History of Human Genetics*

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Abstract Theories and studies in human genetics have a long history. Observations on the inheritance of physical traits in humans can even be found in ancient Greek literature. In the eighteenth and nineteenth centuries observations were published on the inheritance of numerous diseases, including empirical rules on modes of inheritance. The history of human genetics as a theory-based science began in 1865, when Mendel published his Experiments on Plant Hybrids and Galton his studies on Hereditary Talent and Character. A very important step in the development of human genetics and its application to medicine came with Garrod's demonstration of a Mendelian mode of inheritance in alkaptonuria and other inborn errors of metabolism (1902). Further milestones were Pauling's elucidation of sickle cell anemia as a "molecular disease" (1949), the discovery of genetic enzyme defects as the causes of metabolic disease (1950s, 1960s), the determination that there are 46 chromosomes in humans (1956), the development of prenatal diagnosis by amniocentesis (1968–1969) for the detection of chromosomal defects such as Down syndrome, and the large-scale introduction of molecular methods during the last 25 years. Concepts appropriated from human genetics have often influenced social attitudes and introduced the eugenics movement. Abuses have occurred, such as legally mandated sterilization, initially in the United States and later more extensively in Nazi Germany, where the killing of mentally impaired patients was followed by the genocide of Jews and Romani (Gypsy) people.

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The history of human genetics is particularly interesting since, unlike in many other natural sciences, concepts of human genetics have often influenced social and political events. At the same time, the development of human genetics as a science has been influenced by various political forces. Human genetics because of its concern with the causes of human variability has found it difficult to either remain a pure science or one of strictly medical application. Concerns regarding the heritability of IQ and the existence of inherited patterns of behavior again have brought the field into public view. A consideration of the history of human genetics with some attention to the interaction of the field with societal forces is therefore of interest. We will concentrate our attention on historical events of particular interest for human genetics and refer to landmarks in general genetics only insofar as they are essential for the understanding of the evolution of human genetics.

Recently, an excellent history of medical genetics was published by the medical geneticist Peter Harper in 2008 [38]. This highly readable book with many photographs presents critical assessments of various developments in the field since its beginnings. Many tables document major discoveries and a detailed timeline of both human and medical genetics presents important developments ranging from early discoveries to recent findings. This book is currently the only major comprehensive text devoted to the history of human/medical genetics.

A 30-page "History of Medical Genetics" by Victor McKusick was published as Chap. 1 in Emery and Rimoin's *Principles and Practice of Medical Genetics*, 5th edition, 2007 [59]. This remarkably comprehensive chapter emphasizing clinical aspects starts with a brief description of pre-Mendelian concepts and ends with a broadly conceived assessment of current and future trends of medical genetics.

1.1 The Greeks (see Stubbe [83])

Prescientific knowledge regarding inherited differences between humans has probably existed since ancient times. Early Greek physicians and philosophers not only reported such observations but also developed some theoretical concepts and even proposed "eugenic" measures.

In the texts that are commonly ascribed to Hippocrates, the following sentence can be found:

> Of the semen, however, I assert that it is secreted by the whole body – by the solid as well as by the smooth parts, and by the entire humid matters of the body … The semen is produced by the whole body, healthy by healthy parts, sick by sick parts. Hence, when as a rule, baldheaded beget baldheaded, blue-eyed beget blue-eyed, and squinting, squinting; and when for other maladies, the same law prevails, what should hinder that longheaded are begotten by longheaded?

This remarkable sentence not only contains observations on the inheritance of normal and pathological traits but also a theory that explains inheritance on the assumption that the information carrier, the semen, is produced by all parts of the body, healthy, and sick. This theory became known later as the "pangenesis" theory. Anaxagoras, the Athenian philosopher (500–428 B.C.), had similar views (see Capelle [15]).

A comprehensive theory of inheritance was developed by Aristotle (see [6]). He also believed in a qualitatively different contribution by the male and the female principles to procreation. The male gives the impulse to movement whereas the female contributes the matter, as the carpenter who constructs a bed out of wood. When the male impact is stronger, a son is born who, at the same time, is more like his father, when the

female, a daughter, resembling the mother. This is the reason why sons are usually similar to their fathers and daughters are similar to their mothers.

Barthelmess (our translation) [6] writes: "Reading the texts from this culture, one gets the overall impression that the Greeks in their most mature minds came closer to the theoretical problems than to the phenomena of heredity." Aristotle's assertion even provides an early example of how observation can be misled by a preconceived theoretical concept. Sons are not more similar to their fathers, nor daughters to their mothers.

Plato, in the *Statesman (Politikos)* [71], explained in detail the task of carefully selecting spouses to produce children who will develop into bodily and ethically eminent personalities. He wrote:

> They do not act on any sound or self-consistent principle. See how they pursue the immediate satisfaction of their desire by hailing with delight those who are like themselves and by disliking those who are different. Thus they assign far too great an importance to their own likes and dislikes.
>
> The moderate natures look for a partner like themselves, and so far as they can, they choose their wives from women of this quiet type. When they have daughters to bestow in marriage, once again they look for this type of character in the prospective husband. The courageous class does just the same thing and looks for others of the same type. All this goes on, though both types should be doing exactly the opposite …
>
> Because if a courageous character is reproduced for many generations without any admixture of the moderate type, the natural course of development is that at first it becomes superlatively powerful but in the end it breaks out into sheer fury and madness …
>
> But the character which is too full of modest reticence and untinged by valor and audacity, if reproduced after its kind for many generations, becomes too dull to respond to the challenges of life and in the end becomes quite incapable of acting at all.

In the *Republic* [70], Plato not only requires for the "guards" (one of the highest categories in the social hierarchy of his utopia) that women should be common property; children, should be educated publicly but the "best" of both sexes should beget children who are to be educated with care. The children of the "inferior," on the other hand, are to be abandoned. Democritus, on the other hand, writes: "More people become able by exercise than by their natural predisposition." Here (as in other places), the nature–nurture problem appears already.

1.2 Scientists Before Mendel and Galton

The literature of the Middle Ages contains few allusions to heredity. The new attitude of looking at natural phenomena from an empirical point of view created modern science and distinguishes modern humans from those in earlier periods. This approach succeeded first in investigation of the inorganic world and only later in biology. In the work *De Morbis Hereditariis* by the Spanish physician Mercado (1605) [66], the influence of Aristotle is still overwhelming, but there are some hints of a beginning emancipation of reasoning. One example is his contention that both parents, not only the father, contribute a seed to the future child. Malpighi (1628–1694) [83, p 77] proposed the hypothesis of "preformation," which implies that in the ovum the whole organism is preformed in complete shape, only to grow later. Even after the discovery of sperm (Leeuwenhoek et al. 1677) [3, pp 72-73], the preformation hypothesis was not abandoned altogether, but it was believed by some that the individual is preformed in the sperm, only being nurtured by the mother. The long struggle between the "ovists" and the "spermatists" was brought to an end only when C.F. Wolff [99] attacked both sides and stressed the necessity of further empirical research. Shortly thereafter experimental research on heredity in plants was carried out by Gärtner (1772–1850) [33] and Kölreuter (1733–1806) [48]. Their work prepared the ground for Mendel's experiments [60].

The medical literature of the eighteenth and early nineteenth centuries contains reports showing that those capable of clear observation were able to recognize correctly some phenomena relating to the inheritance of diseases. Maupertuis [57], for example, published in 1753 an account of a family with polydactyly in four generations and demonstrated that the trait could be equally transmitted by father or by mother. He further showed, by probability calculation, that chance alone could not account for the familial concentration of the trait. Probably the most remarkable example, however, was Joseph Adams (1756–1818) (see [1,23,62,64]), a British apothecary who, in 1814, published a book with the title *A Treatise on the Supposed Hereditary Properties of Diseases* [1]. The following findings are remarkable:

(a) Adams differentiated clearly between "familial" (i.e., recessive) and "hereditary" (i.e., dominant) conditions.
(b) He knew that in familial diseases the parents are frequently near relatives.

(c) Hereditary diseases need not be present at birth; they may manifest themselves at various ages.
(d) Some disease predispositions lead to a manifest disease only under the additional influence of environmental factors. The progeny, however, is endangered even when the predisposed do not become ill themselves.
(e) Intrafamilial correlations as to age of onset of a disease can be used in genetic counseling.
(f) Clinically identical diseases may have different genetic bases.
(g) A higher frequency of familial diseases in isolated populations may be caused by inbreeding.
(h) Reproduction among persons with hereditary diseases is reduced. Hence, these diseases would disappear in the course of time, if they did not appear from time to time among children of healthy parents (i.e., new mutations!).

Adams' attitude toward "negative" eugenic measures was critical. He proposed the establishment of registries for families with inherited diseases. Weiss [96] recently pointed out that Adams in the same book also hinted at the existence of evolution stressing the concept of adaptive selection saying that environments such as climate put constraints on people: "By these means a race is gradually reared with constitutions best calculated for the climate" [1].

C.F. Nasse, a German professor of medicine, correctly recognized in 1820 one of the most important formal characteristics of the X-linked recessive mode of inheritance in hemophilia and presented a typical comprehensive pedigree [83, p 180]. He wrote (our translation):

> All reports on families, in which a hereditary tendency towards bleeding was found, are in agreement that the bleeders are persons of male sex only in every case. All are explicit on this point. The women from those families transmit this tendency from their fathers to their children, even when they are married to husbands from other families who are not afflicted with this tendency. This tendency never manifests itself in these women. …

Nasse also observed that some of the sons of these women remain completely free of the bleeding tendency.

The medical literature of the nineteenth century shows many more examples of observations, and attempts to generalize and to find rules for the influence of heredity on disease can be found. The once very influential concept of "degeneration" should be mentioned. Some features that older authors described as "signs of degeneration" in the external appearance of mentally deficient patients are now known to be characteristic of autosomal chromosomal aberrations or various types of mental retardation.

In the work of most of the nineteenth century authors, true facts and wrong concepts were inextricably mixed, and there were few if any criteria for getting at the truth. This state of affairs was typical for the plight of a science in its prescientific state. Human genetics had no dominant paradigm. The field as a science was to start with two paradigms in 1865: biometry, which was introduced by Galton, and Mendelism, introduced by Mendel with his pea experiments. The biometric paradigm was influential in the early decades of the twentieth century, and some examples and explanations in this book utilize its framework. With the advent of molecular biology and insight into gene action, the pure biometric approach in genetics is on the decline. Nevertheless, many new applications in behavioral or social genetics, where gene action cannot yet be studied, rely on this paradigm and its modern elaborations. The laws that Mendel derived from his experiments, on the other hand, have been of almost unlimited fruitfulness and analytic power. The gene concept emerging from these experiments has become the central concept of all of genetics, including human genetics. Its possibilities have not been exhausted.

1.3 Galton's Work

In 1865, F. Galton published two short papers with the title "Hereditary Talent and Character." He wrote [29]:

> The power of man over animal life, in producing whatever varieties of form he pleases, is enormously great. It would seem as though the physical structure of future generations was almost as plastic as clay, under the control of the breeder's will. It is my desire to show, more pointedly than – so far as I am aware – has been attempted before, that mental qualities are equally under control.
>
> A remarkable misapprehension appears to be current as to the fact of the transmission of talent by inheritance. It is commonly asserted that the children of eminent men are stupid; that, where great power of intellect seems to have been inherited, it has descended through the mother's side; and that one son commonly runs away with the talent of the whole family.

He then stresses how little we know about the laws of heredity in man and mentions some reasons, such as

long generation time, that make this study very difficult. However, he considers the conclusion to be justified that physical features of humans are transmissible because resemblances between parents and offspring are obvious. Breeding experiments with animals, however, had not been carried out at that time, and direct proof of hereditary transmission was therefore lacking even in animals. In humans, "we have … good reason to believe that every special talent or character depends on a variety of obscure conditions, the analysis of which has never yet been seriously attempted." For these reasons, he concluded that single observations must be misleading, and only a statistical approach can be adequate.

Galton evaluated collections of biographies of outstanding men as to how frequently persons included in these works were related to each other. The figures were much higher than would be expected on the basis of random distribution.

Galton himself was fully aware of the obvious sources of error of such biological conclusions. He stressed that "when a parent has achieved great eminence, his son will be placed in a more favorable position for advancement, than if he had been the son of an ordinary person. Social position is an especially important aid to success in statesmanship and generalship … ."

"In order to test the value of hereditary influence with greater precision, we should therefore extract from our biographical list the names of those that have achieved distinction in the more open fields of science and literature." Here and in the law, which in his opinion was "the most open to fair competition," he found an equally high percentage of close relatives reaching eminence. This was especially obvious with Lord Chancellors, the most distinguished lawyers of Great Britain.

Galton concluded that high talent and eminent achievement are strongly influenced by heredity. Having stressed the social obstacles that inhibit marriage and reproduction of the talented and successful, he proceeded to describe a utopic society,

> In which a system of competitive examination for girls, as well as for youths, had been so developed as to embrace every important quality of mind and body, and where a considerable sum was yearly allotted. … to the endowment of such marriages as promised to yield children who would grow into eminent servants of the State. We may picture to ourselves an annual ceremony in that Utopia or Laputa, in which the Senior Trustee of the Endowment Fund would address ten deeply-blushing young men, all of twenty-five years old, in the following terms… .

In short, they were informed that the commission of the endowment fund had found them to be the best, had selected for each of them a suitable mate, would give them a substantial dowry, and promised to pay for the education of their children.

This short communication already shows human genetics as both a pure and an applied science: on the one hand, the introduction of statistical methods subjects general impressions to scientific scrutiny, thereby creating a new paradigm and turning prescience into science. Later, Galton and his student K. Pearson proceeded along these lines and founded biometric genetics. On the other hand, however, the philosophical motive of scientific work in this field is clearly shown: the object of research is an important aspect of human behavior. The prime motive is the age-old inscription on the Apollo temple at Delphi ("know yourself").

Hence, with Galton, research in human genetics began with strong eugenic intentions. Later, with increasing methodological precision and increasing analytic success, such investigations were removed from this prime philosophical motive. This motive helps to understand the second aspect of Galton's work: the utopian idea to improve the quality of the human species by conscious breeding. During the Nazi era in Germany (1933–1945) we saw how cruel the perverted consequences of such an idea may become (Sect. 1.8.2). The question first posed by Galton remains, even more than ever, of pressing importance: What will be the biological future of mankind?

1.4 Mendel's Work

The other leading paradigm was provided by Mendel in his work *Experiments in Plant Hybridization,* which was presented on 8 February and 8 March 1865 before the *Naturforschender Verein* (Natural Science Association) in Brünn (now Brno, Czech Republic) and subsequently published in its proceedings [60]. It has frequently been told how this work went largely unnoticed for 35 years and was rediscovered independently by Correns, Tschermak, and de Vries in 1900 (see [16, 84, 20]). From then on, Mendel's insights triggered the development of modern genetics, including human genetics. A book by Stern and Sherwood [82], which reprints these and a variety of other articles regarding Mendel's paper, is most helpful to assess the impact of this classic work.

Mendel was stimulated to carry out his experiments by observations on ornamental plants, in which he had tried to breed new color variants by artificial insemination. Here he had been struck by certain regularities. He selected the pea for further experimentation. He crossed varieties with differences in single characters such as color (yellow or green) or form of seed (round or angular wrinkled) and counted all alternate types in the offspring of the first generation crosses and of crosses in later generations. Based on combinatorial reasoning, he gave a theoretical interpretation: the results pointed to free combination of specific sorts of egg and pollen cells. In fact, this concept may have occurred to Mendel before he carried out his studies. He may have verified and illustrated his findings by his "best" results, since agreement between the published figures and their expectation from the theoretical segregation ratios is too perfect from a statistical point of view (Fisher [27]). The interpretation of this discrepancy remains controversial [82, 90]. In any case, there is no question that Mendel's findings were correct.

Mendel discovered three laws: the law of uniformity, which states that after crossing of two homozygotes of different alleles the progeny of the first filial generation (F_1) are all identical and heterozygous; the law of segregation, which postulated 1 : 2 : 1 segregation in intercrosses of heterozygotes and 1 : 1 segregation in backcrosses of heterozygotes with homozygotes; and the law of independence, which states that different segregating traits are transmitted independently.

What is so extraordinary in Mendel's contribution that sets it apart from numerous other attempts in the nineteenth century to solve the problem of heredity? Three points are most important:

1. He simplified the experimental approach by selecting characters with clear alternative distributions, examining them one by one, and proceeding only then to more complicated combinations.
2. Evaluating his results, he did not content himself with qualitative statements but counted the different types. This led him to the statistical law governing these phenomena.
3. He suggested the correct biological interpretation for this statistical law: The germ cells represent the constant forms that can be deduced from these experiments.

With this conclusion Mendel founded the concept of the gene, which has proved so fertile ever since. The history of genetics since 1900 is dominated by analysis of the gene. What had first been a formal concept derived from statistical evidence has emerged as the base pair sequence of DNA, which contains the information for protein synthesis and for life in all its forms.

1.5 Application to Humans: Garrod's Inborn Errors of Metabolism

The first step of this development is described in this historical introduction: A. Garrod's [30] paper on "The Incidence of Alkaptonuria: A Study in Chemical Individuality." There are two reasons for giving special attention to this paper. For the first time, Mendel's gene concept was applied to a human character, and Mendel's paradigm was introduced into research on humans. Additionally, this work contains many new ideas set out in a most lucid way. Garrod was a physician and in later life became the successor of Osler in the most prestigious chair of medicine at Oxford [8]. His seminal contribution to human genetics remained unappreciated during his lifetime. Biologists paid little attention to the work of a physician. Their interest was concentrated more on the formal aspects of genetics rather than on gene action. The medical world did not understand the importance of his observations for medicine. Garrod first mentioned the isolation of homogentisic acid from the urine of patients with alkaptonuria and stated the most important result of the investigations carried out so far:

> As far as our knowledge goes, an individual is either frankly alkaptonuric or conforms to the normal type, that is to say, excretes several grammes of homogentisic acid per diem or none at all. Its appearance in traces, or in gradually increasing or diminishing quantities, has never yet been observed. . . .

As a second important feature "the peculiarity is in the great majority of instances congenital. . . ." Thirdly: "The abnormality is apt to make its appearance in two or more brothers and sisters whose parents are normal and among whose forefathers there is no record of its having occurred." Fourthly, in six of ten reported families the parents were first cousins, whereas the incidence of first-cousin marriages in contemporary England was estimated to be not higher than 3%. On the other hand, however, children with alkaptonuria are observed in a very small fraction only of all first-cousin marriages.

There is no reason to suppose that mere consanguinity of parents can originate such a condition as alkaptonuria in their offspring, and we must rather seek an explanation in some peculiarity of the parents, which may remain latent for generations, but which has the best chance of asserting itself in the offspring of the union of two members of a family in which it is transmitted.

Then, Garrod mentioned the law of heredity discovered by Mendel, which "offers a reasonable account of such phenomena" that are compatible with a recessive mode of inheritance as pointed out by Bateson [37]. He cited another remark of Bateson and Saunders (Report to the Evolution Committee of the Royal Society) [7] with whom he had discussed his data:

> We note that the mating of first cousins gives exactly the conditions most likely to enable a rare, and usually recessive, character to show itself. If the bearer of such a gamete mates with individuals not bearing it the character will hardly ever be seen; but first cousins will frequently be the bearers of similar gametes, which may in such unions meet each other and thus lead to the manifestation of the peculiar recessive characters in the zygote.

After having cited critically some opinions on the possible causes of alkaptonuria, Garrod proceeded:

> The view that alkaptonuria is a "sport" or an alternative mode of metabolism will obviously gain considerably in weight if it can be shown that it is not an isolated example of such a chemical abnormality, but that there are other conditions which may reasonably be placed in the same category.

Having mentioned albinism and cystinuria as possible examples, he went on: "May it not well be that there are other such chemical abnormalities which are attended by no obvious peculiarities [as the three mentioned above] and which could only be revealed by chemical analysis?" And further:

> If it be, indeed, the case that in alkaptonuria and the other conditions mentioned we are dealing with individualities of metabolism and not with the results of morbid processes the thought naturally presents itself that these are merely extreme examples of variations of chemical behavior which are probably everywhere present in minor degrees and that just as no two individuals of a species are absolutely identical in bodily structure neither are their chemical processes carried out on exactly the same lines.

He suggested that differential responses toward drugs and infective agents could be the result of such chemical individualities. The paper presents the following new insights:

(a) Whether a person has alkaptonuria or not is a matter of a clear alternative – there are no transitory forms. This is indeed a condition for straightforward recognition of simple modes of inheritance.

The condition is observed in some sibs and not in parents.

The unaffected parents are frequently first cousins.

This is explained by the hypothesis of a recessive mode of inheritance according to Mendel. The significance of first-cousin marriages is stressed especially for rare conditions; this may be a precursor to population genetics.

(b) Apart from alkaptonuria several other similar "sports" such as albinism and cystinuria may exist. This makes alkaptonuria the paradigm for the "inborn errors of metabolism." In 1909 Garrod published his classic monograph on this topic [31].
(c) These sports may be extreme and therefore conspicuous examples of a principle with *much more widespread applicability.* Lesser chemical differences between human beings are so frequent that no human being is identical chemically to anyone else.

From these concepts Garrod drew more far-reaching conclusions, which are often overlooked. In a book published in 1931 [32] and reprinted with a lengthy introduction by Scriver and Childs [80], Garrod suggested that hereditary susceptibilities or diatheses are a predisposing factor for most common diseases and not merely for the rare inborn errors of metabolism. These concepts were precursors of current work to delineate the specific genes involved in the etiology of common disease. A valuable biography of Garrod was published by A. Bearn [8], who was a pioneer of human biochemical genetics in the 1950s and later.

Throughout this book the principle of a genetically determined individuality will govern our discussions. Garrod's contribution may be contrasted with that of Adams [23, 62, 64]. Apart from the "familial" occurrence of some hereditary diseases, Adams observed a number of phenomena that were not noted by Garrod, such as the late onset of some diseases, the intrafamilial correlation of age of onset, and the genetic predisposition leading to manifest illness only under certain environmental conditions. However, Adams did not have Mendel's paradigm. Therefore, his efforts could not lead to the development of an explanatory theory and coherent field of science. Garrod did have this paradigm and used it, creating a new area of research: human biochemical genetics.

1.6 Visible Transmitters of Genetic Information: Early Work on Chromosomes

Galton's biometric analysis and Mendel's hybridization experiments both started with visible phenotypic differences between individuals. The gene concept was derived from the phenotypic outcome of certain crossings. At the time when Mendel carried out his experiments nothing was known about a possible substantial bearing of genetic information in the germ cells. During the decades to follow, however, up to the end of the nineteenth century, chromosomes were identified, and mitosis and meiosis were analyzed. These processes were found to be highly regular and so obviously suited for orderly distribution of genetic information that in 1900 the parallelism of Mendelian segregation and chromosomal distribution during meiosis was realized, and chromosomes were identified as bearers of the genetic information [18].

Many research workers contributed to the development of cytogenetics [5,6]. O. Hertwig [41] first observed animal fertilization and established the continuity of cell nuclei: *omnis nucleus e nucleo.* Flemming (1880–1882) discovered the separation of sister chromatids in mitosis [83, p 247]; van Beneden (1883) [85] established the equal and regular distribution of chromosomes to the daughter nuclei. Boveri (1888) [5] found evidence for the individuality of each pair of chromosomes. Waldeyer (1888) (see [18]) coined the term "chromosome."

Meanwhile, Naegeli (1885) [77] had developed the concept of "idioplasma," which contains – to use a modern term – the "information" for the development of the next generation [67]. W. Roux [77] seems to have been the first to set out by logical deduction which properties a carrier of genetic information was expected to have. He also concluded that the behavior of cell nuclei during division would perfectly fulfill these requirements. The most important specific property of meiotic divisions, the ordered reduction of genetic material, was first recognized by Weismann.

These results and speculations set the stage for the identification of chromosomes as carriers of the genetic information, which followed shortly after the rediscovery of Mendel's laws and apparently independently by different authors [16, 20, 84].

Chromosome studies and genetic analysis have remained intimately connected in cytogenetics ever since. Most basic facts were discovered and concepts developed using plants and insects as the principal experimental tools. The fruit fly *Drosophila* played a particularly important role.

The development of human cytogenetics was delayed until 1956 when the correct number of human chromosomes was established as 46 by use of rather simple methods. It should be stressed that this delay could not be explained by the introduction of new cytological methods at that time. In fact, this discovery could have been made many years earlier. The delay was probably related to the lack of interest in human genetics by most laboratory-oriented medical scientists. Human genetics did not exist as a scientific discipline in medical schools since the field was not felt to be a basic science fundamental to medicine. Hereditary diseases were considered as oddities that could not be studied by the methodology of medical science as exemplified by the techniques of anatomy, biochemistry, physiology, microbiology, pathology, and pharmacology. Thus, most geneticists worked in biology departments of universities, colleges, or in agricultural stations. They were usually not attuned to problems of human biology and pathology, and there was little interest to study the human chromosomes. The discovery of trisomy 21 as the cause of Down syndrome and the realization that many problems of sex differentiation owe their origin to sex chromosomal abnormalities established the central role of cytogenetics in medicine. Further details in the development of cytogenetics are described in Chap. 3.

1.7 Early Achievements in Human Genetics

1.7.1 AB0 and Rh Blood Groups

The discovery of the AB0 blood group system by Landsteiner in 1900 [50] and the proof that these blood types are inherited (von Dungern and Hirschfeld [87]) was an outstanding example of Mendelian inheritance applied to a human character. Bernstein in 1924 [11] demonstrated that A, B, and 0 blood group characters are due to multiple alleles at one locus. The combined efforts of Wiener, Levine, and Landsteiner 25–30 years later led to discovery of the Rh factor and established that hemolytic disease of the newborn owes its origin

to immunological maternal–fetal incompatibility. The stage was set for the demonstration in the 1960s that Rh hemolytic disease of the newborn can be prevented by administration of anti-Rh antibodies to mothers at risk [73,100].

1.7.2 Hardy-Weinberg Law

Hardy [36], a British mathematici,an, and Weinberg [92], a German physician, at about the same time (1908) set out the fundamental theorem of population genetics, which explains why a dominant gene does not increase in frequency from generation to generation. Hardy published his contribution in the United States in *Science.* He felt that this work would be considered as too trivial by his mathematics colleagues to be published in the United Kingdom. Weinberg was a practicing physician who made many contributions to formal genetics. He developed a variety of methods in twin research [91] and first elaborated methods to correct for biased ascertainment in recessive inheritance [93].

1.7.3 Developments Between 1910 and 1930

The years between 1910 and 1930 saw no major new paradigmatic discoveries in human genetics. Most of the data in formal genetics (such as linkage, nondisjunction, mutation rate) as well as the mapping of chromosomes were achieved by study of the fruit fly, largely in the United States. Many scientists tried to apply the burgeoning insights of genetics to humans. British scientists exemplified by Haldane excelled in the elaboration of a variety of statistical techniques required to deal with biased human data. The same period saw the development of the basic principles of population genetics by Haldane, Fisher, and Penrose [69] in England and by Wright in the United States. This body of knowledge became the foundation of population genetics and is still used by workers in that field. In 1918, Fisher was able to resolve the bitter controversies in England between the Mendelians, on the one hand, and followers of Galton (such as Pearson) on the other, by pointing out that correlations between relatives in metric traits can be explained by the combined action of many individual genes [26]. Novel steps in the development of medical genetics during this period were the establishment of empirical risk figures for schizophrenia and affective disorders by the Munich school of psychiatric genetics.

1.8 Human Genetics, the Eugenics Movement, and Politics

1.8.1 United Kingdom and United States

The first decade of the century saw the development of eugenics in Europe and in the United States [2,19,21,45, 55,76]. Many biological scientists were impressed by their interpretation of an apparently all-pervasive influence of genetic factors on most normal physical and mental traits as well as on mental retardation, mental disease, alcoholism, criminality, and various other sociopathies. They became convinced that the human species should be concerned with encouragement of breeding between persons with desirable traits (positive eugenics) and discourage the sick, mentally retarded, and disabled from procreation (negative eugenics).

A recent reprint of Davenport's 1911 book, *Heredity in Relation to Eugenics*, is accompanied by thoughtful reflections from contemporary geneticists on Davenport's eugenic concepts and recommendations almost one hundred years later [98]. Various eugenic study units were established in the United States (Eugenics Record Office at Cold Spring Harbor) and the United Kingdom. Much of the scientific work published by these institutions was of poor quality. Particularly, many different kinds of human traits such as "violent temper" and "wandering trait" were forced into Mendelian straightjackets. Most serious geneticists became disenchanted and privately disassociated themselves from this work. For various reasons, including those of friendship and collegiality with the eugenicists, the scientific geneticists did not register their disagreement in public. Thus, the propagandists of eugenics continued their work with enthusiasm, and the field acquired a much better reputation among some of the public than it deserved. Thus, many college courses on eugenics were introduced in the United States.

These trends had several important political consequences. Eugenics sterilization laws were passed in many states in the United States, which made it possible to sterilize a variety of persons for traits such as

criminality for which no good scientific basis of inheritance existed. The attitude that led to the introduction of these laws is epitomized by United States Supreme Court Justice Holmes' statement that "three generations of imbeciles are enough."

Eugenic influences also played an important role in the passing of restrictive immigration laws in the United States. Using a variety of arguments the proponents of eugenics claimed to show that Americans of northwestern European origin were more useful citizens than those of southern European origin or those from Asia. Since such differences were claimed to be genetic in origin, immigration from southern and eastern European countries and from Asia was sharply curtailed. Similar trends were also operative in the United Kingdom. While solid work in human genetics was carried out by a few statistical geneticists, there was also much eugenic propaganda, including that by the distinguished statistician Pearson, the successor to Galton's academic chair in London.

Kevles [46] has published a wide-ranging and insightful history of eugenics and human genetics in the Anglo-Saxon countries. His book is a most carefully researched and exhaustive study of the uses and abuses of eugenic concepts.

1.8.2 Germany

In Germany [9, 10, 34, 94, 95] eugenics took the name of *Rassenhygiene* from a book of that title published in 1895 by Ploetz [72]. The *Rassenhygiene* movement became associated with mystical concepts of race, Nordic superiority, and the fear of degeneration of the human race in general and that of the German *Volk* in particular by alcoholism, syphilis, and increased reproduction of the feebleminded or persons from the lower social strata. Often representatives of this movement became associated with a dangerous type of sociopolitical prejudice: antisemitism. They warned the public against contamination of German "blood" by Jewish influences. Most followers of the racial hygiene concept were nationalistic and opposed the development of an open society that allows individual freedom and democratic participation. They shared this attitude with a significant segment of the educated classes in Germany. General eugenic ideas divorced from racism and other nationalist notions were often espoused by intellectuals who were concerned about the biological future of mankind. Thus, socialists publicized such views in Germany [34]. In 1931, two years before Hitler's coming into power, the German Society of Racial Hygiene added eugenics to its name. However, all efforts in this area soon became identified with the Nazi ideology.

Prominent German human geneticists identified themselves with the use of human genetics in the service of the Nazi state. Recognized scientists, such as Fischer, F. Lenz, Rüdin, and von Verschuer, accepted Nazi leadership and Nazi philosophy. While most of the propaganda for the new racial hygiene was not formulated by scientists but by representatives of the Nazi party, men such as Fischer and von Verschuer [95] participated in spreading Nazi race ideology. Jews were declared foreign genetic material to be removed from the German *Volk*. A eugenic sterilization law was already passed in 1933 that made forced sterilization obligatory for a variety of illnesses thought to be genetic in origin [74]. Heredity courts were established to deal with interpretation of the sterilization law. This law was hailed by some eugenicists in the United States even at the end of the 1930s [47]. Sterilization laws for eugenic indications were also passed in some Scandinavian countries around the same time but allowed voluntary (in contrast to forced) sterilization [74].

The exact role of the German human geneticists in the increasing radicalization and excesses of the application of Nazi philosophy has been assessed [65, 74, 95]; von Verschuer's role in sponsoring twin and other genetic research by his former assistant Mengele in the Auschwitz concentration and extermination camp is clear. We have no record that any voices were raised by these men in protest against "mercy killings" of the mentally retarded and newborn children with severe congenital defects nor against the mass killings of Jews. Evidence suggests that von Verschuer must have had some idea of such events, since he had continued contact with Mengele when the mass killings at Auschwitz were at their height. The "final solution" to the "Jewish problem" resulted in the murder of about 6 million Jews in the early 1940s [75]. While there is no record that human geneticists favored this type of "solution," their provision of so-called "scientific" evidence for a justification of Nazi antisemitism helped to create a climate in which these mass murders became possible [88]. This episode is one of the most macabre and tragic chapters in the history of man's inhumanity to man in the name of pseudoscientific nationalism. Yet, despite

their racist publications, several such "scientists" (including von Verschuer) were given academic positions in post-World War II West Germany.

1.8.3 Soviet Union/Russia *(see Harper, Chap. 16 in [38])*

Eugenics was initiated in the Soviet Union [21,34] in the 1920s by the establishment of eugenics departments, a eugenic society, and a eugenics journal. Eugenic ideals soon clashed with the official doctrine of Marxism-Leninism, however, and these efforts were abandoned by the late 1920s. Scientists who had become identified with eugenics left the field to work with plants and animals.

Remarkable work in early human cytogenetics was carried out between 1931 and 1936, such as using hypotonic solutions for spreading of chromosomes, analysis of cultured embryonic cells, chromosome analysis of human oocytes, and cytogenetic studies of leukemia and other cancers [3,4]. These studies were published in international journals and later taken up by American and European scientists some 20 years later. Would the critical chromosome-related discoveries of the 1950s have been made by Russian scientists if such work on human genetics had not been terminated by Soviet antigenetic policies? [38]

Interest in the medical application of human genetics nevertheless persisted. A large institute of medical genetics, with 200 physicians, was established in Moscow during the 1920s. Its director, the physician S.G. Levit, made notable contributions [54], but was executed in 1938 (Chap. 16 in [38]), and human genetics was officially declared a Nazi science. The later ascendance of Lysenko [45] stifled all work in genetics, including that of human genetics, and no work whatever was carried out in this field until the early 1960s, after Lysenko's domination ceased (pp. 435–450 in [38]). The reintroduction of human genetics into the Soviet Union occurred by way of medical genetics. A textbook of medical genetics was published by Efroimson in 1964 [22]. A new institute of medical genetics was established in 1969 under the directorship of the cytogeneticist Bochkov, who had been trained by the well-known *Drosophila* geneticist, Timofeeff-Ressovsky [38]. Work in many areas of medical genetics, similar to that carried out elsewhere, is now done in Russia.

1.8.4 Human Behavior Genetics

Vigorous discussion continues regarding the role of genetic determinants in behavior, IQ, and personality. Some observers entirely deny genetic influences on normal behavior or social characteristics such as personality and intellect. This attitude toward genetics is shared by some psychologists and social scientists and even a few geneticists who are concerned about the possible future political and social misuse of studies in human behavioral genetics that claim to show genetic determinants of intelligence and social behavior.

We do not agree with those who deny any genetic influence on behavior or social traits in humans. However, we also caution against a too ready acceptance of results from comparison of twins and other relatives, which claim high heritabilities for many of these traits. Genetic data and pseudodata may be seriously misused by political bodies. However, as biologists and physicians impressed by biological variation under genetic control, we would be surprised if the brain did not also show significant variation in structure and function. Such variation is expected to affect intellect, personality, and behavior, and usually will interact with environmental factors. The extent to which genetic variation contributes to such traits, and especially the biological nature of such variation, will have to await further studies.

1.9 Development of Medical Genetics (1950–the Present)

1.9.1 Genetic Epidemiology

In the 1940s and 1950s a number of institutions pioneered in research on epidemiology of genetic diseases. T. Kemp's institute in Copenhagen, J.V. Neel's department in Ann Arbor, Michigan, and A.C. Stevenson's in Northern Ireland and later in Oxford contributed much to our knowledge on prevalence, modes of inheritance, heterogeneity, and mutation rates of various hereditary diseases. Recent years have seen a renaissance in this area, with special attention to analysis of common complex diseases (see Chap. 8.1). Utilization of new laboratory methods, including DNA techniques, together with more powerful methods of association studies, and the

search for rare mutations and structural chromosome changes, provide powerful new approaches in this area.

1.9.2 Biochemical Methods

The years after World War II brought a rapid expansion in the field of human genetics by the development of biochemical, molecular, and cytological methods. Human genetics, which had been the concern largely of statistically oriented scientists, now entered the mainstream of medical research. The demonstration by Pauling et al. [68] that sickle cell anemia is a molecular disease was a key event in this area. The hemoglobins allowed detailed study of the consequences of mutation. The genetic code was found to be valid for organisms as far apart as viruses and humans. Many detectable mutations were found to be single amino acid substitutions, but deletions of various sorts and frameshift mutations similar to those discovered in micro-organisms were discovered. The nucleotide sequences of the hemoglobin genes were worked out using techniques developed in biochemistry and molecular genetics. Many inborn errors of metabolism were shown to originate in various enzyme deficiencies, often caused by a genetic mutation that changes enzyme structure. Methemoglobinemia due to diaphorase deficiency and glycogen storage disease were the first enzyme defects to be demonstrated.

1.9.3 Genetic and Biochemical Individuality

Work on hemoglobin and variants of the enzyme glucose-6-phosphate-dehydrogenase and other enzymes helped to establish the concept of extensive mutational variation. Biochemical individuality explained some drug reactions and led to the development of the field of pharmacogenetics [61, 86, 63, 35]. Marked biochemical heterogeneity of human enzymes and proteins was shown [39]. The uniqueness of humans, which is apparent by the physiognomic singularity of each human being, was shown to apply at the biochemical and immunological level as well. Here, as in several other fields (such as the hemoglobin variants and the mechanism of sex determination), studies in humans led the way to generally valid biological rules. The significance of polymorphism for the population structure (including that of humans) is being widely studied by population geneticists. The hypothesis that some expressed polymorphisms are the genetic substrate against which the environment acts to determine susceptibility and resistance to common disease led to the development of the field of ecogenetics [13,17]. The histocompatibility gene complex has become an important paradigm for the understanding of why several genes with related function occur in closely linked clusters. This locus appears to be of great importance to understand susceptibility to autoimmune diseases. An enormous amount of apparently unexpressed genetic variation has been demonstrated at the DNA and chromosomal level.

1.9.4 Cytogenetics, Somatic Cell Genetics, Prenatal Diagnosis, Clinical Genetics

After cytogenetic techniques became available, they were applied to detect many types of birth defects and intersex states. A specific type of malignancy, chronic myelogenous leukemia, was shown to be caused by a unique chromosomal translocation [78]. Banding techniques developed by Caspersson in 1969 made it possible to visualize each human chromosome and gave cytogenetic methods added powers of resolution.

Soon, biochemical and cytogenetic techniques were combined in somatic cell genetics. Specific enzyme defects were identified in single cells grown in tissue cultures. The development of methods to hybridize human with mouse cells by Henry Harris and Watkins [40] and Ephrussi and Weiss [25] soon allowed the assignment of many genes to specific chromosomes and the construction of a human linkage map.

The developments in somatic cell genetics led to the introduction of prenatal diagnosis in the late 1960s, when amniocentesis at the beginning of the second trimester of pregnancy was developed. This allowed tissue cultures of amniotic cells of fetal origin, permitting both cytogenetic and biochemical characterization of fetal genotypes, assignment of sex, and the diagnosis of a variety of disorders in utero. In the early 1980s chorion villus biopsy – a procedure done during the first trimester of pregnancy – was introduced, and is

being widely used. The discovery that neural tube defects are associated with increases in α-fetoprotein of the amniotic fluid permits intrauterine diagnosis of an important group of birth defects [14]. Ultrasound methods to visualize the placenta and to diagnose fetal abnormalities added to the diagnostic armamentarium. This noninvasive method allows phenotypic diagnosis of a variety of fetal defects more frequently.

Clinical Genetics. The field of clinical genetics was initiated in the 1970s [58] and has been growing rapidly. Many medical schools and hospitals are establishing special clinics in which genetic diseases can be diagnosed and genetic counseling provided. The heterogeneity of genetic disease has been increasingly recognized. Genetic counseling – often by specially trained genetic counselors – is now intensified to provide patients and their families with information on the natural history of the disease, recurrence risks, and reproductive options. Screening programs of the entire newborn population for diseases such as phenylketonuria are being introduced in many countries, and other screening programs such as those to detect carriers of Tay-Sachs disease and other conditions more common among Ashkenazi Jews have undergone extensive trials [81].

With the advent of novel biochemical and DNA techniques (Chap. 4), basic work in human genetics is now performed increasingly by biochemists, cell biologists, molecular biologists, and others, who do not necessarily have training in human genetics. However, human genetics is identified with medical genetics in many of its activities. The scientific developments of the past decades are thus being widely applied in practical medicine.

1.9.5 DNA Technology in Medical Genetics

Advances in molecular genetics and DNA technology are being applied rapidly to practical problems of medical genetics. Since understanding of the hemoglobin genes was more advanced than that of other genetic systems, the initial applications related to the diagnosis of hemoglobinopathies (Chap. 11). Several methods are now being utilized. Inherited variation in DNA sequence that is phenotypically silent was found to be common, supplying a vast number of DNA polymorphisms for study. Just as everyone's physiognomy is unique, each person (except for identical twins) has a unique DNA pattern. DNA variants are being used in family or association studies as genetic markers to detect the presence of closely linked genes causing diseases. Direct detection of genetic disease has been achieved by utilizing nucleotide probes that are homologous to the mutations that are searched for. The polymerase chain reaction, together with rapidly increasing knowledge on human DNA sequences, has opened up new opportunities for direct diagnosis at the DNA level. Occasionally, a specific restriction enzyme may detect the mutational lesion. Different DNA mutations at the same locus frequently cause an identical phenotypic disease. This finding makes direct DNA diagnosis without family study difficult unless the specific mutation that causes the disease is known.

Completion of the human gene map and human gene sequence was achieved at the beginning of this century. Several hundred DNA markers and SNPs that are spaced over all chromosomes provide the necessary landmarks for detection of the genes for monogenic diseases and are beginning to hint at the contribution of specific genes to common diseases.

Using normal DNA carried by innocuous viruses to treat patients with genetic diseases carried by defective DNA has been under study for the last 15 years (Chap. 26). Such gene transfer aims to repair affected somatic cells (somatic gene therapy). Human studies have been done but no definitive cures have been reported. However, acute leukemia developed in several children treated for hereditary antibody syndrome presumably due to activation of oncogenes. Germinal gene therapy, i.e., insertion of normal genes into defective germ cells (or fertilized eggs) for treatment of human genetic disease, has never been carried out and is not considered ready for safe study. Such an approach is highly controversial, and is even prohibited by law in some countries.

McKusick [59] described a variety of paradigm shifts in the study of human and medical genetics in recent years. These included an emphasis from structural to functional genomics, from map-based to sequence-based gene discovery, from monogenic disease diagnosis to detection of common disorder susceptibility, from the search for etiology to exploration of mechanisms, from an emphasis on single genes to approaches on systems pathways and gene families, from genomics to proteomics and from "old-fashioned" medical genetics to "genetic medicine," implying that genes may be involved in all diseases. McKusick (p. 28 in [59]) further pointed out that human genetics

in recent years has been "medicalized," "subspecialized," "professionalized," "molecularized," "commercialized," and even "consumerized."

1.9.6 The "Industrialization" of Discoveries and Team Efforts

The technological advances, the enormous amount of data generated, the size of the genomes, the impressive variability of individual genomes, the necessary specialized expertise in several disciplines, and the revolution in communication technologies all resulted in the organization and execution of mega-projects related to human genetics in the last 15 years in order to achieve results freely available to the community that provide genome-wide answers to the objectives. These projects, mostly international and funded by different funding agents, often included more than 50 different laboratories and 200 scientists. This paradigm shift is similar to the evolution of experimentation in physics, and underscores the importance of international cooperation in genomic discoveries. In addition, it is remarkable that most of the funding was provided by public sources. The completion of the human genome sequence was the first example of such international projects [44,49]. Other examples include the sequence of the genomes of other organisms and comparative genome analysis [89], the identification of the common genomic variation in a number of human population groups (HapMap project [28,42,43]), the ENCODE project to identify the functional elements in the human genome and that of selected model organisms [12], and the genome-wide association studies to identify common risk variants for the common complex phenotypes [56,79,97] (Chap. 8.1). More recently, the 1000 Genomes Project (http://www.1000genomes.org) and other related efforts aim to identify all genetic variation in the genomes of individuals. The major challenge in the future is to provide causative links between genomic variants and phenotypic variation.

1.9.7 Unsolved Problems

Human genetics had been most successful by being able to guide work that was made possible by the development of techniques from various areas of biology using Mendelian concepts. Important basic frontiers that are still being extended concern problems of gene regulation, especially during embryonic development, control of the immune system and of brain function. Human genetics is likely to contribute to these problems by imaginative use of the study of genetic variation and disease applying novel concepts and techniques. In medical genetics, the problem of common diseases including many birth defects requires study of the specific genes and their interactions involved in such diseases. Insights into the mechanisms of gene action during the aging process remain to be elucidated.

As shown by the many advances in description of genomic anatomy (see Chap. 2) where function is not yet fully understood, there is much need for research in both basic and translational approaches in order to elucidate the role of genomic biology and post-genomic interactions in health and disease. The remarkable similarity of humans and other mammals (and even of more primitive organisms) in both gene number and gene function had not been entirely expected, demonstrating that both new concepts and technical methods will be required to understand and utilize our current and future knowledge for applications in prevention and treatment of disease.

At first glance, the history of human genetics over the past 50 years reads like a succession of victories. The reader could conclude that human geneticists of the last generation pursued noble science to the benefit of mankind. However, how will posterity judge current efforts to make use of our science for the benefit of mankind as we understand it? Will the ethical distinction between selective abortion of a fetus with Down syndrome and infanticide of severely malformed newborns be recognized by our descendants? Are we again moving down the "slippery slope?"

Issues such as selective termination of pregnancy due to disadvantageous genomic variation need to be re-discussed and re-debated due to the ability to diagnose genomic variants with low-penetrance phenotypic consequences. As the dividing line between "severe phenotype" alleles and "low burden" alleles becomes blurred and individualized, consensus criteria and compromised solutions are fluid and constantly revised. Genetic medicine gradually becomes a central preoccupation of health professionals, the patients and their families, and presymptomatic healthy clients.

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