Genetics* 28 (1991): 224-231.
- Ridley, R. M., C. D. Frith, L. A. Farrer, and P. M. Conneally. "Patterns of inheritance of the symptoms of Huntington's disease suggestive of the effect of genomic imprinting." *Journal of Medical Genetics* 28 (1991): 224-231.
- Roberts, J. A. Fraser. *An Introduction to Medical Genetics*. London: Oxford University Press, 1940.
- Roberts, J. A. Fraser. *An Introduction to Medical Genetics*. 2nd ed. London: Oxford University Press, 1959.
- Roberts, J. A. Fraser. *An Introduction to Medical Genetics*. 3rd ed. London: Oxford University Press, 1963.
- Roberts, J. A. Fraser. *An Introduction to Medical Genetics*. 4th ed. London: Oxford University Press, 1967.
- Roberts, J. A. Fraser. *An Introduction to Medical Genetics*. 5th ed. London: Oxford University Press, 1970.
- Roberts, J. A. Fraser. *An Introduction to Medical Genetics*. 6th ed. London: Oxford University Press, 1974.
- Roberts, J. A. Fraser and M. E. Pembry. *An Introduction to Medical Genetics*. 7th ed. Oxford: Oxford University Press, 1978.
- Roberts, J. A. Fraser and M. E. Pembry. *An Introduction to Medical Genetics*, 8th ed. Oxford: Oxford University Press, 1985.
- Rolleston, Humphrey. "Discussion of Prophylaxis of Mental Disorder." *British Medical Journal* 2 (31 October 1925), 781-784.
- Rosanoff, A. J. "Mendelism and Neuropathic Heredity: A Reply to Some of Dr. David Heron's Criticisms of Recent American Work." *Eugenics Record Office Bulletin* 11 (1914): 27-43.
- Rosanoff, A. J. and Florence I. Orr. "A Study of Heredity of Insanity in the Light of the Mendelian Theory." *Eugenics Record Office Bulletin* 5 (1911): 221-261.

- Rousseau, François., Patricia Rouillard, Marie-Lou Morel, Edward W. Khandjian, and Kenneth Morgan. "Prevalence of carriers of premutation-size alleles of the *FMR1* gene—and implications for the population genetics of the fragile X syndrome." *American Journal of Human Genetics* 57 no. 5 (November 1995): 1006-1018.
- Rousseau, F., L. J. Robb, P. Rouillard, and V. M. Der Kaloustian. "No mental retardation in a man with 40% abnormal methylation at the FMR-1 locus and transmission of sperm cell mutations as premutations." *Human Molecular Genetics* 3 (1994): 927-930.
- Rowland, L P., D. S. Wood, E. A. Schon, and S. DiMauro eds., *Molecular Genetics in Diseases of Brain, Nerve, and Muscle*, New York: Oxford University Press, 1989,
- Rowland, Lewis P. Ed. *Merritt's Neurology*. 11th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.
- Rubinsztein, D. C., W. Amos, J. Leggo, S. Goodburn, R. S. Ramesar, J. Old, R. Bontrop, R. McMahon, D. E. Barton, and M. A. Ferguson-Smith. "Mutational bias provides a model for the evolution of Huntington disease and predicts a general increase in disease prevalence." *Nature Genetics* 7 (August 1994): 525-530.
- Ruden, Douglas M., Mark D. Garfinkel, Li Xiao and Xiangyi Li. "Epigenetic Regulation of Trinucleotide Repeat Expansions and Contractions and the 'Biased Embryo' Hypothesis for Rapid Morphological Evolution." *Current Genomics* 6 no. 3 (May 2005): 145-155.
- Rüdin, Ernst. "Über Vererbung geistiger Störungen." *Zeitschrift für die Gesamte Neurologie und Psychiatrie* 81 (1923): 459-496.
- Rüdin, Ernst. *Studien über Vererbung und Entstehung geistiger Störungen. 1. Zur Vererbung und Neuentstehung Der Dementia Praecox*. Berlin: Verlag von Julius Springer, 1916.
- Ruggles Gates, R. "Human Genetics." *Nature* 144 (November 11, 1939): 821-822.
- Schalling, M., T. J. Hudson, K. H. Buetow, and D. E. Housman. "Direct detection of novel expanded trinucleotide repeats in the human genome." *Nature Genetics* 4 (June 1993): 135-139.
- Schenk, Faith and A. S. Parkes. "The Activities of the Eugenics Society." *Eugenics Review* 60 (1968): 142-161.
- Schuster, E. "Eugenics as a Branch of Medical Sociology." *Eugenics Review* 5 (1913): 270-273.

- Schuster, Edgar. "Methods and Results of the Galton Laboratory for National Eugenics." *Eugenics Review* 3 (1911): 10-24.
- Scott, Leslie, A. F. Tredgold, H. B. Brackenbury, Evelyn Fox. "Mental Deficiency. Case For Institutional Treatment." *The Times* (London), 20 January 1926, pg. 8, Issue 44174, col. D.
- Scott, Leslie, A. F. Tredgold, H. B. Brackenbury, Evelyn Fox. "Mental Deficiency. Case For Institutional Treatment." *The Times* (London), 20 January 1926, pg. 8, Issue 44174, col. D.
- Shaw, D. J., M. McCurrach, S. A. Rundle, H. G. Harley, S. R. Crow, R. Sohn, J. Thirion, M. G. Hamshere, A. J. Buckler, P. S. Harper, D. E. Housman, and J. D. Brook. "Genomic organization and transcriptional units at the myotonic dystrophy locus." *Genomics* 18 (1993): 673-679.
- Sherman, S. L. "A new genetic model for the fragile X syndrome involving an autosomal suppressor gene—comments on the paper by M. H. Israel." *American Journal of Medical Genetics* 26 (1987): 33-36.
- Sherrill, James. "The Diagnosis of Latent Incipient Diabetes." *Journal of the American Medical Association* 77 no. 23 (3 December 1921): 1779-1785.
- Simmons, Harvey G. *From Asylum to Welfare*. Downsview, ON: National Institute on Mental Retardation, 1982.
- Simmons, Harvey G. *Unbalanced: Mental Health Policy in Ontario, 1930-1989*. Toronto: Wall & Thompson, 1990.
- Sinden, R. R. and R. D. Wells. "DNA structure, mutations, and human genetic disease." *Current Opinions on Biotechnology* 3 (1992): 612-622.
- Siomi, Haruhiko., M. C. Siomi, R. L. Nussbaum and G. Dreyfuss. "The protein product of the fragile gene. *FMRI*, has characteristics of and RNA-binding protein." *Cell* 74 (1993): 291-298.
- Siomi, H., M. Choi, M. C. Siomi, R. L. Nussbaum and G. Dreyfuss. "Essential Role for KH Domains in RNA Binding: Impaired RNA Binding by a Mutation in the KH Domain of *FMR1* That Causes Fragile X Mutation." *Cell* 77 (April 8 1994): 33-39.
- Siomi, M. C., H. Siomi, W. H. Sauer, S. Srinivasan, R. L. Nussbaum, and G. Drayfuss. "FXR1, an autosomal homolog of the fragile X mental retardation gene." *EMBO J* 14 (1995): 2401-2408.

- Sjögren, Torsten. "Investigations of the Heredity of Psychoses and Mental Deficiency in Two North Swedish Parishes." *Annals of Eugenics* 6 (1934): 253-315.
- Slater, Eliot. "The Inheritance of Mental Disorder." *Eugenics Review* 28 (1936): 277-284.
- Smeets, H. J. M., A. P. T. Smits, C. E. Verheij, J. P. G. Theelen, R. Willemsen, I. van de Burgt, A. T. Hoogeveen, J. C. Oosterwijk, and B. A. Oostra. "Normal phenotype in two brothers with a full *FMR1* mutation." *Human Molecular Genetics* 4 (1995): 2103-2108.
- Smeets, H. J. M., W. M. Nillesen, F. Los, H. F. M. Busch, R. G. Kornelik, B. Wieringa, H. G. Brunner. "Prenatal diagnosis of myotonic dystrophy by direct mutation analysis." *Lancet* 340 no. 8813 (25 July 25 1992): 237-238.
- Snyder, Laurence H. *Medical Genetics: A Series of Lectures Presented to the Medical Schools of Duke University, Wake Forest College, and the University of North Carolina*. Durham NC: Duke University Press, 1941.
- Sorsby, Arnold. *Clinical Genetics*. London: Butterworth & Co. (Publishers) Ltd., 1953.
- Sorsby, Arnold. "Clinical Varieties of Genetic Disease." in *Clinical Genetics*, 2nd ed. A. Sorsby Ed. London: Butterworths, 1973, 76.
- Spillane, John and Robert Phillips. "Huntington's Chorea in South Wales." *Quarterly Journal of Medicine* 6 (1937): 403-423.
- Steinbach, P. "Mental impairment in Martin-Bell syndrome is probably determined by the interaction of several genes: simple explanation of phenotypic differences between unaffected and affected males with the same X chromosome." *Human Genetics* 72 (1986): 248-252;
- Steinberg, Arthur G. and Russell M. Wilder. "A Reconsideration of the Phenomenon of Anticipation in Diabetes Mellitus." *Proceedings of the Staff Meetings of the Mayo Clinic* 25 no. 23 (8 November 1950): 625-630.
- Steinberg, Arthur G. and Russell M. Wilder. "A Study of the Genetics of Diabetes Mellitus." *American Journal of Human Genetics* 4 no. 2 (June 1952): 113-135.
- Steinberg, Arthur G. and Russell M. Wilder. "An Analysis of the Phenomenon of "Anticipation" in Diabetes Mellitus." *Annals of Internal Medicine* 36 no. 5 (May 1952): 1285-1296.

- Stern, Curt. "Welche Möglichkeiten bieten die Ergebnisse der experimentellen Vererbungslehre dafür, daß durch verschiedene Symptome charakterisierte Nervenkrankheiten auf gleicher erblicher Grundlage beruhen?" *Nervenarzt* 2 (15 May 1929): 257-262.
- Stern, Curt. *Principles of Human Genetics*. San Francisco CA: Freeman and Co., 1949.
- Stern, Curt. *Principles of Human Genetics*. San Francisco: W. H. Freeman & Co., 2nd ed. 1960.
- Stevens, H. C. "Environment v. Heredity in Feeble-mindedness." *Eugenics Review* 9 (1917): 373-374.
- Stone, Theodore T. and Eugene I. Falstein. "Genealogical studies in Huntington's chorea." *Journal of Nervous and Mental Disease* 89 (1939): 795-809.
- Sutcliffe, J. S., D. L. Nelson, F. Zhang, M. Pieretti, C. T. Caskey, D. Saxe, and S. T. Warren. "DNA methylation represses *FMR-1* transcription in fragile X syndrome." *Human Molecular Genetics* 1 (1992): 397-400.
- Sutherland, G. R., E. A. Haan, E. Kremer, M. Lynch, M. Pritchard, S. Yu, and R. I. Richards. "Hereditary unstable DNA: a new explanation for some old genetic questions?" *Lancet* 338 no. 8762 (3 August 1991): 289-292.
- Suthers, G. K., S. M. Huson, and K. E. Davies. "Instability versus predictability: the molecular diagnosis of myotonic dystrophy." *Journal of Medical Genetics* 29 (1992): 761-765.
- Sutton, H. Eldon. *Introduction to Human Genetics*. 2nd ed. New York: Holt, Reinhart and Winston, 1975
- The Eugenics Society. *Annual Report 1932-1933*. London: The Eugenics Society, 1933.
- Thomasen, Eivind. *Myotonia: Thomsen's Disease (Myotonia Congenita), Paramyotonia, and Dystrophia Myotonica. A Clinical and Heredobiologic Investigation*. Denmark: Universitetsforlaget i Aarhus, 1948.
- Thompson, James S. and Margaret W. Thompson. *Genetics in Medicine*. Philadelphia: W. B. Saunders Company, 1966.
- Thurstone, L. L. and Richard L. Jenkins. *Order of Birth Parent-Age and Intelligence*. Chicago: University of Chicago Press, 1931.
- Tredgold, Alfred Frank. *A Text-Book of Mental Deficiency (Amentia)*. 6th ed. London: Baillière, Tindall, & Cox, 1937.

- Tredgold, Alfred Frank. *A Text-Book of Mental Deficiency (Amentia)*. 7th ed. London: Baillière, Tindall, & Cox, 1947. Reprinted 1949.
- Tredgold, A. F. *A Text-Book of Mental Deficiency (Amentia)*. Assisted by R. F. Tredgold. 8th ed. Baltimore: The Williams & Wilkins Company, 1952.
- Tredgold, A. F. "Art. 2.—The Study of Eugenics." *Quarterly Review* No. 433 (October, 1912): 43-67.
- Tredgold, A. F. "Eugenics and the Future Progress of Man." *Eugenics Review* 3 no. 2 (1911): 94-117.
- Tredgold, A. F. "Marriage Regulation and National Family Records." *Eugenics Review* 4 (1912): 74-90.
- Tredgold, A. F. *Manual of Psychological Medicine: For Practitioners and Students*. 2nd ed. London: Baillière, Tindall and Cox, 1945. Reprinted 1946.
- Tredgold, A. F. *Mental Deficiency (Amentia)*. London: Baillière, Tindall and Cox, 1908.
- Tredgold, A. F. *Mental Deficiency (Amentia)*, 2nd ed. revised. Toronto: The Macmillan Company of Canada, Ltd., 1914
- Tredgold, A. F. *Mental Deficiency (Amentia)*, 3rd ed. London: Baillière, Tindall and Cox, 1920.
- Tredgold, A. F. *Mental Deficiency (Amentia)*. 4th ed. revised, London: Baillière, Tindall and Cox, 1922.
- Tredgold, A. F. *Mental Deficiency (Amentia)*. 5th ed. Largely rewritten, London: Baillière, Tindall and Cox, 1929.
- Tredgold, A. F. *Mental Deficiency (Amentia)*. 5th ed. New York: William Wood and Co., 1929.
- Tredgold, A. F. "Mental Disease in Relation to Eugenics." *Eugenics Review* 19 no. 1 (April 1927): 1-11.
- Tredgold, A. F. "Mental Disease in Relation to Eugenics." *Lancet* 209 no. 5401 (5 March 1927): 526-528.
- Tredgold, A. F. "The feeble-minded – A social danger." *Eugenics Review* 1 (1909): 97-104.
- Tredgold, A. F. "The Study of Eugenics." *Quarterly Review* 214 no. 432 (July 1912): 43-67.

- Tredgold, R. F. and K. Soddy. *A Textbook of Mental Deficiency. First compiled by A. F. Tredgold.* Ninth Edition. London: Baillière, Tindall, & Cox, 1956.
- Tredgold, R. F. and K. Soddy. With the assistance of E. W. Dunkley, G. Rawlings, B. C. Marshall, J. F. Smith, D. A. Pond, and W. R. Trotter. *Tredgold's Textbook of Mental Deficiency (Subnormality).* Tenth Edition. London: Baillière, Tindall, & Cox, 1963.
- Tredgold, R. F. and K. Soddy. With the assistance of E. W. Dunkley, G. Rawlings, J. Gibson, D. W. Smith, B.C. Marshall, J. F. Smith, D. A. Pond, and W. R. Trotter. *Tredgold's Mental Retardation.* Eleventh Edition. London: Baillière, Tindall, and Cassell, 1970.
- Tsuang, Ming-Tso. "A Study of Pairs of Sibs both Hospitalized for Mental Disorder." *British Journal of Psychiatry* 113 no. 496 (1967): 283-310.
- Usher, C. H. "A Pedigree Showing Mental Defect in Four Generations." *Annals of Eugenics* 5 (1932): 56-58.
- Vanier, T. M. "Dystrophia myotonica in childhood." *The British Medical Journal* 2 (29 October 1960): 1284-1288.
- Verheij, C., C. E. Bakker, E. de Graaff, J. Keulemans, R. Willemsen, A. J. M. H. Verkerk, H. Galjaard, A. J. J. Reuser, A. T. Hoogeveen, and B. A. Oostra. "Characterization and localization of the *FMR-1* gene product associated with fragile X syndrome." *Nature* 363 (24 June 1993): 722-724.
- Verheij, C., E. de Graaff, C. E. Bakker, R. Willemsen, P. J. Willems, N. Meijer, H. Galjaard, A. J. J. Reuser, B. A. Oostra, and A. T. Hoogeveen. "Characterization of *FMR1* proteins isolated from different tissues." *Human Molecular Genetics* 4 (1995): 895-901.
- Verkerk, A. J. M. H., E. de Graaff, K. De Boule, E. E. Eichler, D. S. Konecki, E. Rayniers, A. Manca, A. Poustka, P. J. Willems, D. L. Nelson, and B. A. Oostra. "Alternative splicing in the fragile X gene in *FMR1*." *Human Molecular Genetics* 2 (1993): 399-404.
- Verkerk, A. J. M. H., M. Pieretti, J. S. Sutcliffe, Y. Fu, D. P. A. Kuhl, A. Pizzuti, O. Reiner, S. Richard, M. F. Victoria, F. Zhang, B. E. Eussen, G. B. van Ommen, L. A. J. Blonden, G. J. Riggins, J. L. Chastain, C. B. Kunst, H. Galjaard, C. T. Caskey, D. L. Nelson, B. A. Oostra, and S. T. Warren. "Identification of a Gene (*FMR-1*) Containing a CGG Repeat Coincident with a Breakpoint Cluster Region Exhibiting Length Variation in Fragile X Syndrome." *Cell* 65 (May 31, 1991): 905-914.

- Vincent A., D. Heitz, C. Petit, C. Kretz, I. Oberlé, and J. Mandel. "Abnormal pattern detected in fragile-X patients by pulsed-field gel electrophoresis." *Nature* 349 (1991): 624-626.
- Von Katzenstein-Sutro, Erich. "Beitrag zur Myotonischen Dystrophie." *Schweizer Archiv für Neurologie und Psychiatrie* 42 (1938): 249-297.
- von Monakow, C. "Sir Frederick Mott, K.B.E.: His Life and Work." In *Contributions to Psychiatry, Neurology and Sociology dedicated to the late Sir Frederick Mott, K.B.E. Hon.LL.D., M.D., F.R.C.P., F.R.S. by his colleagues, friends and former pupils*. Ed. J. R. Lord. London: H. K. Lewis & Co. Ltd., 1929, 383-389.
- Vos, T. A. "25 Years Dystrophia Myotonica (D.M.)." *Ophthalmologica* 141 (1961): 37-45.
- Waardenburg, Petrus Johannes. "Discussion." *Folia Psychiatrica, Neurologica et Neurochirurgica Neerlandica* 54 (1951): 193.
- Waardenburg, Petrus Johannes. *Bibliographia Genetica*. Vol. 7, *Das Menschliche Auge und seine Erbanlagen*, ed. J. P. Lötjens and W. A. Goddijn. The Hague: Martinus Nijhoff, 1932.
- Wasum, Kurt. "Chorea-Huntington-Sippe (Beschreibung einer an reiner Chorea Huntington erkrankten Sippe mit Stammbaum)." *Archiv für Psychiatrie und Nervenkrankheiten* 103 (1935): 78-100.
- Watson, J. D. and F. H. C. Crick. "Genetical Implications of the Structure of Desoxyribonucleic Acid." *Nature* 171 (30 May 1953): 964-967.
- Watson, J. D. and F. H. C. Crick. "Molecular Structure of Nucleic Acids. A Structure for Deoxyribose Nucleic Acid." *Nature* 171 (25 April 1953): 737-738.
- Watt, David. "Lionel Penrose, F.R.S. (1898-1972) and eugenics: Part One." *Notes and Records of the Royal Society* 52 (1988): 131-151.
- Watt, David. "Lionel Penrose, F.R.S. (1898-1972) and eugenics: Part Two." *Notes and Records of the Royal Society* 52 (1988): 339-354.
- Watters, G. V. and T. W. Williams. "Early onset myotonic dystrophy." *Archives of Neurology* 17 (1967): 137-152.
- Weatherall, D. J. *The New Genetics and Clinical Practice*. Oxford: Oxford University Press, 1982.
- Weatherall, D. J. *The New Genetics and Clinical Practice*. 2nd ed. Oxford: Oxford University Press, 1985.

- Webb, Sidney. "Eugenics and the Poor Law: The Minority Report." *Eugenics Review* 2 no. 3 (October 1910): 233-241.
- Webb, Sidney. *The Decline in the Birth-Rate*. London: The Fabian Society, 1907. Fabian Tract No. 131.
- Weber, James L. "Informativeness of Human (dC-dA)_n • (dG-dT)_n Polymorphisms." *Genomics* 7 (1990): 524-530.
- Weil, Max. "Correspondence: Genetic Defect." *New England Journal of Medicine* 266 no. 1 (4 January 1962): 54.
- Weil, Max and Bertram Allenstein. "A Report of Congenital Heart Disease in Five Members of One Family." *New England Journal of Medicine* 265 no. 14 (5 October 1961): 661-667.
- Weinberg, Wilhelm. "Auslesewirkungen bei biologisch-statistischen Problemen. I." *Archiv für Rassen und Gesellschafts Biologie* 10 no. 4 (1914): 417-451.
- Weinberg, Wilhelm. "Auslesewirkungen bei biologisch-statistischen Problemen. II." *Archiv für Rassen und Gesellschafts Biologie* 10 no. 5 (1914): 557-581.
- Welsh, Jack D, Gunter R. Haase, and T. E. Bynum. "Myotonic Muscular Dystrophy: Systemic Manifestations." *Archives of Internal Medicine* 114 no. 5 (1964): 669-679.
- Went, L. N., M. Vegter-van der Vlis, and G. W. Bruyn. "Parental transmission in Huntington's disease." *Lancet* 323 no. 8386 (19 May 1984): 1100-1102.
- Went, L. N., M. Vegter-van der Vlis, G. W. Bruyn, and W. S. Volkers. "Huntington's chorea in the Netherlands: the problem of genetic heterogeneity." *Annals of Human Genetics* 47 (1983): 205-214.
- Whetham, W. C. D. "Heredity and Destitution." *Eugenics Review* 3 (1911): 131-142.
- White, Hill Wilson. "The Investigation of Twenty-Five Pedigrees of Insane Persons." *Archives of Neurology and Psychiatry (London)* 6 (1914): 99-126.
- Whittinghill, Maurice. *Human Genetics and Its Foundations*. New York: Reinhold Publishing Corporation, 1965.
- Wiedemann, Hans-Rudolf and John Opitz. "In Memoriam: Widukind Lenz, 1919-1995." *American Journal of Medical Genetics* 65 no. 2 (16 October 1996): 142-145.

- Willems, Patrick J., B. Van Roy, K. De Boule, L. Vits, E. Reyniers, O. Beck, J. E. Dumon, A. Verkerk, and B. Oostra. "Segregation of the fragile X mutation from an affected male to his normal daughter." *Human Molecular Genetics* 1 (October 1992): 511-515.
- Wilson, Claude and Douglas Stanley. "A Sequel to some cases showing Hereditary Enlargement of the Spleen." *Transactions of the Clinical Society of London* 26 (1893): 163-171.
- Wöhrle, D., D. Kotzot, M. C. Hirst, A. Manca, B. Korn, A. Schmidt, G. Barbi, H. Rott, A. Poustka, K. E. Davies, and P. Steinbach. "A Microdeletion of Less than 250 kb, Including the Proximal Part of the FMR-1 Gene and the Fragile-X Site, in a Male with the Clinical Phenotype of Fragile-X Syndrome." *American Journal of Human Genetics* 51 (1992): 299-306.
- Wöhrle, D., I. Henning, W. Vogel, and P. Steinbach. "Mitotic stability of fragile X mutations in differentiated cells indicates early post-conceptual trinucleotide repeat expansion." *Nature Genetics* 4 (June 1993): 140-142.
- Woodyat, R. T. and M. Spetz. "Anticipation in the Inheritance of Diabetes." *Journal of the American Medical Association* 120 (24 October 1942): 602-605.
- Wootton, J. C. "The Investigation of a Number of Family Histories of Patients in Cane Hill Asylum." *Archives of Neurology and Psychiatry (London)* 6 (1914): 127-138.
- Yu, S., M. Pritchard, E. Kremer, M. Lynch, J. Nancarrow, E. Baker, K. Holman, J. C. Mulley, S. T. Warren, D. Schlessinger, G. R. Sutherland, R. I. Richards. "Fragile X Genotype Characterized by an Unstable Region of DNA." *Science* 252 no. 5009 (24 May 1991): 1179-1181.
- Zellweger, H and V. Ionasescu, *Myotonic Dystrophy and its Differential Diagnosis*, Copenhagen: Munksgaard, 1973.
- Zerbin-Rüdin, E and K. S. Kendler. "Ernst Rüdin (1874-1952 and His Genealogic-Demographic Department in Munich (1917-1986): An Introduction to Their Family Studies of Schizophrenia." *American Journal of Medical Genetics* 67 (1996): 332-337.
- Zhang, L., E. P. Leeflang, J. Yu, and N. Arnheim. "Studying human mutations by sperm typing: instability of CAG trinucleotide repeats in the human androgen receptor gene." *Nature Genetics* (August 1994): 531-535.
- Zhong, N., C. Dobkin, and W. T. Brown. "A complex mutable polymorphism located within the fragile X gene." *Nature Genetics* 5 (November 1993): 248-253.

Ziegler, Ernst. *General Pathology*. Translated and Updated by Aldred Scott Warthin.
New York: William Wood and Company, 1908. Originally published as
Allgemeinen Pathologie 11th ed. Jena: Gustav Fisher, 1905.

SECONDARY SOURCES

Unpublished Materials Including Dissertations

Coffin, Jean-Christophe. "Heredity, Milieu and Sin: the works of Bénédict Augustin Morel (1809-1873)." In *A Cultural History of Heredity II: 18th and 19th Centuries*. Preprint 222. Berlin: Max-Planck-Institut Für Wissenschaftsgechichte, 2003, 153-164.

Leeming, William. "Medical Specialization and Medical Genetics in Canada (1947 and After)." Ph.D. thesis, York University, 1999.

López-Beltrán, Carlos. "Human Heredity 1750-1870; The Construction of a Domain." PhD Thesis, King's College University of London, 1992.

Miller, Fiona Alice. "A Blueprint for Defining Health: Making Medical Genetics in Canada, c. 1935-1975." Ph.D. thesis, York University, 2000.

Articles and Books

Abir-Am, Pnina. "Beyond Deterministic Sociology and Apologetic History: Reassessing the Impact of Research Policy upon New Scientific Disciplines (Reply to Furst, Bartels, Olby and Yoxen)." *Social Studies of Science* 14 no. 2 (May, 1984): 252-263.

Abir-Am, Pnina. "The Biotheoretical Gathering, Trans-Disciplinary Authority and the Incipient Legitimation of Molecular Biology in the 1930s: New Perspective on the Historical Sociology of Science." *History of Science* 25 (1987): 1-70.

Abir-Am, Pnina. "The Discourse of Physical Power and Biological Knowledge in the 1930s: A Reappraisal of the Rockefeller Foundation's 'Policy' in Molecular Biology." *Social Studies of Science* 12 no. 3 (August 1982): 341-382.

Abir-Am, Pnina. "The Rockefeller Foundation and the rise of molecular biology." *Nature Reviews Molecular Cell Biology* 3 (January 2002): 65-70.

Abir-Am, Pnina. "The Rockefeller Foundation and the rise of molecular biology." *Nature Reviews Molecular Cell Biology* 3 (January 2002): 65-70.

Adams, Mark B. ed., *The Wellborn Science: Eugenics in Germany, France, Brazil, and Russia*. New York: Oxford University Press, 1990.

- Adams, Mark B., Garland E. Allen, and Sheila Faith Weiss. "Human Heredity and Politics: A Comparative Institutional Study of the Eugenics Record Office at Cold Spring Harbor (United States), the Kaiser Wilhelm Institute for Anthropology, Human Heredity, and Eugenics (Germany), and the Maxim Gorky Medical Genetics Institute (USSR)." *Osiris* 20 (2005): 232-262.
- Allan, Garland E. "The Eugenics Record Office at Cold Spring Harbor, 1910-1940: An Essay in Institutional History." *Osiris* 2 (1986): 225-264.
- Allen, Garland E. "Opposition to the Mendelian-Chromosome Theory: The Physiological and Developmental Genetics of Richard Goldschmidt." *Journal of the History of Biology* 7 no. 1 (1974): 49-92.
- Allen, Garland E. "The Misuse of Biological Hierarchies: The American Eugenics Movement, 1900-1940." *History and Philosophy of Life Sciences* 5 (1983):105-128.
- Anonymous. "Bittersweet anticipation: the logistics of inheritance." *Art & Research: A Journal of ideas, contexts, and methods* 1 no. 1 (Winter 2006/7), retrieved April 2, 2007, from <http://www.artandresearch.org.uk/v1n1/donachie.html>.
- Anonymous. "Obituary: A. F. Tredgold, M.D., F.R.C.P.." *British Medical Journal* 2 (27 September 1952): 726-727.
- Anonymous. "Obituary: Alfred Frank Tredgold M.D. Durh., F.R.C.P., F.R.S.E." *Lancet* 260 no. 6735 (27 September 1952): 642-643.
- Arksey, Hilary. "Expert and lay participation in the construction of medical knowledge." *Sociology of Health and Illness* 16 no. 4 (1994): 448-468.
- Ashley Jr., Claude T. and Stephen T. Warren. "Trinucleotide Repeat Expansion and Human Disease." *Annual Review of Genetics* 29 (1995): 703-728.
- Barker, David. "The Biology of Stupidity: Genetics, Eugenics and Mental Deficiency in the Inter-War Years." *British Journal for the History of Science* 22 (1989): 347-375.
- Bartels, Ditta. "The Rockefeller Foundation's Funding Policy for Molecular Biology: Success or Failure?" *Social Studies of Science* 14 no. 2 (May, 1984): 238-248.
- Batchelor, C., E. Parsons, P. Atkinson. "The Career of a Medical Discovery." *Qualitative Health Research* 6 (May 1996): 224-255.
- Bean, R. Bennet. "Human Types in Relation to Medicine." *American Naturalist* 61 no. 673 (March 1927): 160-172.

- Black, Edwin. *War Against the Weak: Eugenics and America's Campaign to Create a Master Race*. New York: Four Walls Eight Windows, 2003.
- Blacker, C. P. "Voluntary Sterilization: The Last Sixty Years." *Eugenics Review* 54 no. 1 (April 1962): 9-23.
- Bowler, Peter J. *Biology and Social Thought: 1850-1914*. Berkeley: Office for History of Science and Technology, University of California at Berkeley, 1993.
- Bowler, Peter J. "Development and Adaptation: Evolutionary Concepts in British Morphology, 1970-1914." *British Journal for the History of Science* 22 (1989): 283-297.
- Bowler, Peter J. *Evolution: The History of an Idea*. 3rd ed. Revised and expanded, Berkeley: University of California Press, 2003.
- Bowler, Peter J. *The Mendelian Revolution: The Emergence of Hereditarian Concepts in Modern Science and Society*. Baltimore: The Johns Hopkins University Press, 1989.
- Branford, William A.. "Nettleship, Edward (1845–1913)." In *Oxford Dictionary of National Biography*, edited by H. C. G. Matthew and Brian Harrison. Oxford: OUP, 2004. <http://www.oxforddnb.com/view/article/35201> (accessed February 20, 2006).
- Brannigan, Augustine. "The Reification of Mendel." *Social Studies of Science* 9 no. 4 (1979): 423-454.
- Brewster, Barry. Patricia Groenen and Bé Wieringa. "Myotonic Dystrophy: Clinical and Molecular Aspects." In *Neuromuscular Disorders: Clinical and Molecular Genetics*. Alan E. H. Emery Ed. Chichester: John Wiley and Sons, 1998, 323-364.
- Brock, D. J. H. *Molecular genetics for the clinician*. Cambridge: Cambridge University Press, 1993.
- Brogerg, Gunnar., and Nils Roll-Hansen. eds., *Eugenics and the Welfare State: Sterilization Policy in Denmark, Sweden, Norway, and Finland*. East Lansing, MI: Michigan State University Press, 1995.

- Brook, J. David, Mila E. McCurrach, Helen G. Harley, Alan J. Buckler, Deanna Church, Hiroyuki Aburatani, Kent Hunter, Vincent P. Stanton, Jean-Paul Thirion, Thomas Hudson, Robert Sohn, Boris Zemelman, Russell G. Snell, Shelley A. Flundle, Steve Crow, June Davies, Peggy Shelbourne, Jessica Buxton, Clare Jones, Vesa Juvonen, Keith Johnson, Peter S. Harper, Duncan J. Shaw, and David E. Housman. "Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member." *Cell* 68 (21 February 1992): 799-808.
- Bruyn, G. W. "Huntington's Chorea – Historical, Clinical and Laboratory Synopsis." In *Handbook of Clinical Neurology*. Vol. 6 Eds. P. J. Vinken and G. W. Bruyn. Amsterdam: North Holland Publishing Company, 1968, 298-378.
- Budney, Sarah. "Julia Bell MRCS LRCP FRCP (1979-1979). Steamboat lady, statistician and geneticist." *Journal of Medical Biography* 4 (1996): 8-13.
- Budney, Sarah. "Julia Bell MRCS LRCP FRCP (1979-1979). Steamboat lady, statistician and geneticist." *Journal of Medical Biography* 4 (1996): 8-13.
- Burbridge, David. "Francis Galton on twins, heredity and social class." *British Journal for the History of Science* 34 (2001): 323-340.
- Burian, Richard M, Jean Gayon and Doris Zallen. "The Singular Fate of Genetics in the History of French Biology, 1900-1940." *Journal of the History of Biology* 21 no. 3 (1988): 357-402.
- Burkhardt Jr., Richard. "Lamarckism in Britain and the United States." In *The Evolutionary Synthesis: Perspectives on the Unification of Biology*. Ernst Mayr and William Provine eds., Cambridge MA: Harvard University Press, 1980, 343-352.
- Bynum, W. F., Roy Porter, and Michael Shepherd eds. *The Anatomy of Madness: Essays In the History of Psychiatry*. Vol. 1, *People and Ideas*. London: Tavistock Publications, 1985.
- Campbell, Margaret. "The Concepts of Dormancy, Latency, and Dominance in Nineteenth-Century Biology." *Journal of the History of Biology* 16 no. 3 (Fall 1983): 409-431.
- Carlen, Claudia. ed., *The Papal Encyclicals: 1903-1939*. Ann Arbor MI: Pierian Press, 1990.
- Carlson, Elof Axel. "H. J. Muller and human genetics." In *The History & Development of Human Genetics: Progress in Different Countries, Washington DC, 6 October 1991*. Krishna Dronamraju, ed., Singapore: World Scientific, 1992, 21-47.

- Carlson, Elof Axel. *Mendel's Legacy: The Origin of Classical Genetics*. New York: Cold Spring Harbor Press, 2004.
- Carlson, Elof Axel. "The Eugenic World of Charles Benedict Davenport." In *Davenport's Dream: 21st Century Reflections on Heredity and Eugenics*. Eds. Jan A. Wikowski and John R. Inglis. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2008, 59-76.
- Carlson, Elof Axel. *The Gene: A Critical History*. Philadelphia: W. B. Saunders Company, 1966.
- Carlson, Elof Axel. *The Unfit: A History of a Bad Idea*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 2001.
- Carlson, Eric T. "Medicine and Degeneration: Theory and Praxis." In *Degeneration: The Dark Side of Progress*, ed. Edward J. Chamberlain and Sander L. Gilman, 121-144. New York: Columbia University Press, 1985.
- Cartron, Laure. "Degeneration and 'Alienism' in Early Nineteenth-Century France." In *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870*. Eds. Staffan Müller-Wille and Hans-Jörg Rheinberger. Cambridge MA: The MIT Press, 2007, 155-174.
- Caskey, C. Thomas. "DNA-Based Medicine: Prevention and Therapy." In *The Code of Codes: Scientific and Social Issues in the Human Genome Project*. Daniel J. Kevles and Leroy Hood Eds. Cambridge MA: Harvard University Press, 1992, 112-135.
- Chadarevian, Soraya de. *Designs for Life: Molecular Biology after World War II*. Cambridge: Cambridge University Press, 2002.
- Chamberlain, J. Edward and Sander L. Gilman eds. *Degeneration: The Dark Side of Progress*. New York: Columbia University Press, 1985.
- Chambers, Donald A. Ed. "DNA: The Double Helix: Perspective and Prospective at Forty Years." *Annals of the New York Academy of Sciences* 758 (1995).
- Churchill, Frederick B. "August Weismann and a Break from Tradition." *Journal of the History of Biology* 16 (1968): 91-112.
- Churchill, Frederick B. "From Heredity Theory to Vererbung: The Transmission Problem, 1850-1915." *Isis* 78 no. 3 (1987): 336-364.
- Cobb, Matthew. "Heredity before genetics: a history." *Nature Reviews Genetics* 7 (December 2007): 953-958.

- Cock, Alan. "William Bateson, Mendelism and Biometry." *Journal of the History of Biology* 6 no. 1 (1973): 1-36.
- Comfort, Nathaniel. "'Polyhybrid Heterogeneous Bastards': Promoting Medical Genetics in America in the 1930s and 1940s." *Journal of the History of Medicine and Allied Sciences* 61 no. 4 (2006): 415-455.
- Cowan, Ruth Schwartz. "Francis Galton's Contributions to Genetics." *Journal of the History of Biology* 5 no. 2 (1972): 389-412.
- Cowan, Ruth Schwartz. "Francis Galton's Statistical Ideas: The Influence of Eugenics." *Isis* 63 no 4 (1972): 509-528.
- Cowan, Ruth Schwartz. "Nature and Nurture: The Interplay of Biology and Politics in the Work of Francis Galton." *Studies in the History of Biology* 1 (1977): 133-208.
- Craver, Carl F. and Lindley Darden. "Introduction." *Studies in the History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 233-244.
- Crow, James F. "Hardy, Weinberg and Language Impediments." *Genetics* 152 (July 1999): 821-825.
- Darden, Lindley. "Relations among fields: Mendelian, cytological and molecular mechanisms." *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 349-371,
- Darden, Lindley. "William Bateson and the Promise of Mendelism." *Journal of the History of Biology* 10 no. 1 (1977): 87-106.
- Davies, Kay E. and Stephen T. Warren. Eds. *Genome Analysis Volume 7: Genome Rearrangement and Stability*. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 1993.
- Dawkins, Richard. *The Selfish Gene*. New Edition, Oxford: Oxford University Press, 1989.
- de Marrais, Robert. "The Double-Edged Effect of Sir Francis Galton: A Search for the Motives in the Biometrician-Mendelian Debate." *Journal of the History of Biology* 7 no. 1 (1974): 141-174.
- Deichmann, Ute. *Biologists under Hitler*. Translated by Thomas Dunlap. Cambridge MA: Harvard University Press, 1996.
- Dietrich, Michael R. "Richard Goldschmidt: hopeful monsters and other 'heresies'." *Nature Reviews Genetics* 4 (January 2003): 68-74.

- Dowbiggin, Ian Robert. "Degeneration and hereditarianism in French mental medicine 1840-90: psychiatric theory as ideological adaptation." In *The Anatomy of Madness: Essays in the History of Psychiatry*. Volume I: People and Ideas. Edited by W. F. Bynum, Roy Porter, and Michael Shepherd. London: Tavistock Publications, 1985, 188-232.
- Dowbiggin, Ian Robert. *Inheriting Madness: Professionalization and Psychiatric Knowledge in Nineteenth-Century France*. Berkeley: University of California Press, 1991.
- Dowbiggin, Ian Robert. *Keeping America Sane: Psychiatry and Eugenics in the United States and Canada, 1880-1940*. Ithaca: Cornell University Press, 1997.
- Dronamraju, Krishna R. *The Foundations of Human Genetics*. Springfield IL: Charles C Thomas, 1989.
- Dronamraju, Krishna, ed., *The History & Development of Human Genetics: Progress in Different Countries, Washington, DC, 6 October 1991*. Singapore: World Scientific, 1992.
- Dunn, L. C. "Cross Currents in the History of Human Genetics." *American Journal of Human Genetics* 14 (1962): 1-13.
- Dunn, L. C. "Ideas About Living Units, 1864-1909: A Chapter in the History of Genetics." In *Genetic Perspectives in Biology and Medicine*, ed. Edward D. Garber, 5-16. Chicago: University of Chicago Press, 1985.
- Edwards, A. W. F. *Foundations of Mathematical Genetics*. 2nd ed. Cambridge: Cambridge University Press, 2000.
- Emery, Alan E. H. *Elements of Medical Genetics*. 3rd ed. Edinburgh: Churchill Livingstone, 1974.
- Emery, Alan E. H. *Elements of Medical Genetics*. 5th ed. Edinburgh: Churchill Livingstone, 1979.
- Emery, Alan E. H. *Elements of Medical Genetics*. 6th ed. Edinburgh: Churchill Livingstone, 1983.
- Emery, Alan E. H. "Molecular Genetics of Neuromuscular Disorders: Applications in Clinical Medicine." In *Neuromuscular Disorders: Clinical and Molecular Genetics*. Alan E. H. Emery Ed. Chichester: John Wiley and Sons, 1998, 1-20.
- Emery, Alan E. H. and R. F. Mueller, *Elements of Medical Genetics*. 7th ed. Edinburgh: Churchill Livingstone, 1988.

- Emery, Alan E. H. and Robert F. Mueller. *Elements of Medical Genetics*. 8th ed. Edinburgh: Churchill Livingstone, 1992.
- Engel, Eric. "As Genes Do ... In Memoriam David Klein." *American Journal of Medical Genetics* 53 no. 3. (November 1994): 294-295.
- Farrall, Lyndsay Andrew. "Controversy and Conflict in Science: A Case Study – The English Biometric School and Mendel's Laws." *Social Studies of Science* 5 (1975): 269-301.
- Farrall, Lyndsay. "The History of Eugenics: a Bibliographical Review." *Annals of Science* 36 (1979): 111-123.
- Farrall, Lyndsay Andrew. *The Origins and Growth of the English Eugenics Movement 1865-1925*. New York: Garland Publishing, Inc., 1985.
- Fischer, Christine., Sabine Schweigert, Cord Spreckelsen, and Friedrich Vogel, "Programs, databases, and expert systems for human geneticists—a survey." *Human Genetics* 97 (1996): 129-137.
- Frank-Kamenetskii, Maxim. *Unravelling DNA: The Most Important Molecule of Life*. Reading, MA: Addison-Wesley, 1997.
- Fremantle, Anne. ed., *The Papal Encyclicals In Their Historical Context*. With and introduction by Gustave Weigel, S. J., Toronto: The New American Library of Canada Limited, 1963.
- Fuerst, John A. "The Definition of Molecular Biology and the Definition of Policy: The Role of the Rockefeller Foundation's Policy for Molecular Biology." *Social Studies of Science* 14 no. 2 (May, 1984): 22-237.
- Garber, Edward D, ed. *Genetic Perspectives in Biology and Medicine*. Chicago: University of Chicago Press, 1985.
- Gardner, A., R. T. Howell, and T. Davies. *Human Genetics*. London: Arnold, 2000.
- Geison, Gerald L. "Scientific Change, Emerging Specialties, and Research Schools." *History of Science* 19 no. 1 (March 1981): 20-40.
- Gelehrter, Thomas D., Francis S. Collins, David Ginsburg. *Principles of Medical Genetics*. 2nd ed. Baltimore: William & Wilkins, 1998.
- Gillham, Nicholas Wright. *A Life of Sir Francis Galton: From African Exploration to the Birth of Eugenics*. Oxford: Oxford University Press, 2001.

- Gilman, Stuart G. "Political Theory and Degeneration: From Left to Right, From Up to Down." In *Degeneration: The Dark Side of Progress*, ed. Edward J. Chamberlain and Sander L. Gilman, 165-198. New York: Columbia University Press, 1985.
- Glass, Bentley. "A Hidden Chapter of German Eugenics between the Two World Wars." *Proceedings of the American Philosophical Society* 125 no. 5 (October 1981): 357-367.
- Glennan, Stuart. "Modeling mechanisms." *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 443-464.
- Gokyigit, Emil. "The Reception of Francis Galton's Hereditary Genius." *Journal of the History of Biology* 27 (1994): 215-240.
- Gottesman, Irving I. and Askel Bertelsen. "Legacy of German Psychiatric Genetics: Hindsight Is Always 20/20." *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 no. 4 (26 July 1996): 317-322.
- Griffiths, Anthony J. F., Susan R. Wessler, Richard C. Lewontin, William M. Gelbart, David T. Suzuki, Jeffrey H. Miller. *Introduction to Genetic Analysis*. 8th ed. New York: W. H. Freeman and Company, 2005.
- Grob, Gerald N. "The Severely and Chronically Mentally Ill in America: Retrospect and Prospect." In *Sickness and Health in America: Readings in the History of Medicine and Public Health*, eds., Judith Walzer Levitt and Ronald L. Numbers, 334-348. Madison: University of Wisconsin Press, 1997.
- Haller, Mark H. *Eugenics: Hereditarian Attitudes in American Thought*. New Brunswick: Rutgers University Press, 1963.
- Harper, Peter S. "Julia Bell and the *Treasury of Human Inheritance*." *Human Genetics* 116 (2005): 422-432.
- Harper, Peter S. ed., *Landmarks in Medical Genetics: Classic Papers with Commentaries*. Oxford: Oxford University Press, 2004.
- Harper, Peter S. "Myotonic dystrophy and related disorders." In *Principles and Practice of Medical Genetics*. 2nd ed. Vol. 1. Alan E. H. Emery and David L. Rimoin, Eds. Edinburgh: Churchill Livingstone, 1990, 579-597.
- Harper, Peter S. *Myotonic Dystrophy*. 1st ed. Philadelphia: W. B. Saunders Company, 1979.
- Harper, Peter S. *Myotonic Dystrophy*. 2nd ed. London: W. B. Saunders Company, 1989.

- Harper, Peter S. "William Bateson, human genetics and medicine." *Human Genetics* 118 (2005): 141-151.
- Harper, Peter S. and P. R. Dyken. "Early onset dystrophia myotonica—evidence supporting a maternal environmental factor." *Lancet* 300 no. 7767 (8 July 1972): 53-55.
- Harper, Peter S., Helen G. Harley, William Reardon, and Duncan J. Shaw. "Anticipation in Myotonic Dystrophy: New Light on an Old Problem." *American Journal of Human Genetics* 51 no. 1 (July 1992): 10-16.
- Harris, Harry. "Lionel Sharples Penrose, 1898-1972 Elected F.R.S. 1953." *Biographical Memoirs of Fellows of the Royal Society* 19 (1973): 521-561.
- Harwood, Jonathan. "Editor's Introduction: Genetics, Eugenics and Evolution." *British Journal for the History of Science* 22 (1989): 257-265.
- Harwood, Jonathan. "National Styles in Science: Genetics in Germany and the United States between the World Wars." *Isis* 78 no. 3 (September 1987): 390-414.
- Harwood, Jonathan. *Styles of Scientific Thought: The German Genetics Community 1900-1933*. Chicago: University of Chicago Press, 1993.
- Herndon, C. Nash. "Genetics in the Medical School Curriculum." *American Journal of Human Genetics* 8 no. 1 (March 1956): 1-7.
- Hill, W. G. ed., *Quantitative Genetics, Part I: Explanation and Analysis of Continuous Variation*. New York: Van Nostrand Reinhold Company, 1984.
- Hill, W. G. ed., *Quantitative Genetics, Part II: Selection*. New York: Van Nostrand Reinhold Company, 1984.
- Hodge, M. J. S. "Generation and the Origin of Species (1837-1937): A Historiographical Suggestion." *British Journal for the History of Science* 22 (1989): 267-281.
- Holdroff, B. "Founding Years of Clinical Neurology in Berlin Until 1933." *Journal of the History of the Neurosciences* 13 no. 3 (September 2004): 223-238.
- Höweler, Christiaan. J., H. F. M. Busch, J. P. M. Geraedts, M. F. Niermeijer, and A. Staal. "Anticipation in Myotonic Dystrophy: Fact or Fiction?" *Brain* 112 no. 3 (June 1989): 779-797.
- Huertas, Rafael. "Madness and degeneration, I. From 'fallen angel' to mentally ill." Edited by C. M. Winston, *History of Psychiatry* 3 no. 12 (1992): 391-411.

- Jablonka, Eve. *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioural, and Symbolic Variation in the History of Life*. Cambridge MA: The MIT Press, 2005.
- Jackson, Mark. "Images of deviance: visual representations of mental defectives in early twentieth-century medical texts." *British Journal of the History of Science* 28 (1995): 319-337.
- Jones, Edgar and Shahina Rahman, "Framing Mental Illness, 1923-1939: The Maudsley Hospital and its Patients." *Social History of Medicine* 21 no. 1 (2008): 107-125.
- Jorde, Lynne B., John C. Carey, and Raymond L. White. *Medical Genetics*. St Louis: Mosby, 1995.
- Jorde, Lynne B., John C. Carey, Michael J. Bamshad and Raymond L. White. *Medical Genetics*. 2nd ed. St Louis: Mosby, 2000.
- Jorde, Lynne B., John C. Carey, Michael J. Bamshad and Raymond L. White. *Medical Genetics*. 3rd ed. St Louis: Mosby, 2003.
- Judson, Horace Freeland. "A History of Science and Technology Behind Gene Mapping and Sequencing." In *The Code of Codes: Scientific and Social Issues in the Human Genome Project*. Daniel J. Kevles and Leroy Hood Eds. Cambridge MA: Harvard University Press, 1992, 37-80.
- Judson, Horace Freeland. *The Eighth Day of Creation: Makers of the Revolution in Biology*. Expanded Edition. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 1996.
- Kay, Lily E. *The Molecular Vision of Life: Caltech, The Rockefeller Foundation, and the Rise of the New Biology*. New York: Oxford University Press, 1993.
- Kay, Lily. *Who Wrote the Book of Life: A History of the Genetic Code*. Stanford: Stanford University Press, 2000.
- Keller, Evelyn Fox. *The Century of the Gene*. Cambridge, MA: Harvard University Press, 2000.
- Kendler, Kenneth S. and Edith Zerbin-Rüdin. "Abstract and Review of "Zur Erbpathologie der Schizophrenie" (Contribution to the Genetics of Schizophrenia)." *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 no. 4 (26 July 1996): 343-346.

- Kendler, Kenneth S. and Edith Zerbin-Rüdin. "Abstract and Review of "Studien Über Vererbung und Entstehung Geistiger Störungen. I. Zur Vererbung und Neuentstehung der Dementia praecox." (Studies on the Inheritance and Origin of Mental Illness: I. To the Problem of the Inheritance and Primary Origin of Dementia Praecox." *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 no. 4 (26 July 1996):338-342.
- Kevles, Daniel. "Eugenics in North America." In *Essays in the History of Eugenics: Proceedings of a Conference organised by the Galton Institute, London, 1997.* ed., Robert Peel, London: The Galton Institute, 208-226.
- Kevles, Daniel J. "Genetics in the United States and Great Britain, 1890-1930: A Review with Speculations." *Isis* 71 no. 3 (September 1980): 441-455.
- Kevles, Daniel J. "Genetics in the United States and Great Britain 1890-1930: A Review with Speculations." In *Biology, Medicine and Society 1840-1940.* ed., Charles Webster. Cambridge: Cambridge University Press, 1981, 193-215.
- Kevles, Daniel J. *In the name of Eugenics: Genetics and the uses of human heredity.* with a new preface. Cambridge, MA: Harvard University Press, 1995.
- Kevles, Daniel J. "Out of Eugenics: The Historical Politics of the Human Genome." In *The Code of Codes: Scientific and Social Issues in the Human Genome Project.* Daniel J. Kevles and Leroy Hood Eds. Cambridge MA: Harvard University Press, 1992, 3-36.
- Kevles, Daniel J. and Gerald L. Geison. "The Experimental Life Sciences in the Twentieth Century." *Osiris* 10 (1995): 97-121.
- Kevles, Daniel J. and Leroy Hood. Eds. *The Code of Codes: Scientific and Social Issues in the Human Genome Project.* Cambridge MA: Harvard University Press, 1992.
- Keynes, Milo, A. W. F. Edwards, and Robert Peel, eds., *A Century of Mendelism in Human Genetics: Proceedings of a symposium organized by the Galton Institute and Held at the Royal Society of Medicine, London, 2001.* New York: CRC Press, 2004.
- Kingston, Helen. *ABC of Clinical Genetics.* London: British Medical Association, 1989.
- Klein, David. "Living History—Autobiography: Genetics and Environment From a Personal Perspective." *American Journal of Medical Genetics* 37 no. 3 (November 1990): 325-335.
- Klein, David. "Nécrologie: Professeur L. S. Penrose, 1898-1972." *Journal de Génétique Humaine* 20 no. 2 (1972): 177-178.

- Kline, Wendy. *Building a Better Race: Gender, Sexuality, and Eugenics from the Turn of the Century to the Baby Boom*. Berkeley: University of California Press, 2001.
- Klug, William S. and Michael R. Cummings. *Concepts of Genetics*. 2nd ed. Glenview IL: Scott, Foreman and Company, 1986.
- Klug, William S. and Michael R. Cummings. *Concepts of Genetics*. 4th ed. Engelwood Cliffs, NJ: Prentice Hall, 1994.
- Korf, Bruce R. *Human Genetics: A Problem-Based Approach*. Malden MA: Blackwell Science, 2000.
- Kühl, Stefan. *The Nazi Connection. Eugenics, American Racism, and German National Socialism*. Oxford: Oxford University Press, 1994.
- Kuhn, Thomas S. *The Structure of Scientific Revolutions*. 2nd ed. enlarged. Chicago: University of Chicago Press, 1970.
- Lane, Russell J. M., Peggy Shelbourne and Keith J. Johnson. "Myotonic Dystrophy." In *Handbook of Muscle Disease*. Russell J. M. Lane ed. New York: Marcel Dekker, Inc., 1996, 311-328.
- Laxova, Renata. "Lionel Sharples Penrose, 1898-1972: A Personal Memoir in Celebration of the Centenary of His Birth." *Genetics* 150 (December 1998): 1333-1340.
- Leavitt, Judith Walzer and Ronald L. Numbers, eds. *Sickness and Health in America: Readings in the History of Medicine and Public Health*, 3rd ed. rev. Madison: University of Wisconsin Press, 1997.
- Leeming, William. "Ideas about heredity, genetics, and 'medical genetics' in Britain, 1900-1982." *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 538-558.
- Leeming, William. "Professionalization theory, medical specialists and the concept of 'national patterns of specialization.'" *Studies of Science* 40 no. 3 (2001): 455-485.
- Leeming, William. "The Early History of Medical Genetics in Canada." *Social History of Medicine* 17 no. 3 (2004): 481-500.
- Lenz, Widukind. "Living History—Biography: Nature and Nurture." *American Journal of Medical Genetics* 37 no. 3 (November 1990): 356-361.
- Lewin, Benjamin. *Genes IV*. Oxford: Oxford University Press, 1990.

- Lewin, Benjamin. *Genes VIII*. Upper Saddle River NJ: Pearson Prentice Hall, 2004.
- Lloyd, G. E. R. ed., *Hippocratic Writings*. London: Penguin Books, 1983.
- López-Beltrán, Carlos. "Forging heredity: From metaphor to cause, a reification story." *Studies in History and Philosophy of Science* 25 no. 2 (April 1994): 211-235.
- López-Beltrán, Carlos. "In the Cradle of Heredity; French Physicians and *l'hérédité naturelle* in the Early 19th Century." *Journal of the History of Biology* 37 (2004): 39-72.
- López-Beltrán, Carlos. "Storytelling, statistics and hereditary thought: the narrative support of early statistics." *Studies in History and Philosophy of Biological and Biomedical Sciences* 37 (2006): 41-58.
- López-Beltrán, Carlos. "The Medical Origins of Heredity." In *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870*. Eds. Staffan Müller-Wille and Hans-Jörg Rheinberger. Cambridge MA: The MIT Press, 2007, 105-132.
- Lubinsky, Mark. "Degenerate Heredity: The History of a Doctrine I Medicine and Biology." *Perspectives in Biology and Medicine* 37 no. 1 (1993): 74-90.
- Ludmerer, Kenneth. "American Geneticists and the Eugenics Movement: 1905-1935." *Journal of the History of Biology* 16 (1969): 337-362
- MacKenzie, Donald. "Eugenics in Britain." *Social Studies of Science* 6 (September 1976): 499-532.
- MacKenzie, Donald A. "Sociobiologists in Competition: The Biometrician-Mendelian Debate." In *Biology, Medicine and Society 1840-1940*. ed., Charles Webster Cambridge: Cambridge University Press, 1981, 243-288.
- MacKenzie, Donald A. *Statistics in Britain 1865-1930: The Social Construction of Scientific Knowledge*. Edinburgh: Edinburgh University Press, 1981.
- Macnicol, John. "Eugenics and the Campaign for Voluntary Sterilization in Britain Between the Wars." *Social History of Medicine* 2 no. 2 (1989): 147-169.
- Macnicol, John. "In Pursuit of the Underclass." *Journal of Social Policy* 16 no. 3 (July 1987): 293-318.
- Macnicol, John. "The Voluntary Sterilization Campaign in Britain, 1918-1939." *Journal of the History of Sexuality* 2 no. 3 (January 1992): 422-438.
- Maddox, J. "Competition and the death of science." *Nature* 363 (24 June 1993): 667.

- Maddox, J. "Melodrama in research publication." *Nature* 355 (27 February 1992): 767.
- Mandel, Jean-Louis. "Trinucleotide diseases on the rise." *Nature Genetics* 7 (August 1994): 453-455.
- Margolis, Russell L., Melvin G. McInnis, Adam Rosenblatt, Christopher A. Ross. "Trinucleotide Repeat Expansion and Neuropsychiatric Disease." *Archives of General Psychiatry* 56 no. 11 (November 1999): 1019-1031
- Mayr, Ernst. "Prologue: Some Thoughts on the History of the Evolutionary Synthesis." In *The Evolutionary Synthesis: Perspectives on the Unification of Biology*. Ernst Mayr and William Provine eds., Cambridge MA: Harvard University Press, 1980, 1-48.
- Mayr, Ernst. "Weismann and Evolution." *Journal of the History of Biology* 16 (1985): 295-329.
- Mayr, Ernst and William B. Provine eds., *The Evolutionary Synthesis: Perspectives on the Unification of Biology*. Cambridge MA: Harvard University Press, 1980.
- Mazumdar, Pauline M. H. *Eugenics, Human Genetics and Human Failings: The Eugenics Society, its sources and its critics in Britain*. London: Routledge, 1992.
- Mazumdar, Pauline M. H. "Two Models for Human Genetics: Blood Grouping and Psychiatry in Germany between the World Wars." *Bulletin of the History of Medicine* 70 no. 4 (1996): 609-657.
- McInnis, Melvin G., Francis J. McMahon, Gary A. Chase, Sylvia G. Simpson, Christopher A. Ross, and J. Raymond DePaulo, Jr., "Anticipation in Bipolar Affective Disorder." *American Journal of Human Genetics* 53 (1993): 385-390.
- McKusick, Victor A. "History of medical genetics." In *Emery and Rimoin's Principles and Practice of Medical Genetics*. Vol. 1. 4th ed. Eds., David Rimoin, J. Michael Connor, Reed Pyeritz, and Bruce Korf. Edinburgh: Churchill Livingstone, 2002, 3-36.
- McKusick, Victor A. "Mendelian Inheritance in Man and Its Online Version, OMIM." *American Journal of Human Genetics* 80 no. 4 (April 2007): 588-604.
- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. Baltimore: Johns Hopkins University Press, 1966.

- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 2nd ed. Baltimore: Johns Hopkins University Press, 1968.
- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 3rd ed. Baltimore: Johns Hopkins University Press, 1971.
- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 4th ed. Baltimore: Johns Hopkins University Press, 1975.
- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 5th ed. Baltimore: Johns Hopkins University Press, 1978.
- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 6th ed. Baltimore: Johns Hopkins University Press, 1983.
- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 7th ed. Baltimore: Johns Hopkins University Press, 1986.
- McKusick, Victor A. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 8th ed. Baltimore: Johns Hopkins University Press, 1988.
- McKusick, Victor A., Clair A. Francomano, and Stylianos E. Antonarakis. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes*. 9th ed. Baltimore: Johns Hopkins University Press, 1990.
- McKusick, Victor A. "The Growth and Development of Human Genetics as a Clinical Discipline." *American Journal of Human Genetics* 27 (1975): 261-273.
- McLaren, Angus. *Our Own Master Race: Eugenics in Canada, 1885-1945*. Toronto: Oxford University Press, 1990.
- Micklos, David and Elof Carlson. "Engineering American society: the lesson of eugenics." *Nature Review Genetics* 1 (November 2000): 153-158.
- Miller, Fiona. "The importance of being marginal: Norma Ford Walker and a Canadian school of medical genetics." *American Journal of Medical Genetics* 115 no. 2 (2002): 102-110.

- Moore, John A. *Science as a Way of Knowing: The Foundations of Modern Biology*. Cambridge MA: Harvard University Press, 1993.
- Morgan, Kenneth O, ed. *The Oxford History of Britain*. Oxford: Oxford University Press, 2001.
- Motulsky, Arno. G. "Medical and Human Genetics 1977: Trends and Directions." *American Journal of Human Genetics* 30 (1978): 123-131.
- Motulsky, A. G. "The William Allan Memorial Award Lecture. Human and Medical Genetics: A Scientific Discipline and an Expanding Horizon." *American Journal of Human Genetics* 23 no. 2 (1971): 107-123.
- Müller-White, Staffan. and Hans-Jörg Rheinberger Eds., *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870*. Cambridge MA: The MIT Press, 2007.
- Müller-White, Staffan. and Hans-Jörg Rheinberger. "Heredity—The Formation of an Epistemic Space." In *Heredity Produced: At the Crossroads of Biology, Politics, and Culture, 1500-1870*. Eds. Staffan Müller-Wille and Hans-Jörg Rheinberger. Cambridge MA: The MIT Press, 2007, 3-34.
- Nairns, Brigham. Ed., *Notable Scientists from 1900 to the Present*. Vol. 2, Farmington Hills, MI: The Gale Group, 2001.
- Neel, James V. "Curt Stern, 1902-1981." *Annual Review of Genetics* 17 no. 1 (December 1983): 1-10.
- Neel, James V. "The 'Recovery' of Human Genetics." In *The History & Development of Human Genetics: Progress in Different Countries, Washington DC, 6 October 1991*. Krishna Dronamraju, ed., Singapore: World Scientific, 1992, 6-10.
- Nesbitt, Rebecca Gordon. "It's fascinating, it's beautiful, it's aesthetic, it's gorgeous; but, in the end, people are dying." In *Tomorrow Belongs to Me*. Jacqueline Donachie and Darren G. Monckton. Glasgow: University of Glasgow, 2006, 11-17.
- Norton, Bernard J. "Karl Pearson and Statistics: The Social Origins of Scientific Innovation." *Social Studies of Science* 8 no. 1 (February 1978): 3-34.
- Nussbaum, Robert L., Roderick R. McInnes, and Huntington F. Willard. *Thompson & Thompson: Genetics in Medicine*. 6th ed. Philadelphia: W. B. Saunders Company, 2001.

- Nussbaum, Robert L., Roderick R. McInnes, and Huntington F. Willard. *Thompson & Thompson: Genetics in Medicine*. 6th ed. Revised Reprint. Philadelphia: Saunders, 2004.
- Nye, Robert A. "Sociology and Degeneration: The Irony of Progress." In *Degeneration: The Dark Side of Progress*, ed. Edward J. Chamberlain and Sander L. Gilman, 49-71. New York: Columbia University Press, 1985.
- O'Malley, Maureen and Yan Boucher. "Paradigm change in evolutionary microbiology." *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 183-208.
- Olby, Robert C. "Mendelism and the Theory of Hereditary Diathesis." In *The History & Development of Human Genetics: Progress in Different Countries, Washington, DC, 6 October 1991*. Edited by Krishna Dronamraju. Singapore: World Scientific, 1992, 257-265.
- Olby, Robert C. *Origins of Mendelism*. With an introduction by C. D. Darlington. London: Constable and Company Ltd., 1966.
- Olby, Robert C. "The Dimensions of Scientific Controversy: The Biometric-Mendelian Debate." *British Journal of the History of Science* 22 (1988): 299-320.
- Olby, Robert C. *The Path to the Double Helix: The Discovery of DNA*. New York: Dover Publications, Inc., 1994.
- Olby, Robert C. "The Sheriff and the Cowboys: or Weaver's Support of Astbury and Pauling." *Social Studies of Science* 14 no. 2 (May, 1984): 244-247.
- Olby, Robert C. "William Bateson's Introduction of Mendelism to England: A Reassessment." *British Journal for the History of Science* 20 (1987): 399-420.
- Olson, Maynard V. "Davenport's Dream." In *Davenport's Dream: 21st Century Reflections on Heredity and Eugenics*. Eds. Jan A. Wikowski and John R. Inglis. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2008, 77-98.
- Opitz, John M. "David Klein: An Appreciation." *American Journal of Medical Genetics* 37 no. 3 (November 1990): 320-324.
- Opitz, John. M. "The American Journal of Medical Genetics—Forward." *American Journal of Medical Genetics* 1 no. 1 (1977): 1-2.
- Opitz, John M. and Hans-Rudolf Wiedermann. "In Memoriam: Widukind Lenz, 1919-1995." *American Journal of Medical Genetics* 65 no. 2 (October 1996): 142-145.
- Oxford English Dictionary Online*, 2nd ed., s.v. "Anticipate."

- Passarge, Eberhard. *Color Atlas of Genetics*. 2nd ed. Revised and Enlarged. New York: Thieme, 2001.
- Paul, Diane B. *Controlling Human Heredity: 1865 to the Present*. New Jersey: Humanities Press, 1995.
- Paul, Diane B. "Eugenics and the Left." *Journal of the History of Ideas* 45 no. 4 (1984): 567-590.
- Paul, Diane B. "Eugenic Origins of Medical Genetics." In *The Politics of Heredity: Essays on Eugenics, Biomedicine, and the Nature-Nurture Debate*. Albany, NY: State University of New York Press, 1988, 133-156.
- Paul, Diane B. "From Eugenics to Human Genetics." In *Controlling Human Heredity: 1865 to the Present*. Atlantic Highlands NJ: Humanities Press International, 1995, 115-135.
- Paul, Diane B. "Genes and Contagious Disease: The Rise and Fall of a Metaphor." In *The Politics of Heredity: Essays on Eugenics, Biomedicine, and the Nature-Nurture Debate*. Albany, NY: State University of New York Press, 1988, 157-171.
- Paul, Diane B. *The Politics of Heredity: Essays on Eugenics, Biomedicine and the Nature-Nurture Debate*. New York: State University of New York Press, 1998.
- Peel, Robert A, ed. *Essays in the History of Eugenics: Proceedings of a Conference organised by the Galton Institute, London, 1997*. London: The Galton Institute, 1998.
- Penrose, Lionel. S. *The Biology of Mental Defect*. With a preface by J. B. S. Haldane. London: Sidgwick and Jackson Limited, 1949.
- Penrose, L. S. "The Galton Laboratory: Its Work and Aims." *Eugenics Review* 41 no. 1 (1949): 17-27.
- Penrose, L. S. "The Problem of Anticipation in Pedigrees of Dystrophia Myotonica." *Annals of Eugenics* 14 (1948): 125-132.
- Pennisi, Elizabeth. "Genetics: A Ruff Theory of Evolution: Gene Stutters Drive Dog Shape." *Science* 306 no. 5705 (24 December 2004): 2172.
- Pick, Daniel. *Faces of Degeneration: A European Disorder, c. 1848-1918*. Cambridge: Cambridge University Press, 1989.

- Polge, Christopher. "Sir Alan Sterling Parkes. 10 September 1900 – 17 July 1990." *Biographical Memoirs of Fellows of the Royal Society* 52 (December 2006): 263-283.
- Portugal, Franklin H. and Jack S. Cohen. *A Century of DNA: A History of the Discovery of the Structure and Function of the Genetic Substance*. Cambridge MA: MIT Press, 1977.
- Provine, William. "England: Introduction." In *The Evolutionary Synthesis: Perspectives on the Unification of Biology*. Ernst Mayr and William Provine eds., Cambridge MA: Harvard University Press, 1980, 329-334.
- Provine, William. *The Origins of Theoretical Population Genetics*. Chicago: University of Chicago Press, 1971.
- Rabinow, Paul. *Making PCR: A Story of Biotechnology*. Chicago: University of Chicago Press, 1996.
- Ray, L. J. "Eugenics, Mental Deficiency and Fabian Socialism between the Wars." *Oxford Review of Education* 9 no. 3 (1983): 213-222.
- Reid, Robert G. B. *Biological Emergences: Evolution by Natural Experiment*. Cambridge MA: MIT Press, 2007.
- Roberts, J. A. Fraser. "Reginald Ruggles Gates. 1882-1962." *Biographical Memoirs of Fellows of the Royal Society* 10 (November 1964): 83-106.
- Roll-Hansen. "The Progress of Eugenics: Growth of Knowledge and Change in Ideology." *History of Science* 26 (1988): 295-331.
- Rosen, Christine. *Preaching Eugenics: Religious Leaders and the American Eugenics Movement*. Oxford: Oxford University Press, 2004.
- Rosner, Fred. "Judaism, Genetic Screening and Genetic Therapy." *Mt. Sinai Medical Journal* 65 no. 5&6 (1998): 406-413.
- Ruse, Michael. "Darwinism and mechanism: metaphor in science." *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 285-302.
- Rushton, Alan R. "Nettleship, Pearson and Bateson: The Biometric-Mendelian Debate in a Medical Context." *Journal of the History of Medicine and Allied Sciences* 55 (2000): 134-157.
- Sack, George H. *Medical Genetics*. New York: McGraw-Hill, 1999.

- Sapp, Jan. "The Struggle for Authority in the Field of Heredity, 1900-1932: New Perspectives on the Rise of Genetics." *Journal of the History of Biology* 16 no. 3 (Fall 1983): 311-342.
- Sapp, Jan. *Beyond the Gene: Cytoplasmic Inheritance and the Struggle for Authority in Genetics*. New York: Oxford University Press, 1987.
- Sapp, Jan. *Evolution by Association: A History of Symbiosis*. New York: Oxford University Press, 1994.
- Sapp, Jan. *Genesis: The Evolution of Biology*. Oxford: Oxford University Press, 2003.
- Sapp, Jan. *Where the Truth Lies: Franz Moewus and the Origins of Molecular Biology*. Cambridge: Cambridge University Press, 1990.
- Schenk, Faith and A. S. Parkes. "The Activities of the Eugenics Society." *Eugenics Review* 60 (1968): 142-161.
- Schneider, William H. *Quality and Quantity: The Quest for Biological Regeneration in Twentieth-Century France*. Cambridge: Cambridge University Press, 1990.
- Searle, G. R. "Eugenics and Class." In *Biology, Medicine and Society 1840-1940*. ed., Charles Webster. Cambridge: Cambridge University Press, 1981, 217-242.
- Searle, G. R. "Eugenics and Politics in Britain in the 1930s." *Annals of Science* 36 (1979): 159-169.
- Searle, G. R. *Eugenics and Politics in Britain: 1900-1914*. Leyden: Noordhoff International Publishing, 1976.
- Siegel, Sandra. "Literature and Degeneration: The Representation of "Decadence"." In *Degeneration: The Dark Side of Progress*, ed. Edward J. Chamberlain and Sander L. Gilman, 199-219. New York: Columbia University Press, 1985.
- Simmons, Harvey G. *Unbalanced: Mental Health Policy in Ontario, 1930-1989*. Toronto: Wall & Thompson, 1990.
- Snyder, Laurence H. "Old and New Pathways in Human Genetics." *American Journal of Human Genetics* 3 no. 1 (March 1951): 1-16.
- Soloway, Richard A. *Demography and Degeneration: Eugenics and the Declining Birthrate in Twentieth Century Britain*. Chapel Hill NC: University of North Carolina Press, 1990.

- Soloway, Richard. "From Mainline to Reform Eugenics – Leonard Darwin and C P Blacker." In *Essays in the History of Eugenics: Proceedings of a Conference organised by the Galton Institute, London, 1997*. ed., Robert Peel, London: The Galton Institute, 1998, 52-80.
- Soltan, Hubert C. "Lionel Penrose." In *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*. ed., H. C. Soltan, London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992, 36-40.
- Soltan, H. C. "Madge Macklin." In *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*. ed., H. C. Soltan, London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992, 11-26.
- Soltan, H. C. ed., *Medical Genetics in Canada: Evolution of a Hybrid Discipline. Essays on the Early History*. London ON: The University of Western Ontario Regional Medical Genetics Centre, 1992.
- Soltan, H. C. "The early history and development of human and medical genetics in Canada." In *The History & Development of Human Genetics: Progress in Different Countries, Washington DC, 6 October 1991*, Krishna Dronamraju, ed., Singapore: World Scientific, 1992, 57-82.
- Stepan, Nancy Leys. "Biological Degeneration: Races and Proper Places." In *Degeneration: The Dark Side of Progress*, ed. Edward J. Chamberlain and Sander L. Gilman, 97-120. New York: Columbia University Press, 1985.
- Stepan, Nancy Leys. *"The Hour of Eugenics" Race, Gender and Nation in Latin America*. Ithaca NY: Cornell University Press, 1991.
- Stern, Curt. "The Hardy-Weinberg Law." *Science* 97 no. 2510 (5 February 1943): 137-138.
- Sturtevant, A. H. *A History of Genetics*. Introduction by Edward B. Lewis. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2001.
- Sutherland, Grant R. and Robert I. Richards. "Anticipation Legitimized: Unstable DNA to the Rescue." *American Journal of Human Genetics* 51 no. 1 (July 1992): 7-9.
- Suzuki, David T., Anthony J. F. Griffiths, Jeffrey H. Miller, and Richard C. Lewontin. *An Introduction to Genetic Analysis*. 4th ed. New York: W. H. Freeman and Company, 1989.
- Tamarin, Robert H. *Principles of Genetics*. 5th ed. Dubuque IA: Wm. C. Brown Publishers, 1996.

- Theunissen, Bert. "Knowledge is power: Hugo de Vries on science, heredity and social progress." *British Journal of the History of Science* 27 (1994): 291-311.
- Thomson, Mathew. "Sterilization, segregation and community care: ideology and solutions to the problem of mental deficiency in inter-war Britain." *History of Psychiatry* 3 no. 12 (1992): 473-498.
- Thomson, Mathew. *The Problem of Mental Deficiency: Eugenics, Democracy, and Social Policy in Britain c. 1870-1959*. Oxford: Clarendon Press, 1998.
- Tiley, N. A. *Discovering DNA: Meditations of Genetics and a History of Science*. New York: Van Nostrand Reinhold Company, 1983.
- Timson, John. "Human Genetics." In *Essays in the History of Eugenics: Proceedings of a Conference organised by the Galton Institute, London, 1997*. ed., Robert Peel, London: The Galton Institute, 112-127.
- Trent, R. J. *Molecular Medicine: An Introductory Text for Students*. Edinburgh: Churchill Livingstone, 1993.
- Trent, R. J. *Molecular Medicine: An Introductory Text for Students*. 2nd ed. New York: Churchill Livingstone, 1996.
- Trent, R. J. *Molecular Medicine: An Introductory Text for Students*. 3rd ed. Amsterdam: Elsevier Academic Press, 2005.
- Vogel, Friedrich. "Widukind Lenz—An Encomium." *American Journal of Medical Genetics* 37 no. 3 (November 1990): 352-355.
- Vogel, Friedrich., and Arno G. Motulsky. *Human Genetics: Problems and Approaches*. 3rd ed. Berlin: Springer, 1997.
- Wallace, Bruce. "Changes in the Genetic Mentality." In *Genetic Perspectives in Biology and Medicine*, ed. Edward D. Garber, 79-91. Chicago: University of Chicago Press, 1985.
- Wallace, Bruce. *The Search for the Gene*. Ithaca: Cornell University Press, 1992.
- Waller, John C. "Becoming a Darwinian: the Micro-politics of Sir Francis Galton's Scientific Career 1859-65." *Annals of Science* 61 (2004): 141-163.
- Waller, John C. "Ideas of Heredity, Reproduction and Eugenics in Britain, 1800-1875." *Studies in History and Philosophy of Biological and Biomedical Sciences* 32 no. 3 (2001): 457-489.

- Waller, John C. "Parents and children: ideas of heredity in the 19th century." *Endeavour* 27 no. 2 (June 2003): 51-56.
- Waller, John C. "Poor Old Ancestors: The Popularity of Medical Hereditarianism, 1770-1870." In *A Cultural History of Heredity II: 18th and 19th Centuries*. Preprint 222. Berlin: Max-Planck-Institut Für Wissenschaftsgechichte, 2003, 131-144.
- Waller, John C. "'The Illusion of an Explanation': The Concept of Hereditary Disease, 1770-1870." *Journal of the History of Medicine* 57 (October 2002): 410-448.
- Warner, John Harley. "The History of Science and the Sciences of Medicine." *Osiris* 10 (1995): 164-193.
- Watt, David C. "Lionel Penrose, F.R.S. (1898-1972) and Eugenics: Part One." *Notes and Records of the Royal Society of London* 52 no. 1 (1998): 137-151.
- Watt, David C. "Lionel Penrose, F.R.S. (1898-1972) and Eugenics: Part Two." *Notes and Records of the Royal Society of London* 52 no. 2 (1998): 339-354.
- Weber, Matthias M. "Ernst Rüdin, 1874-1952: A German Psychiatrist and Geneticist." *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 no. 4 (26 July 1996): 323-331.
- Weber, Matthias M. "Psychiatric research and science policy in Germany. The history of the *Deutsche Forschungsanstalt für Psychiatrie* (German Institute for Psychiatric Research) in Munich from 1917 to 1945." *History of Psychiatry* 11 (2000): 235-258.
- Webster, Charles ed., *Biology, Medicine and Society 1840-1940*. Cambridge: Cambridge University Press, 1981.
- Weindling, Paul. *Health, race and German politics between national unification and Nazism, 1870-1945*. Cambridge: Cambridge University Press, 1989.
- Weingart, Peter. "German Eugenics between Science and Politics." *Osiris* 5 (1989): 260-282.
- Weindling, Paul. "The 'Sonderweg' of German Eugenics: Nationalism and Scientific Internationalism." *British Journal for the History of Science* 22 (1989): 321-333.
- Weiss, Sheila. "The Race Hygiene Movement in Germany 1904-1945." In *The Wellborn Science" Eugenics in Germany, France, Brazil, and Russia*. ed., Mark Adams. New York: Oxford University Press, 1990, 8-68.
- Wersksy, Gary. "Nature and Politics between the Wars." *Nature* 224 (November 1 1969): 462.472.

- Werskey, Gary. *The Visible College*. London: Penguin Books, Ltd., 1978.
- Who Was Who, 1981-1990*, 1991 ed., S. v. "PATERSON, Arthur Spencer."
- Who's Who*, 1984 ed. S. v. "PATERSON, Arthur Spencer."
- Winther, Ramsus G. "Darwin on Variation and Heredity." *Journal of the History of Biology* 33 (2000): 425-455.
- Witkowski, Jan A. "Charles Benedict Davenport, 1866-1944." In *Davenport's Dream: 21st Century Reflections on Heredity and Eugenics*. Eds. Jan A. Wikowski and John R. Inglis. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2008, 35-58.
- Witkowski, Jan A. and John R. Inglis Eds., *Davenport's Dream: 21st Century Reflections on Heredity and Eugenics*. Cold Spring Harbor NY: Cold Spring Harbor Laboratory Press, 2008.
- Young, Ian D. *Medical Genetics*. Oxford: Oxford University Press, 2005.
- Yoxen, Edward. "Scepticism about the Centrality of Technology Transfer in the Rockefeller Foundation Programme in Molecular Biology." *Social Studies of Science* 14 no. 2 (May, 1984): 248-252.
- Zerbin-Rüdin, Edith and Kenneth S. Kendler. "Ernst Rüdin (1874-1952) and His Genealogic-Demographic Department if Munich (1917-1986): An Introduction to Their Family Studies of Schizophrenia." *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 67 no. 4 (26 July 1996): 332-337.