


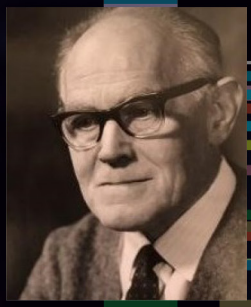

THE EVOLUTION OF MEDICAL GENETICS

A BRITISH PERSPECTIVE

PETER S. HARPER

CRC Press
Taylor & Francis Group








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Dedication

To all workers in the field of Medical Genetics, past, present and future; in Britain and elsewhere across the world.

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Preface

Why do I feel the need to write a book specifically on the history of medical genetics in *Britain*, rather than on the topic worldwide? There are several reasons, including the following:

First, I have already attempted to cover the field from an international perspective in my earlier (2008) book *A Short History of Medical Genetics*. While writing this I found that I had accumulated a large amount of material on British work and workers which was important, but which could not possibly be included in that book without unjustly omitting contributions from other countries. A second reason is that over the 12-year period from 2003 to 2016 I had been undertaking a series of recorded interviews, totalling more than 100 altogether, with key older scientists and clinicians in human and medical genetics, many of which were, for mostly logistic reasons, with British workers. Fortunately I had been able to make the transcripts available on the Web (www.genmedhist.org/interviews) as I went along, but they contained much material that I felt needed weaving together and synthesising into a more cohesive account; although I have tried to do this in some published papers, it was impossible to do the topic justice without the space and freedom provided by a book. I have quoted frequently from the interviews throughout the following chapters and they are listed in Appendix 2 (Table A2.4), being cited in the text by a number enclosed in square brackets [--].

A final reason, probably the most important, is that, in my opinion at least, Britain has indeed made particularly important contributions to the field of medical genetics, especially if one uses the term in its widest sense, as I have done here, to include both laboratory and clinical aspects, whether research or service orientated. Many of these contributions have been made by people who would not be considered, or consider themselves, as medical geneticists, but it has been this wide-ranging collaborative network, international as well as between UK individuals and groups, that has perhaps been the principal characteristic of British medical genetics, and probably its greatest strength. This is a community whose workers deserve to be remembered as a whole, even if many of them may not have individually made spectacular discoveries. The detailed record provided by the interview series again provides a graphic picture of the excitement felt by

these workers in the field and their enjoyment and pride in forming part of it, even when their contribution may only have been a small one.

Although little more than a decade ago there seemed to be a real danger that much of the more recent history of this field would be irretrievably lost, something urgently emphasised in my previous book, this is fortunately no longer the case, at least for Britain; Appendix 2 gives details of the now rich resource of material, both written and oral, that is available to historians and others for detailed and critical analysis, something that has only just begun, but which at least now has an abundance of facts to be based on. I have not attempted a detailed historical approach here, principally because I have been too involved personally, having seen much of modern medical genetics evolve over my own professional lifetime. I have, though, frequently expressed my own opinions throughout this book – perhaps indeed too frequently – so it will be good when historically trained workers study the field more objectively than I have been able to.

I need to note another limitation of this account, which results from my being primarily a clinician and clinical research worker; my emphasis is thus more on the clinical aspects of medical genetics than on the basic science and technology underpinning it. Likewise, I have frequently focused on the people responsible for advances and applications in the field more than on the detailed underlying science, and have also included a number of quotes and other material that some may consider too anecdotal.

Who have I written this book for? First and foremost, for my colleagues and friends working in medical genetics, and perhaps especially for those in allied fields, who are less likely to be familiar with the rich history of genetics in medicine. Equally I have had in mind those in medical genetics outside the UK, who will be familiar with much current British work but probably not with its origins and history. I hope, too, that historians will find the book of interest, since it touches on numerous themes that deserve more detailed study by them. And finally, given the widespread interest in genetics today among the wider public, some general readers should find it of interest and I have tried to write it simply, with them in mind.

I have recorded my principal sources in the text and the appendices, but have drawn extensively on my own experience of more than 50 years in various aspects of medical genetics. I also found of the greatest value the accounts given by those whom I interviewed of their own teachers and mentors, which reach back almost a century to the dawn of genetics and which supplement the incomplete written records from that time.

Acknowledgements

I owe a great debt to many people who have made it possible for me to write this book, though I must emphasise that the opinions expressed and any errors made are entirely my own responsibility.

My first thanks are due to all those who agreed to take part in the recorded interview series and to allow the edited transcripts to be placed in the public domain on the Web. I hope that many readers will take the opportunity to move from the brief quotes from these interviews given in this book to the full versions on www.genmedhist.org/interviews. An increasing number of interviewees are now no longer living, which makes me particularly glad that I was able to capture their memories in a permanent form.

Many workers across the UK have contributed photographs of themselves and of former colleagues. I thank them all, but must apologise to those numerous people whose photographs, for reasons of space, have not in the end been used; also to those, even more numerous, who are not mentioned in the book at all, an indication of how the field has grown in recent years. I am most grateful to Brian Marsh, of the University Hospital of Wales Media Resources Department, for greatly improving the quality of many of the illustrations.

My colleagues and successors in Cardiff, Julian Sampson and Angus Clarke, generously took on the onerous task of reading and criticising a full early draft of the book, making a number of helpful suggestions and correcting some major errors and omissions, while Peter Farndon (Birmingham) and Andrew Wilkie (Oxford) kindly reviewed specific chapters, making valuable comments.

Most of my own historical work has been carried out post-retirement, and has fortunately not required specific grant funding, but I must thank Wellcome Trust for its financial support of a number of areas of my work, notably the series of international workshops mentioned in Appendix 2, and for much general support and encouragement, which was especially valuable in the early stages before the overall project gained momentum. Cardiff University has continued to allow me access to its IT and other facilities, and I am especially grateful to Karen Pierce from Cardiff University libraries and to Peter Keelan, Alan Hughes and Alison Harvey from Cardiff University Special Collections and Archives. Cardiff University also hosted the Genetics and Medicine Historical Network

(Genmedhist) website for the first 12 years of its existence, something now continued by the European Society of Human Genetics.

In putting this book together from a large amount of previously scattered fragments and in the transcription of the recorded interviews I have been helped by a series of able and willing clerical workers, notably Christine Holness. All have given considerably more time to this than they were officially meant to, but equally they have all commented to me how interesting they found the topic, something which encourages me to think that other general readers may also enjoy it.

Taylor & Francis Group have proved helpful and sympathetic publishers and I am especially grateful to them for their tolerance in relation to the large number of illustrations in the book, something that I am sure readers will agree adds greatly to the interest of the book.

Finally, my family have, as always, continued to be supportive and tolerant of my book writing activities, even though they might reasonably have expected these to have ceased some years ago. I am deeply grateful for their support and affection, without which this book would never have been completed.

Cardiff
August 2019

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Forerunners: Genetics and medicine before World War II

ABSTRACT

The history of genetics in British medicine goes back several centuries, with a long series of articles on familial disorders, as well as of studies into the nature of heredity. The nineteenth century especially saw many detailed reports in the medical literature on hereditary conditions, but no underlying basis for their occurrence could be found until the recognition of Gregor Mendel's work in 1900. After this many of the previously observed families could be interpreted along mendelian lines, in studies by William Bateson and others, so that by 1914 the specific patterns of single gene inheritance were well established, with evidence from genetic disorders playing a major role in genetics overall. The quantitative aspects of normal human variation, originally studied by Francis Galton, likewise became well established and gave a basis for the inheritance of common non-mendelian diseases.

In the twentieth century, despite the initial lack of laboratory approaches, the period between the wars produced a series of highly original studies on human genetics by workers such as JBS Haldane, RA Fisher and others, so that the foundations for future medical genetics were largely in place by the outbreak of World War II.

Human and medical genetics have a long history, far longer than the history of genetics itself as a field of science. Physicians and others have over the centuries recorded familial aspects of disorders in patients under their care, even though most did not attempt any explanation for this. Natural philosophers across Europe from the earliest times, especially during the eighteenth century Enlightenment, speculated on the nature of heredity in animals and plants, and human inheritance was often at the forefront of their interest.

I do not attempt to cover these early aspects here in any detail. I have done so from a worldwide perspective in my earlier book *A Short History of Medical*

Genetics (Harper, 2008), where a fuller range of sources can also be found; others have done so for their own countries and fields of interest. Rushton's valuable book (2009), *Genetics and Medicine in Great Britain, 1600–1939*, gives detailed listings of early clinical reports. Here I give just a few examples that seem to me to be of particular relevance to the field of medical genetics, using the term in the widest sense, and where the contributions have been made by those living and working in Britain. It has always been a surprise to me how early were some of these observations, and how much we can still learn from them, particularly now that we have the detailed scientific knowledge which was lacking to observers and recorders at the time.

WILLIAM HARVEY (1578–1657) AND THE IMPORTANCE OF 'RARE DISORDERS'

William Harvey is now best remembered for his observations on circulation of the blood, but his wide-ranging observations and experimental studies on embryonic development led to his dictum *ex ovo omnia* — 'all things from the egg', as relevant to genetics as to embryology (Figure 1.1). Harvey's most detailed findings were on the developing hen's egg, but as physician to the king (Charles I) he had access to

Figure 1.1 William Harvey (1578–1657). (Courtesy of Royal College of Physicians, London.)

deer and other animals killed during royal hunts, and closely examined the fetal roe deer, including the amniotic fluid and membranes.

> I saw long since a foetus the magnitude of a peasecod cut out of the uterus of a doe, which was complete in all its members and I showed this pretty spectacle to our late King and Queen. It did swim, trim and perfect, in such a kinde of white, most transparent and crystalline moysture (as if it had been treasured up in some most clear glassie receptacle about the bignesse of a pigeon's egge, and was invested with its proper coat.
>
> *Harvey 1651; quoted in Needham J 1931; vol 1, page 139.*

Harvey's practical observations were enhanced by his willingness (like Charles Darwin two centuries later), to talk with and learn from those involved in practical matters, like huntsmen and gamekeepers.

Even more relevant for medical genetics is his often-quoted statement, in a 1652 letter to Dr Vlackweld of Haarlem, Netherlands, on the value of studying rare diseases:

> Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of useful or applicable nature is hardly perceived unless we are deprived of them, or they become deranged in some way.
>
> *Harvey 1652*

A number of mostly younger friends and colleagues of William Harvey, including Sir Thomas Browne and Nathaniel Highmore, continued his approach of direct observation and experiment, despite disruption, especially in London, from the civil war; Oxford was a major centre for these people, before the focus returned to London after restoration of the monarchy. The newly formed Royal Society now became the centre for exchange of ideas, rather than the Royal College of Physicians as previously. Invention and development of the compound microscope by Robert Hooke and others, notably Anton van Leeuwenhoek in the Netherlands, whose drawings of human sperm are especially notable, gave a new dimension, especially for studies of development, but clinical observations of inherited disorders in families also began to appear. One of the clearest of these was that reported by Kenelm Digby (1603–1665; Figure 1.2), who became a naval 'privateer' and during a visit to Algiers was fortunate enough to be given direct

Figure 1.2 Kenelm Digby (1603–1665). (Courtesy of National Portrait Gallery, London.)

access to a family with 'double thumbs' which he described from three members seen by himself and two older generations stated as affected:

> And another particular that I saw when I was at Algiers… was of a woman that having two thumbs upon the left hand; four daughters that she had all resembled her in the same accident, and so did a little child, a girl of her eldest daughter, but none of her sonnes. While I was there I had a particular curiosity to see them, although it is not easily permitted unto a Christian to speak familiarly with Mohametan women; yet the condition I was in there and the civility of the Bassha, gave me the opportunity of full view and discourse with them; and the old woman told me that her mother and grandmother had been in the same manner.
>
> *Digby 1645*

ALBINISM IN CENTRAL AMERICA AND LIONEL WAFER

One cannot always take the accounts of the early British explorers at face value, but there is no reason to doubt that the observation by Lionel Wafer (1660–1705?)

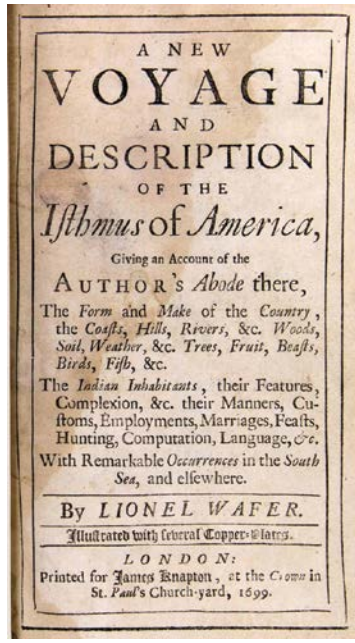

A NEW
VOYAGE
AND
DESCRIPTION
OF THE
Isthmus of *America*,
Giving an Account of the
AUTHOR's *Abode* there,
The *Form* and *Make* of the *Country*, the *Coasts*, *Hills*, *Rivers*, &c. *Woods*, *Soil*, *Weather*, &c. *Trees*, *Fruit*, *Beasts*, *Birds*, *Fish*, &c.
The *Indian Inhabitants*, their Features, Complexion, &c. their Manners, Customs, Employments, Marriages, Feasts, Hunting, Computation, Language, &c.
With Remarkable *Occurrences* in the *South Sea*, and elsewhere.
By *LIONEL WAFER*.
Illustrated with several Copper-Plates.
LONDON:
Printed for James Knapton, at the Crown in St. *Paul*'s Church-yard, 1699.

Figure 1.3 Lionel Wafer's book *'A New Voyage and Description of the Isthmus of America'* contains the first detailed description of albinism as 'white Indians' (Wafer, 1699).

of 'white Indians' in the isthmus of central America represents true albinism. Wafer, a ship's surgeon originally from Wales, was also one of the 'buccaneering' Caribbean explorers who combined serious observations with occasional piracy when the opportunity arose; a severe leg injury (from exploding gunpowder) gave him the enforced opportunity of living for several months with the local tribes, who seem to have been hospitable, and of making his observations in detail and at first hand, reporting them in a book (Wafer 1699; Figure 1.3), which is accessible in entirety as a facsimile on the internet.

White Indians

There is one complexion so singular among a sort of people of this country, that I never saw nor heard of any like them in any part of the world.

They are white, and there are of them of both sexes; yet there are few of them in comparison to the copper coloured, possibly but one to two or three hundred.

Their bodies are beset all over, more or less, with a fine short milk-white down, which adds to the whiteness of their skins.

Their eyebrows are milk-white also, and so is the hair of their heads and very fine withal.

> For they see not very well in the sun, poring in the clearest day; their eyes being weak, and running with water if the sun shines towards them, so that in the day-time they care not to go abroad, unless it be a cloudy dark day.
>
> They are not a distinct race by themselves, but now and then one is bred of a copper-coloured father and mother; and I have seen a child of less than a year old of this sort. But besides that the Europeans come little here, and have little commerce with the Indian women when they do come. These white people are as different from the Europeans in some respects, as from the copper-coloured Indians in others. And besides, where an European lies with an Indian women, the child is always a Mostese or Tawney, as is well known to all who have been in the West-Indies. But neither is the child of a man and women of these white Indians, white like the parents, but copper-coloured as their parents were.
>
> *Wafer 1699*

Albinism has been recognised since antiquity, but Wafer is probably the first to have described the inheritance pattern that with hindsight is clearly autosomal recessive. It would be another 200 years before this would be confirmed scientifically by Castle (1903). Wafer does, however, give one inconsistency, since he implies that offspring of two affected parents are of the normal 'coppery' colour, whereas one would expect, at least in a small population with a single mutation likely, all to be albino. He gives this as an observation made by someone else and does not distinguish it from the much more frequent situation where just one parent was affected, for which his statement would be correct.

JOHN DALTON (1766–1844)

A noted scientist of the late eighteenth century, ranging widely in his experimental work from meteorology to the properties of gases and other chemicals, and who first proposed a detailed atomic theory, Dalton (Figure 1.4) was the first person to note accurately what would later become recognised as X-linked inheritance, by recording colour blindness in himself and in family members. He spent most of his life in Manchester, and in his 1794 paper to the Manchester Literary and Philosophical Society he described his own anomalous colour vision:

> I have often seriously asked a person whether a flower was blue or pink, but was generally considered to be in jest. Notwithstanding this, I was never convinced of a peculiarity in my vision, till I accidentally observed the colour of the flower of the Geranium zonale by candle-light, in the Autumn of 1792. The flower was pink, but appeared to me almost an exact sky-blue by day; in candle-light, however, it was astonishingly changed, not having then any blue in it, but being what I called red, a colour which forms a striking contrast to blue.
>
> *Dalton 1798*

Figure 1.4 John Dalton (1766–1844). First identifier of red-green colour-blindness (he was himself affected). Portrait by Joseph Allen. (Courtesy of Harris Manchester College, Oxford University.)

He analysed his vision by a series of tests, made more rigorous by the fact that he was himself expert in optics. For the colour green, seen by daylight:

> I take my standard idea from grass. This appears to me very little different from red. The face of a laurel-leaf (Prunus Lauro-cerasus) is a good match to a stick of red sealing-wax; and the back of the leaf answers to the lighter red of wafers. Hence it will be immediately concluded, that I see either red or green, or both, different from other people.

His brother was similarly affected and, recognising that it seemed to be confined to males, Dalton obtained an approximate estimate of its frequency by sending strips of coloured thread to his past and present students, finding 3 out of 50 to have red-green colour-blindness, which has also been named 'Daltonism'. His studies have a modern postscript since in his will he left to the Manchester Literary and Philosophical Society not only his papers but his eyes, from which molecular geneticists 200 years later have been able to isolate DNA, which has confirmed a mutation for red-green colour-blindness (Hunt et al. 1995). Fortunately for posterity, the tissue had been allowed to dry, not placed in formalin fixative, so destructive to the preservation of DNA! At the time of this study the possibility of molecular analysis on such preserved tissue was novel, but it has since become

commonplace; only 20 years later the use of genetic and now whole genome analysis is revolutionising the entire field of human evolution and anthropology (see Chapter 11).

Mention should be made at this point of another important Enlightenment figure, the English mathematician and nonconformist clergyman *Thomas Bayes* (1702–1761), whose work on probability has become of key later importance in relation to genetic risk estimation. His notes were assembled and presented to the Royal Society of London after his death and a recent very readable book (McGrayne 2012) shows how widely his concepts are now applied. Medical geneticists have used them for over 50 years (see Chapter 6) and they have become very much an integral part of 'genetic thinking'.

JOSEPH ADAMS (1756–1818)

None of those people mentioned so far would seem to have had any concept of genetics playing a direct role in the practice of medicine, which makes Joseph Adams such an important figure for the future field of medical genetics. Adams wrote his book, *A Treatise on the Supposed Hereditary Properties of Diseases* (Figure 1.5), in 1814, not long before he died, so his views reflect his long experience in medical practice as well as his tolerant and humane

(a)

(b)

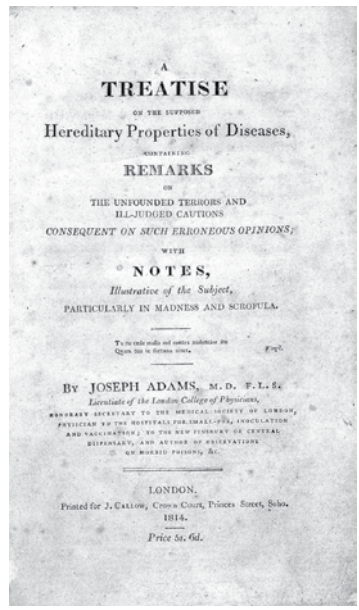

A
TREATISE
ON THE SUPPOSED
Hereditary Properties of Diseases,
CONTAINING
REMARKS
ON
THE UNFOUNDED TERRORS AND
ILL-JUDGED CAUTIONS
CONSEQUENT ON SUCH ERRONEOUS OPINIONS;
WITH
NOTES,
Illustrative of the Subject,
PARTICULARLY IN MADNESS AND SCROFULA.
BY JOSEPH ADAMS, M.D. F.L.S.
Licentiate of the London College of Physicians,
HONORARY SECRETARY TO THE MEDICAL SOCIETY OF LONDON,
PHYSICIAN TO THE HOSPITALS FOR SMALL-POX, INOCULATION
AND VACCINATION; TO THE NEW DISPENSARY, OR CENTRAL
DISPENSARY, AND AUTHOR OF OBSERVATIONS
ON MORBID POISONS, &c.
LONDON.
Printed for J. Callow, Crown Court, Princes Street, Soho.
1814.
Price 5s. 6d.

Figure 1.5 **(a)** Joseph Adams (1756–1818) and **(b)** his book (Adams 1814). Adams has been described as the first medical geneticist. (Courtesy of the Royal College of Surgeons, London.)

nature. He distinguished between *disposition*, by which he meant the clear-cut inheritance of a specific disorder, and *predisposition*, where a disorder would occur only in the presence of some environmental factor, which might itself be avoided:

> If the family or hereditary susceptibility is such, that the disease, though not existing at birth, is afterwards induced without any external causes, or by causes which can not be distinguished from the functions of the economy, such a state may be called, a DISPOSITION to the disease.
>
> But if the susceptibility, though greater than is remarked in other families, is so far less than a disposition as always to require the operation of some external cause to induce the disease; this minor susceptibility may be called, a PREDISPOSITION to the disease.

These categories correspond broadly to what we now recognise as mendelian and multifactorial diseases.

He also cautioned (see Chapter 6) against the advising of celibacy if there were a family history of mental illness, on the grounds that this might deprive society of some of those best suited to be parents. Later proponents of eugenics would have done well to heed his advice.

Two valuable articles on Joseph Adams by prominent medical geneticists, Arno Motulsky (1959) and Alan Emery (1989), have been written, while Adams' book itself has been digitised and placed on the website of the Genetics and Medicine Historical Network (www.genmedhist.org/digitalresources).

CHARLES DARWIN (1809–1883)

Although Charles Darwin's own theory of heredity, 'pangenesis', based on the migration of supposed particles ('gemmules') scattered throughout the body to the gonads, proved to be erroneous, his lifelong interest in variation and its causes led him to document a range of human genetic disorders (Darwin 1868, 1890), thanks to his extensive network of correspondents scattered across the world in various parts of the then British Empire. A notable example is given in the second edition of his book *The Variation of Animals and Plants under Domestication*:

> I may give an analogous case, communicated to me by Mr W Wedderburn, of a Hindoo family in Scinde, in which 10 men, in the course of four generations, were furnished, in both jaws taken together, with only four small and weak incisor teeth and with eight posterior molars. The men thus affected have very little hair on the body, and become bald early in life. They also suffer much during hot weather from excessive dryness of the skin. It is remarkable that no instance has occurred of a daughter being thus affected; and

> this fact reminds us how much more liable men are in England to become bald than women. Though daughters in the above family are never affected, they transmit the tendency to their sons; and no case has occurred of the son transmitting it to his sons. The affection thus appears only in alternate generations, or after longer intervals.
>
> *Darwin 1890*

This description can confidently be recognised today as the X-linked disorder hereditary anhidrotic ectodermal dysplasia and emphasises the value of accurate historic descriptions (and illustrations) of genetic disorders, as noted below.

GENETIC DISORDERS RECORDED BY CLINICIANS

A considerable number of nineteenth century British physicians recorded and published observations on familial disorders in patients under their care, and a detailed listing of these can be found in Rushton's book (Rushton 2009). Among these clinicians the early contribution of the London physician Edward Meryon, who gave the first description in 1852 of muscular dystrophy in boys (Meryon 1852) should not be forgotten, although Duchenne's 1862 full description and pictures of what is now known worldwide as 'Duchenne muscular dystrophy' gave more details of the clinical features, pathology and familial nature of this disorder, with its name understandably assigned to Duchenne himself. A valuable book by Alan and Marcia Emery (1995) gives a detailed history of the condition from its initial recognition to recent research on its molecular basis. There must be numerous other genetic disorders where a comparable historical approach would be possible and interesting, but so far my pleas to those who have written theses on such specific disorders to develop and publish their often lengthy historical introductions as fuller historical studies have fallen on deaf ears!

Other inherited disorders documented during the nineteenth century included numerous reports of haemophilia, though the first publications on this were of American families (Otto 1803, Hay 1813). Various forms of hereditary blindness were recorded, including optic atrophy and cataract, some of which later formed part of the *Treasury of Human Inheritance*, collated and analysed by Julia Bell (see below). For skin diseases Jonathan Hutchinson in London took a special interest in inheritance; after his death his papers were shipped to Johns Hopkins Hospital in Baltimore, where they were stored in the library basement; 50 years later, they were assiduously studied by the young Victor McKusick, still a cardiologist at the time (Harper 2012). Table 1.1 lists some of the disorders described by British clinicians that would now be recognised as following mendelian inheritance.

From the descriptions given in these reports and from many others in the medical literature, it can be seen that for the 200 years prior to the recognition

Table 1.1 Some early nineteenth century descriptions of inherited disorders by British clinicians

Disorder	Describer	Date
Aniridia (with microphthalmia)	Cooper	1857
Brittle bones (osteogenesis imperfecta)	Arnott	1833
Cataract, juvenile (numerous reports)	Saunders	1811
Haemophilia (numerous reports)	Osborne	1835
Hypertrichosis ('hairy men of Ava', Burma)	Hamilton	1827
Ichthyosis hystrix (Lambert family). Supposed Y chromosome inheritance disproved by Penrose and Stern (1958)	Machin	1732
Polydactyly	Carlisle	1814
Syndactyly	Thomson	1858

of Mendel's work there had been a near-continuous series of British reports on or relevant to human inheritance and inherited diseases, increasingly numerous in the mid and late nineteenth century; comparable examples could have also been given from France and America, but they do seem especially abundant in Britain and have been assiduously gathered together by Rushton (2009).

'ROYAL MALADIES'

While the British Royal family in the nineteenth century (and subsequently) has not been scientifically inclined, apart from the imported Prince Albert, it has supplied copious case material for discussion and speculation in relation to the occurrence of haemophilia (undoubted) and porphyria (less certain) among its members. This has been well studied and documented by Rushton (2008), though molecular analyses akin to those on John Dalton for colour blindness have so far not been conclusive.

FRANCIS GALTON (1822–1911)

Galton's name is now associated with two very different and largely opposed topics: eugenics, of which he was one of the first and most prominent British proponents, as well as the person who coined the term; and the Galton Laboratory at University College, London, which he endowed and which became the world's foremost centre for human genetics after World War II, under the leadership of Lionel Penrose (see Chapter 2), who was a fervent opponent of eugenics (Figure 1.6). The Galton Laboratory and its achievements are a recurring theme throughout this book, but the widely perceived association of anything bearing Galton's name with eugenics persists, something reinforced by the relatively recent (1989) and confusing name change of the former 'Eugenics Society' to 'Galton Institute' (see below).

Figure 1.6 Francis Galton (1822–1911). Founder of much of human quantitative genetics and of 'biometry'.

Francis Galton was a half first cousin to Charles Darwin, their shared grandfather being Erasmus Darwin. Born in Birmingham, he started to study medicine, but gave it up and instead read mathematics at Cambridge. With the advantage of an independent income, he embarked on travel, notably to South-west Africa (now Namibia), collecting his experiences into an early 'handbook', *The Art of Travel* (Galton, 1872). He settled down into an established London life, with his scientific work based on quantitative aspects of heredity, statistics, meteorology and a wide range of other topics – including eugenics, to which he gave the name. On his death he endowed what became the 'Galton Laboratory' and the Chair associated with it.

Galton's life has been well described in several biographies (Pearson 1914, Gilham 2001, Bulmer 2003); but what is relevant here is that he made indisputable major contributions to would later become the discipline of human genetics, especially the area of quantitative and statistical genetics known at the time as 'biometry'. Throughout his life he was a compulsive measurer, in a wide range of scientific fields apart from heredity, and his successors, notably Karl Pearson and Ronald Fisher, would provide many of the key contributions to statistics.

Galton, like his cousin Charles Darwin, was unaware of Mendel's work; while he himself formulated a possible system of particulate inheritance, and did not accept Darwin's 'pangenesis', he never developed his own ideas into a satisfactory foundation for heredity, the credit for which belongs entirely to Mendel himself. Nevertheless, Galton's quantitative approach did provide the foundations for the analysis of the genetic basis of normal variation, and in due course for the study of common birth defects and other polygenic disorders, which would be taken forward by Penrose, Falconer, Carter and others (Chapter 2) to give a parallel stream of knowledge that would later, alongside mendelism, underpin much of the practice, as well as the theory of medical genetics.

Among Galton's key contributions were his studies on fingerprints (though he was not their discoverer) and on human height, where he utilised the 1884 London International Health Exhibition to set up a booth to measure the large number of visitors, obtaining widespread biometric data on more than 9000 individuals. His analysis of human intelligence was flawed, though, by his failure to take into account the major biases resulting from social and educational factors. Outside the genetic field he, along with Robert Fitzroy (former captain of HMS Beagle, on which Charles Darwin had voyaged), pioneered the field of meteorology and weather forecasting, while his 'study of the efficacy of prayer', in which he showed no increased longevity

of the monarchy despite being prayed for weekly by millions across the country (Galton, 1872), proved to be a let-down for both royalty and clergy.

Mendel and mendelism

It seems irreverent to write on the history of genetics without any mention of Gregor Mendel, but by no stretch of the imagination could he be called British, though he did attend the Great Exhibition in London in 1851, but it is not known if he visited Galton's 'measuring booth'. His most notable 'connection' with Britain was his lack of connection with Darwin, which might have had a profound effect on both men and on science generally had it occurred.

Both Darwin and Galton had struggled, and largely failed, to come up with a convincing mechanism for heredity, despite their valuable contributions, so it is not surprising that when a satisfactory theoretical basis finally became available from Mendel's work (Mendel 1866), many of these early observations rapidly fell into place; the numerous family reports of rare disorders, involving a wide variety of different systems and specialists, now could be looked on as examples of a major general principle rather than just as curiosities. Conversely, examples from human disease provided much of the initial evidence confirming the existence and universality of mendelism. Perhaps surprisingly, this process of acceptance was much more rapid in Britain than for most other European countries, where much of the renewed interest in Mendel was from botanists and plant breeders, rather than physicians. Most of the credit for this progress is due to the energy and collaborative work of William Bateson who, more than anyone else worldwide, established both the universal application of mendelian inheritance and its importance in medicine.

WILLIAM BATESON (1861–1926)

The often-told story of Bateson's recognition of mendelism in 1900, while reading of its rediscovery on a train journey between Cambridge and London to lecture there and rewriting his text as a result, was included in Bateson's biography by his wife (Bateson B 1928a) (Figure 1.7). It is almost certainly no more than a story, but it shows how he, along with others, was receptive to a theory of heredity that could provide a new and unifying explanation for the many facts that had been accumulating since Mendel had published his original unrecognised paper 30 years before.

William Bateson was at the time primarily a zoologist, who had worked on anatomical variation in various species (Bateson W 1894) and had also made major explorations in Russian central Asia (Bateson B 1928b). Back in Cambridge he was finding difficulty in attracting interest or funding for his animal breeding work (a recurrent theme in this book for Cambridge workers over the following century), but after becoming aware of Mendel's work he realised the importance of establishing its applications outside Mendel's domain of plants.

Bateson was tireless in his efforts to promote mendelism, in Britain and internationally; his wider activities included the foundation of the *Genetical Society* (now *Genetics Society*) (Figure 1.8) in 1919; he was also the first to use the

Figure 1.7 William Bateson (1861–1926). Pioneer of mendelian inheritance and collaborator with medical workers on numerous inherited disorders. (Courtesy of the John Innes Archive, Norwich.)

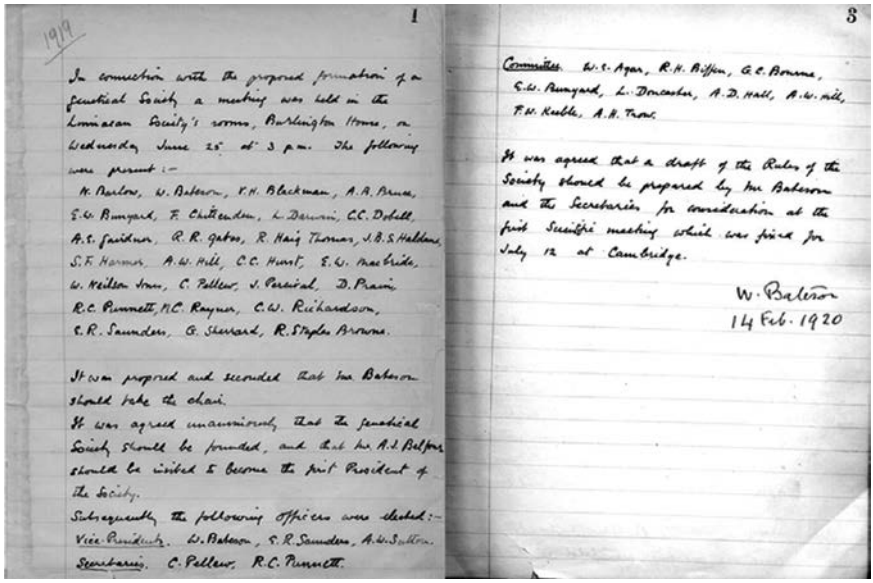
William Bateson was born in Cambridge and studied zoology there, making links with William Brooks at the Chesapeake Bay marine biology station attached to Johns Hopkins University. He then traveled widely in central Asia, analysing variation in the marine life in the various lakes there, work that would later inspire the famous Russian geneticist Nikolai Vavilov to work with him in Britain. Back in Cambridge he continued his work on the inheritance of anatomical variation, making him well prepared to recognise the importance of Mendel's principles when these were rediscovered in 1900. Cambridge University persistently refused to create an established department for him, and he was largely dependent on his wife Barbara in organising his breeding experiments. This lack of support led him to move to the new John Innes Horticultural Institution as its first director, remaining there up to his death in 1926.

word 'Genetics' for the field, a term that has worn well now for over a century. In a 1905 letter unsuccessfully suggesting that a bequest be used to establish a new Chair, he stated:

> If the Quick fund were used for the foundation of a Professorship relating to Heredity and Variation, the best title would, I think, be the Quick Professorship of the study of Heredity. No simple word in common use quite gives this meaning. Such a word is badly wanted, and if it were desirable to coin one, 'Genetics' might do.
>
> *18th April, 1905; letter [probably draft] in John Innes Archive.*

Like Harvey 250 years earlier, Bateson was well aware of the value of rare abnormalities, whether anatomical or physiological. As he states in his 1909 book *Mendel's Principles of Heredity*:

> Treasure your exceptions! When there are none, the work gets so dull that no one cares to carry it further. Keep them always uncovered and in sight. Exceptions are like the rough brickwork of a growing building which tells that there is more to come and shows where the next construction is to be.
>
> *Bateson 1909*


1919

1

In connection with the proposed formation of a Genetical Society a meeting was held in the Linnaean Society's rooms, Burlington House, on Wednesday June 25th at 3 p.m. The following were present:–

N. Barlow, W. Bateson, F.F. Blackman, A.A. Bruce, E.W. Bunyard, F. Chittenden, L. Darwin, C.C. Dobell, A.S. Gaidner, R.R. Gates, R. Hall Thomas, J.B.S. Haldane, S.F. Harmer, A.W. Hill, C.C. Hurst, E.W. Macbride, W. Neilson Jones, C. Pellew, J. Percival, D. Prain, R.C. Punnett, H.C. Rayner, C.W. Richardson, E.R. Saunders, G. Steward, R. Styles Browne.

It was proposed and seconded that Mr Bateson should take the chair.

It was agreed unanimously that the Genetical Society should be founded, and that Mr A.J. Balfour should be invited to become the first President of the Society.

Subsequently the following Officers were elected:–

Vice-Presidents. W. Bateson, E.R. Saunders, A.W. Sutton.

Secretaries. C. Pellew, R.C. Punnett.

3

Committee. W.T. Agar, R.H. Biffen, G.C. Bourne, E.W. Bunyard, L. Doncaster, A.D. Hall, A.W. Hill, F.W. Keeble, A.H. Trow.

It was agreed that a draft of the Rules of the Society should be prepared by Mr Bateson and the Secretaries for consideration at the first Scientific meeting which was fixed for July 12 at Cambridge.

W. Bateson
14 Feb. 1920

Figure 1.8 Foundation of the Genetical Society, minutes of the inaugural meeting 1920. Bateson was the first Secretary. (Courtesy of the John Innes Archive.)

Despite a somewhat gruff nature, reflected in most photographs of him (Figure 1.7 is the most genial that I could find), Bateson seems to have been a good communicator and collaborator, and soon established links with several London-based medical men; this not only provided ample evidence for the operation of mendelian inheritance, but generated a widespread interest in the topic among London medical circles. As early as 1906 he was invited to lecture on genetics to the London Neurological Society (see Chapter 4). Fortunately, much of Bateson's correspondence has been preserved in the archive of the John Innes Centre (now near Norwich, previously at Merton, outside London).

The best known of Bateson's medical collaborations was with the physician Archibald Garrod, whose interest in chemical abnormalities in disease had led him to study alkaptonuria, in which accumulation of the pigment homogentisic acid occurred in tissues and urine. After Garrod had published his 1901 paper showing occurrence of the disorder in sibs and frequent consanguinity among parents, Bateson wrote to him suggesting that this might be an example of mendelian recessive inheritance; Garrod was able to cite this in his fuller 1902 article and Bateson likewise cited Garrod in a paper with his colleague Elizabeth Saunders, also in 1902. Thus alkaptonuria became the first example of mendelism in human disease, being followed by albinism and by brachydactyly as an example of dominant inheritance, both of these observations coming from the American group of Castle (Castle 1903, Farabee 1905).

Garrod was able to use alkaptonuria as the foundation for his fundamental concept of 'inborn errors of metabolism', brought together in his book and Croonian lecture series under this title (Garrod 1908, 1909) and rightly placing him as the founder of human biochemical genetics.

Despite his fundamental discoveries, Garrod was not really interested in genetics in its own right. The most valuable collaborator for Bateson over the next decade was the ophthalmologist Edward Nettleship (see Chapter 4), who not only provided him with a wealth of detail on inherited eye disorders but corresponded with him widely on inheritance in general (though professing not to understand genetics). Nettleship even gave up his ophthalmologic practice to work on inherited eye disease and his contributions were recognised by the volume dedicated to him in Julia Bell's *Treasury of Human Inheritance* (see below) being given the title of the 'Nettleship Memorial Volume'.

By 1909 Bateson had sufficient material on human mendelian inheritance to bring together as a chapter in his book *Principles of Mendelian Heredity* (Bateson 1909). Non-lethal dominantly inherited disorders, likely to be multigenerational, are prominent in this, especially those affecting skin and eye; it is interesting that Bateson placed Huntington's disease as uncertain, the archived correspondence showing this to be mainly due to most affected individuals in previous generations being no longer living, with the diagnosis unconfirmed. This would prove to still be a problem 70 years later when the first genetic linkage studies on the condition were being done (see Chapter 12).

Although Bateson recognised a special category of 'sex limited' disorders, and the general field of sexual dimorphism had been studied for many years, by Darwin among others, the role of the sex chromosomes in human disease would not be recognised until the work of Wilson (1911) in America, though they had already been discovered in insects by Nettie Stevens in 1905. Bateson was, and for a long time remained sceptical about chromosomes generally. In relation to haemophilia, it was Nettleship again who helped him to avoid a serious error by insisting that the condition never passed from male to male, whereas Bateson had originally thought that half the male offspring of affected men were affected.

Bateson's early zoological work had focused on discontinuous structural variation, and his views on this had, even before the rediscovery of Mendel's work, brought him into conflict with Galton's followers Karl Pearson and Walter Weldon, who opposed any suggestions of particulate inheritance, including mendelism. The controversy deepened as the evidence for mendelian disorders increased, becoming personal when Weldon died suddenly and Bateson was blamed for this by his widow. It was partly to try to resolve this polarised situation that the London Royal Society of Medicine decided to have a debate on heredity and disease in November 1908, an event not seen previously in the world, and which had major consequences for what in the future would become medical genetics.

THE ROYAL SOCIETY OF MEDICINE 'DEBATE ON THE INFLUENCE OF HEREDITY AND DISEASE'

The Royal Society of Medicine had recently been formed in 1907 by a merger of a number of the principal London medical societies, including the London Neurological Society to which William Bateson had given his address in 1906

(Bateson 1906). Most of its members were practicing clinicians in various branches of medicine, and thus had extensive experience of families with unusual disorders in their particular field, though the subtitle of the event, 'with special reference to tuberculosis, cancer and diseases of the nervous system' indicates that they were also considering more common conditions. The meeting was held in weekly sessions over four successive weeks of November 1908 and was published in full in the Society's proceedings (Royal Society of Medicine 1909). A century later (2008) an anniversary meeting was held at the Royal Society of Medicine to mark the event.

The text shows that the views expressed by participants were pragmatic and sober (reflecting the recent death of Weldon during the preceding controversy). Bateson in particular was careful to emphasise that mendelian patterns should not be expected to be found in all disorders and that for common diseases the influence was likely to be on predisposition. Nevertheless the information presented by clinicians from various specialties strongly confirmed that Mendelian inheritance applied to numerous disorders across all systems.

The meeting effectively ended the conflict between 'mendelians' and 'biometricians', and it was left to RA Fisher, Pearson's successor in the Galton Chair, to point out that quantitative inheritance was entirely compatible with particulate mendelian inheritance, and that the conflict between the two groups had been largely unnecessary (Fisher 1918). We still see echoes of this division today, though, with some workers on common disease genetics tending to regard any focus on rare mendelian disorders as less relevant. Medical geneticists, though, have always recognised that the two categories each form essential parts of the overall whole picture of genetic disease; in this they are lineal descendants of Archibald Garrod a century earlier, and indeed of Joseph Adams two hundred years ago.

THE TREASURY OF HUMAN INHERITANCE

Following the Royal Society of Medicine debate, a further important step was the decision of Karl Pearson, the principal proponent for those favouring continuous rather than mendelian inheritance, and newly appointed as the first 'Galton Professor of Eugenics', to launch the *Treasury of Human Inheritance*, under the auspices of the Galton Laboratory. His idea was to publish the raw pedigree data on a range of human genetic disorders, leaving it to others to form opinions on the theoretical basis of their inheritance. Pearson had been bruised by the debates with Bateson and the increasingly successful supporters of mendelism.

> For a publication of this kind to be successful at the present time, it should, as I have indicated above, be entirely free from controversial matter. The Treasury of Human Inheritance therefore contains no reference to theoretical opinions.
>
> *Pearson 1912*

Figure 1.9 Julia Bell (1879–1979), principal author of the *Treasury of Human Inheritance*. For details of Bell's life and work see Bundey (1996) and Harper (2006).

While some of the initial sections were little more than a catalogue, the development of the *Treasury* was taken on as what would become her life's work by Julia Bell (Figure 1.9), who combined a thorough search of the world literature (something still possible at that time) with a detailed quantitative analysis of family data (Bell J, 1931–1947). While she followed Pearson's injunction to avoid 'theoretical opinions', it was clear from the data that most of the conditions studied did indeed follow mendelian inheritance, and after Pearson had retired, to be succeeded as Galton Professor and general editor of the *Treasury* by Ronald Fisher and even later by Lionel Penrose, she was able to state her conclusions on this clearly.

I have written elsewhere about the importance of Bell's work (Harper 2006), while a valuable article on her life has been written by Sarah Bundey (1996), but the lasting value of this monumental work makes the *Treasury* a permanent memorial for Julia Bell, reflecting not only her persistence over a period of 50 years, outliving three successive Galton Professors, but her combination of mathematical and clinical skills, not to mention her clarity of writing.

GH HARDY AND THE HARDY WEINBERG EQUILIBRIUM

Gregor Mendel himself built a mathematical approach into his experimental work, as did Francis Galton, but not all the early geneticists were mathematically inclined. William Bateson's skills in this area did not extend much beyond the mendelian ratios, nor did those of Thomas Hunt Morgan in America. A question that arose at the 1908 Royal Society of Medicine 'Debate' (see above) was why, if a disorder or trait followed dominant inheritance, did it not increase in relation to the normal allele in the general population?

Figure 1.10 GH Hardy (1877–1947). Cambridge mathematician and co-originator of the 'Hardy-Weinberg equilibrium'. (Courtesy Professor Anthony Edwards.)

Bateson and his colleague (and later successor in Cambridge) Reginald Punnett were unable to answer this; it is surprising that Karl Pearson did not, as he easily could have. Fortunately Punnett had as a friend the brilliant Cambridge mathematician GH Hardy (1877–1947; Figure 1.10), who, as related by Punnett (1950), not only produced the solution but was persuaded, reluctantly,

to write a brief note on the topic that was published in the American journal *Science*; the initial part is given below. Despite its brevity, Hardy's paper identifies the key factors that relate gene and genotype frequencies, and their stability over time.

> To the Editor of Science: I am reluctant to intrude in a discussion concerning matters of which I have no expert knowledge, and I should have expected the very simple point which I wish to make to have been familiar to biologists. However, some remarks of Mr. Udny Yule, to which Mr. R.C. Punnett has called my attention, suggests that it may still be worth making.
>
> In the Proceedings of the Royal Society of Medicine (Vol. I., p. 165) Mr. Yule is reported to have suggested, as a criticism of the Mendelian position, that if brachydactyly is dominant "in the course of time one would expect, in the absence of counteracting factors, to get three brachydactylous persons to one normal."
>
> It is not difficult to prove, however, that such an expectation would be quite groundless. Suppose that Aa is a pair of Mendelian characters, A being dominant, and that in any given generation the numbers of pure dominants (AA), heterozygotes (Aa), and pure recessives (aa) are as p:2q:r. Finally, suppose that the numbers are fairly large, so that the mating may be regarded as random, that the sexes are evenly distributed among the three varieties, and that all are equally fertile. A little mathematics of the multiplication table type is enough to show that in the next generation the numbers will be as
>
> $$(p + q)^2 : 2(p + q)\,(q + r) : (q + r)^2,$$
>
> or as
>
> $$P_1 : 2q_1 : r_1, \quad \text{say}$$
>
> The interesting question is - in what circumstances will this distribution be the same as that in the generation before? It is easy to see that the condition for this is $q^2 = pr$. And since $q_1^2 = p_1 r_1$, whatever the values of p,q and r may be, the distribution will in any case continue unchanged after the second generation.
>
> *Hardy 1908*

At the same time and independently, what became known as the 'Hardy-Weinberg equilibrium' was set out by Wilhelm Weinberg in Germany (Weinberg 1908). Unlike Hardy, who was, according to Punnett, totally uninterested in genetics, Weinberg was a physician with a strong interest in all aspects of heredity. He also proposed the 'Weinberg method' for correcting for ascertainment bias in pedigree analysis by deducting the proband.

JBS HALDANE AND HUMAN GENETICS

The life of John Burdon Sanderson Haldane (1892–1964), known universally as 'JBS', was a remarkable one, even without genetics forming part of it, but it is fair to say that no other single person contributed as much worldwide in advancing the field of genetics in the period between the two world wars and extending up to 1960 (Figure 1.11). Many of his main contributions were based on human genetic disorders, even though he was himself not medically trained (indeed he admitted that he had no formal biological training or degree whatsoever). Some of these contributions are listed in Table 1.2.

Haldane also had a gift for expressing himself clearly and simply in articles for the general public on genetics and other topics, notably in his regular pieces for the Communist party newspaper, the *Daily Worker*. Always controversial and often inconsistent over political matters, he brought the field of genetics into the public eye in a way that has probably not been seen since. Despite this he was apparently a hopeless lecturer, according to some of his London University students, several of whom I was able to interview (see Appendix 2).

Haldane's early career was passed in the Cambridge biochemistry department headed by Frederick Gowland Hopkins, giving him a clear appreciation of the relationship of enzymes to genetics, but his ideas found fullest expression in the remarkable scientific environment of University College, London, where

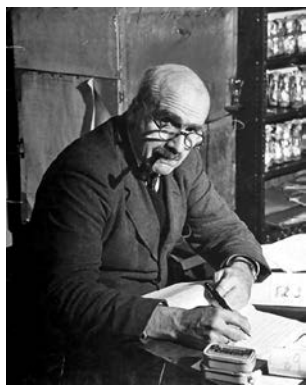


Figure 1.11 JBS Haldane (1892–1964). (Courtesy of Professor Peter Kalmus.)

Born in Oxford, son of the renowned physiologist John Scott Haldane, JBS Haldane studied Classics at Oxford, but had already begun his first experiments in genetics at home with his work on genetic linkage (then termed 'reduplication') in mice. He was severely wounded in World War I, and in 1923 joined the new Cambridge biochemistry department under Frederick Gowland Hopkins, also linking with Bateson's John Innes Institute. In 1933 he moved to University College, London, in a succession of Chairs, and remained based there (with an interruption from joining the International Brigade in the Spanish civil war) until 1957, when he moved to India for the last years of his life, which were shortened by colorectal cancer. Haldane's active political life as a communist party member was somehow combined with dangerous war-related submarine physiology research for the government during World War II. He eventually left the Party, after much prevarication, following the Russian suppression of genetics by Lysenko and Stalin. The biography by Clark (1968) gives a fascinating account of his colourful, contradictory, but scientifically highly important life and career.

Table 1.2 JBS Haldane: some contributions to human genetics

Mutation rate of a human gene (haemophilia), 1935
First human gene linkage (haemophilia, with Julia Bell), 1937
Use of linked markers in genetic prediction (1937)
Modifying genes in human inherited disorders (1941)
Selective advantage of sickle haemoglobin against malaria (1949)

workers at the Galton Laboratory (Julia Bell, RA Fisher, Lionel Penrose), and allied departments (Hans Grüneberg, John Maynard-Smith), as well as Lancelot Hogben at the neighbouring London School of Economics, gave full scope for interaction and debate, making it hard at times to assign a contribution to one person in particular. In my own interviews with a number of students of these workers during this period (see Appendix 2), an indication can be obtained of the atmosphere of this unique circle.

Haldane's special skill was to combine the data collected by others on human inherited disorders with his own mathematical abilities so as to extract every possible fragment of information on genetic problems that must at that time have seemed intractable, such as mutation rate (haemophilia and tuberous sclerosis) and genetic linkage (haemophilia again; see Chapter 12). He also laid the foundations for the 'formal analysis' of genetic disorders and, along with Fisher (see below), and Sewall Wright in America, for population genetic analysis. He predicted (1936) the future use of genetic linkage data for the presymptomatic testing of genetic disorders and suggested selective advantage as the reason for maintaining genetic polymorphism in sickle cell disease.

Two other British workers who, alongside Haldane, made major contributions to advancing genetics in the inter-war period were Ronald (RA) Fisher (Figure 1.12a) and Lancelot Hogben (Figure 1.12b). Both were highly skilled mathematically, and their work ranged over a wide variety of topics and species, including human genetics, though neither was medically trained. While they were no longer alive at the time of my recorded interview series, I was able to interview a number of their former students (see Appendix 2); their character, as with Haldane, emerges more clearly, perhaps, from these interviews than it might have done from direct interviews during their lifetime, though the numerous anecdotes have doubtless evolved over the years! It is interesting too, how these various students have reflected their mentors' characteristics and are often fiercely loyal to their reputations. Good biographies also exist, though those of Haldane (Clark 1968) and Hogben (Hogben and Hogben 1998) focus mainly on their wider life. Clark's book contains a complete bibliography of Haldane's remarkably varied writings. Fisher's biography is by his daughter Joan (Box 1978), herself a scientist.

Fisher, after some years based at the Rothamsted Agricultural Station, followed Karl Pearson in the Galton Chair at University College London (UCL) and in theory was a supporter of eugenics, though he quarrelled with the British Eugenics Society, whose policies he considered were unsound scientifically. Many of his statistical methods have continued in use for experimental analysis until