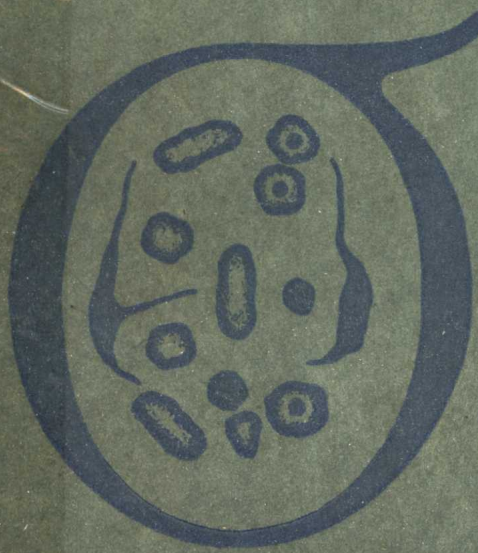
Human Heredity



Neel and Schull

Human Heredity

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CHAPTER 1

Man as an Object of Genetic Study

1.1. *Special problems in the study of human heredity.*—Man as an object of genetic study presents both peculiar advantages and disadvantages. We will consider the disadvantages first. Although the beginnings of genetics go back much further, it is customary to place the emergence of genetics as an exact science in the year 1900. This was the year in which three European biologists independently rediscovered the basic principles of genetics, which had been enunciated by Gregor Mendel in 1866 but which had gone almost entirely unnoticed by the scientific world for the next thirty-four years. Geneticists in the first several decades following the rediscovery of Mendel's laws in 1900 were largely occupied with what we may term the "mechanisms" of heredity, i.e., the definition of how the determiners of inherited characteristics, the *genes*, were transmitted from one generation to the next, and the criteria for deciding whether a given trait was due to one or several genes and whether these genes were located on the same or different chromosomes. For a variety of reasons, man is not a favorable subject for studies of this nature: (1) Controlled matings between two individuals of known genetic background, followed by the production of large numbers of offspring from a single mating—upon which the plant and animal geneticists rely so heavily—are, of course, not characteristic of human societies. (2) A further disadvantage of human material is the practical impossibility, in the study of the genetics of a particular trait, of standardizing or altering the environment at will; this is a particularly serious drawback where the manifestations of the gene are influenced by nutrition, training, etc. (3) The length of the interval between birth and reproduction in man, combined with the poor records which society generally maintains with respect to its deceased members, are scarcely favorable to genetic inquiries. (4) Lastly, the rather considerable number of human chromosomes (twenty-four different pairs, as contrasted, e.g., to *Drosophila melanogaster* with four) renders it difficult to establish the chromosomal relations of the genes responsible for the various traits known to be inherited in man.

Because of these shortcomings of human material, students of human heredity in the early decades of this century were for the most part led to

confine their observations to the collection of extensive pedigrees in which a given obvious trait appeared repeatedly in successive generations. There was a tendency to judge the value of the study in terms of the number of individuals in the pedigree. Under these circumstances the bulk of the attention was diverted to traits exhibiting simple dominant heredity. It was this early search for—and preoccupation with—families containing many persons affected with a given trait that has given rise to the belief, still encountered in some circles, that the study of human heredity consists in the collection of unusual, striking, and/or quaint pedigrees. As we shall see, this is far from the truth.

1.2. *Special advantages of human material.*—We turn now to the advantages of man for genetic studies. A generation of geneticists trained on animals as easily manipulated as the fruit fly and the mouse has been quick to recognize the difficulties involved in working out the exact genetic basis of the more complex human traits. This has led to frequent statements regarding man's unsuitability for genetic studies. This unsuitability is not so serious as is frequently pictured. It is obvious that human beings are not to be crossed like cattle or flies. But while controlled matings are impossible in human societies, we now realize that man in his time and numbers has contrived to enter into many of the matings desired by the geneticist; it remains only to locate these matings for study. Furthermore, the combined efforts of many investigators have resulted in the development of a powerful set of mathematical techniques specifically designed to extract as much information as possible from human genetic data. These techniques at least partly offset the problems created by the small size of human families and the difficulty in obtaining reliable data extending over many generations.

There are two subdivisions of genetics which are currently under intensive investigation in which as much can be learned from the study of man as from any other animal. These are physiological genetics and population genetics. Physiological genetics is concerned with the problem of how the genes work, i.e., with the definition of the developmental sequence between the presence in an individual of a particular gene and the appearance in that same individual of a particular morphological or biochemical trait. We are more familiar with the detailed anatomy, physiology, and biochemistry of man than of any other animal. Small departures from the norm which might go undetected in a fruit fly or a mouse are relatively much more apparent in man. There is therefore the possibility, once an inherited trait has been identified in man, of bringing a great many correlated observations to bear on the ultimate nature of the inherited defect. On the debit side, on the other hand, is the impossibility of deriving pure strains with which to work and the relative

inaccessibility of embryological material. There is growing evidence, as we shall see later, that genes work through controlling the many biochemical reactions which occur during the development and the adult life of every organism. In chapter 12 we shall consider some of the many biochemical reactions of man which have been shown to be under genetic control.

Population genetics deals with the nature of the genetic differences between groups of individuals. There are large numbers of readily accessible members of the human species, most of whom will be found to be sufficiently co-operative to yield data of value to the geneticist. On the basis of various morphological characteristics, the anthropologist has separated the human species into a number of distinct stocks. Recent advances in serology have put into the hands of the geneticist a number of easily identified, inherited serological differences between individuals. The study of the frequency with which these and other inherited traits are represented in different groups of people is a powerful supplement to the more traditional anthropological methods of studying the relationships between peoples. Chapter 15 will be devoted to this development.

Man is a curious creature, and he is particularly curious about man. Aberrant human individuals—as well as differences between groups of individuals—have excited comment from earliest times. Some of this comment has been preserved in the incredibly voluminous medical and anthropological literature. Although the descriptions are sometimes biased and incomplete and often omit data considered important by the geneticist, there is no denying the existence of a large literature pertinent to the problems of human genetics. This is in striking contrast to the situation which obtains with respect to many of the important common domestic animals. Commercial breeders of horses, cows, pigs, and sheep have usually done their best to conceal the occurrence of off-types in their herds, since information as to the occurrence of such off-types lowered the financial value of the herd. Consequently, aside from man, we have extensive data concerning aberrant individuals among mammalian species only for certain laboratory animals—mice, rats, and guinea pigs—where the occurrence of such abnormalities may be studied in an environment free of special bias.

Certain organisms lend themselves particularly well to the study of special aspects of genetics. Thus the fruit fly, Drosophila, approximates the ideal laboratory animal for the study of the "mechanisms" of inheritance. The mold Neurospora has proved excellent material for the study of genetically controlled biochemical reactions. The inheritance of quantitative traits is well studied in various agriculturally important plants—corn, beans, wheat. But while a great deal is known about various specific phases of genetics in particular plant and animal species, it is probable that, in the aggregate,

more is known about the heredity of man than of any other form, with the possible exception of Drosophila and corn. And yet, as we shall see, only the barest sort of start has been made on the subject of human heredity.

1.3. *Purpose of this book.*—In a small book like this, it would be impossible to attempt to review all that we know about human inheritance. Although the study of human genetics is still in its infancy, it would require several large volumes for even a skeleton summary of the techniques and knowledge in this field. We shall therefore attempt to introduce the reader to some of the landmarks of past work in human heredity and some of the signposts for future development. It is hoped that, with these reference points clearly in mind, the reader will be oriented with respect to a variety of problems which may arise in the future. We shall, then, emphasize the methodology of human genetics far more than the established facts of human inheritance. Even thus limiting ourselves, we shall be forced to slight some topics. Some of our readers will be disappointed at certain omissions and emphases in this book. To this we can only say that we have attempted to include those matters which in our experience most need treatment.

The reader who has not had college courses in the calculus and biometry may experience difficulty in places. We offer no apologies for this. The complexities of the study of human heredity are such that knowledge of certain branches of mathematics is no less essential to the serious student of human heredity than to the astronomer or the physical chemist. The text which attempts to disguise this fact is, in the long run, doing the student a disservice. But in recognition of the fact that some "serious students" may acquire their mathematical background later than others, the book is designed so that the two chapters which draw heaviest on a mathematical background, chapters 13 and 14, may be omitted without great loss of continuity.

1.4. *References.*—The student will undoubtedly profit by referring from time to time to other textbook presentations of general genetics as well as of human heredity. The bibliography which follows gives suggested references.

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There are a number of journals especially devoted to the publication of material on human inheritance. The two English-language journals which the student will find interesting are the *Annals of Eugenics* (Cambridge: At the University Press) and the *American Journal of Human Genetics* (Baltimore: Waverly Press).

1.5. *Acknowledgments.*—It is a pleasure to acknowledge the constructive criticism of many of our friends and colleagues. Drs. J. N. Spuhler, Earl Green, Madge Macklin, Duncan McDonald, Newton Morton, J. H. Renwick, and T. E. Reed generously went over the entire manuscript, while Drs. C. C. Li, Brian McMahon, Allan Fox, Sidney Cobb, and Leonard Kurland read selected portions. We are deeply indebted to Mrs. Jane Schneidewind for outstanding secretarial assistance and to Miss Grace Yesley for the preparation of most of the illustrative material.

It is also a pleasure to acknowledge our indebtedness to the numerous publishers and our colleagues for their permission to reproduce copyright items. We are indebted to Professor Sir Ronald A. Fisher, Cambridge, and to Messrs. Oliver and Boyd, Limited, Edinburgh, for permission to reprint Table 13.9 from *Statistical Methods for Research Workers.*

CHAPTER 2

The Physical Basis of Heredity in Man

IN MAN, as in plants and other animals, the key to an understanding of the laws of heredity lies in an understanding of the behavior of the chromosomes at the time of cell division. This is because the units of heredity, the genes, are, with very few exceptions, an integral part of the chromosomes.

2.1. *Chromosomes.*—The chromosomes are small bodies of various sizes and shapes located in the cell nucleus. They take up certain dyes with avidity and appear quite dark in the usual stained preparation of a cell. With few exceptions, every cell of the body contains a set of chromosomes. The average number of chromosomes per cell varies widely from one species to the next. The cells of some animals contain as few as 2 chromosomes, while the cells of other animals contain as many as 200.

In man, the usual number of chromosomes is 48. These consist of twenty-four pairs, one member of each pair derived from the father and the other member from the mother. We refer to the members of a pair of chromosomes as "homologous" chromosomes.

2.2. *Genes.*—The term "gene" has been used to designate the submicroscopic, intracellular determiners of the inherited characteristics of an organism. Suitable experiments have revealed that the genes are arranged in a linear sequence along the length of the chromosomes. The sequence in which the genes are arranged tends to be the same for all the individuals of a particular species. At one time in the development of genetics it was customary to envision the genes, even adjacent ones, as sharply separated from one another both morphologically and functionally. It is now realized that, in the chromosomal continuum, adjacent genes may not be independent of one another in their functioning. In other words, in contrast to the earlier point of view, genes are currently envisioned as "much more loosely defined parts of an aggregate, the chromosome, which in itself is a unit and reacts readily to certain changes in the environment" (Demerec, 1951).

2.3. *Mitosis.*—In preparation for the ordinary (*mitotic*) cell divisions of the body, each of the chromosomes contained within the nucleus of the cell re-

duplicates itself, in a fashion not now understood. The reduplication remains incomplete at one point, termed the "centromere." The membrane which bounds the nucleus then disintegrates, and each reduplicated chromosome, with the two strands still attached at the centromere, migrates toward the center of the cell. The intracellular forces which are responsible for this movement of the chromosomes are poorly understood. One of the chief visible manifestations of these forces is the so-called "spindle" which appears at cell

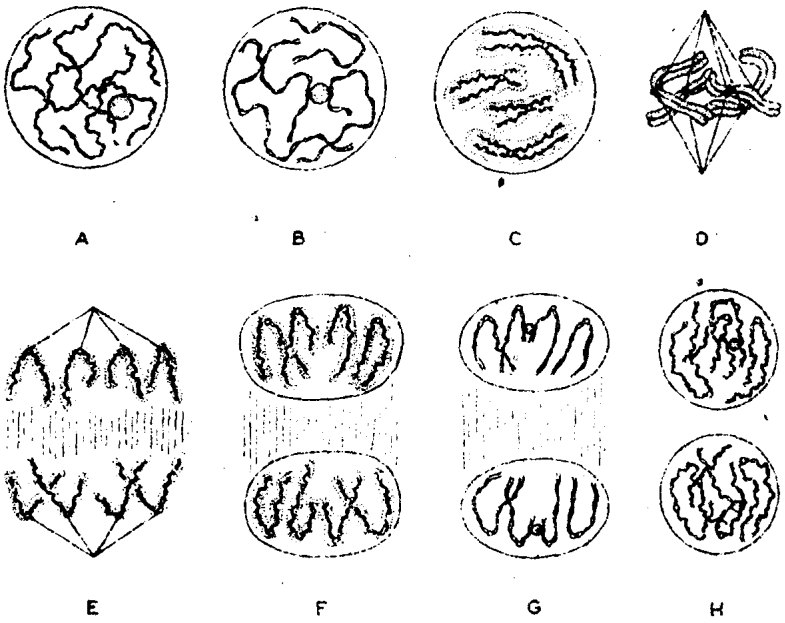

FIG. 2-1.—Mitosis. For simplicity, the cell has been depicted as possessing only two pairs of chromosomes. Each of the two daughter-cells has the same chromosomal complement as the mother-cell. For convenience in discussing the events of mitosis, it is customary to recognize the prophase (*A–C*), metaphase (*D*), anaphase (*E*), and telophase (*F–H*). (Modified, by permission, from Fundamentals of cytology, by Dr. L. W. Sharp, copyright 1943, McGraw-Hill Book Co.)

division. When the chromosomes reach the equatorial position of the spindle, the centromere divides, and the products of the reduplication move away from each other to opposite poles of the spindle. Usually each daughter-cell receives an exact replica of each chromosome present in the original cell, with the result that there are 48 chromosomes in each daughter-cell. Figure 2-1 is a diagram of this sequence of events. From the beginning of the process to the arrangement of the chromosomes on the spindle, there is a progressive shortening or contraction of the chromosomes.

2.4. *Meiosis.*—The two cell divisions (*meiotic*) which precede the formation of the germ cells follow a somewhat different pattern. At an early stage homologous chromosomes pair lengthwise in a manner designed to bring corresponding parts of the two chromosomes together. Just before or just after this pairing, each chromosome reduplicates as before, the process again remaining incomplete at the centromere. At this stage the products of the reduplication, termed "chromatids," remain in close contact with one another. While the chromosomes are thus paired, there may be an exchange of segments between chromatids of homologous chromosomes. Again the chromosomes undergo a progressive shortening. There follow in rapid succession two cell divisions. The first of these divisions separates the two centromeres, each with two attached chromatids. The centromere now divides, and the next cell division separates the two chromatids. Each of the four resulting daughter-cells receives one representative of each pair of chromosomes, so that the number of chromosomes is now 24 rather than 48. However, as a result of the above-mentioned exchange of segments, termed "crossing-over," this single representative of the original pair of chromosomes may be composed of elements derived from both members of the original pair. The sequence of events is shown in Figure 2-2.

The behavior of a given pair of chromosomes at meiosis is independent of the behavior of any other pair. Thus, if with respect to chromosome pair 1, a germ cell receives the member of the pair derived from the father, with respect to chromosome pair 2 the germ cell may receive either a paternally or a maternally derived chromosome, and so on for chromosomes 3, 4, etc. The genes located on the chromosomes will, of course, exhibit the same behavior.

2.5. *Cytological maps of chromosomes.*—Figure 2-3 is a photomicrograph of the chromosomes of man as they appear during a mitotic cell division just before the split in each chromosome becomes readily apparent. During the earlier stages of cell division ("prophase"), the chromosomes are much less compact than this, appearing as slender strands of darkly staining material, along the length of which there occur unequally sized aggregations of even more darkly stained material, termed "chromomeres." In various plant and animal species, certain chromosomes are regularly associated with collections of peculiarly staining material termed "nucleoli" (singular: "nucleolus"). In the nuclei of human cells there are two nucleolus-bearing chromosomes. By careful attention to the chromomere pattern and the presence or absence of a nucleolus and its characteristics, a start has been made on a cytological map of the human chromosomes (Schultz and St. Lawrence, 1949; Kodani, unpublished). Figure 2-4 is a drawing of the prophase appear-

ance in testicular material of what may arbitrarily be designated chromosomes 1 and 2 of man, the chromosomes associated with nucleoli. It is apparent that the chromomeres of each of these chromosomes differ from one another in size and in the relative distance from one to the next. These are constant differences, appearing in cell after cell. With patience and practice, a chromomere "pattern" can be recognized, which, together with the presence of the nucleolus, makes the identification of each of these two chromosomes possible in properly prepared material. The possibility exists that, with

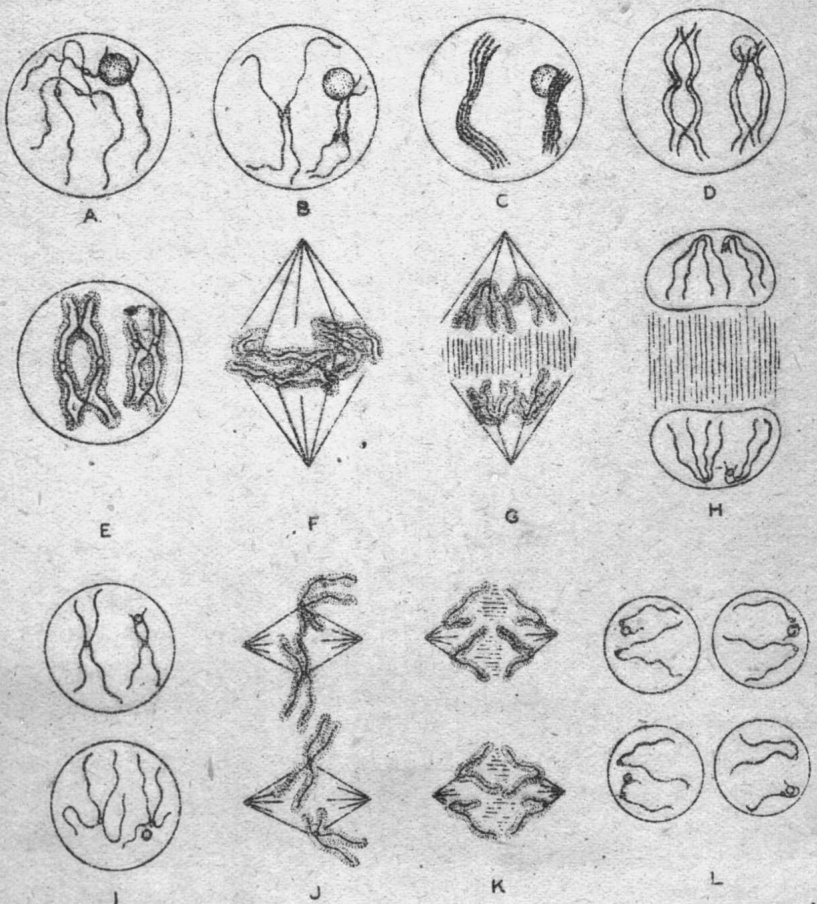

FIG. 2-2.—Meiosis. Again for the sake of simplicity, only two pairs of chromosomes have been depicted. As described in the text, the cells which result from the meiotic divisions receive only one representative of each original pair of chromosomes. The globular body within the nucleus depicted in this and the preceding figure is a nucleolus, of use in preparing cytological maps of chromosomes. (Modified, by permission, from Fundamentals of cytology, by Dr. L. W. Sharp, copyright 1943, McGraw-Hill Book Co.)

time, a similar map could be constructed for each of the 22 other chromosomes. However, even in the best preparations the chromosomes overlie one another in such a fashion as to make it difficult to get a clear view of any particular chromosome. Furthermore, the chromosomes often become fragmented in the course of preparing slides. This renders the task of preparing chromomere maps difficult.

This constancy in the sequence of chromomeres along the length of a chromosome is the cytological basis for the constancy in the sequence of the genes which was referred to earlier. Each chromomere in reality may be associated with one or several genes. The intimate, detailed structure of a

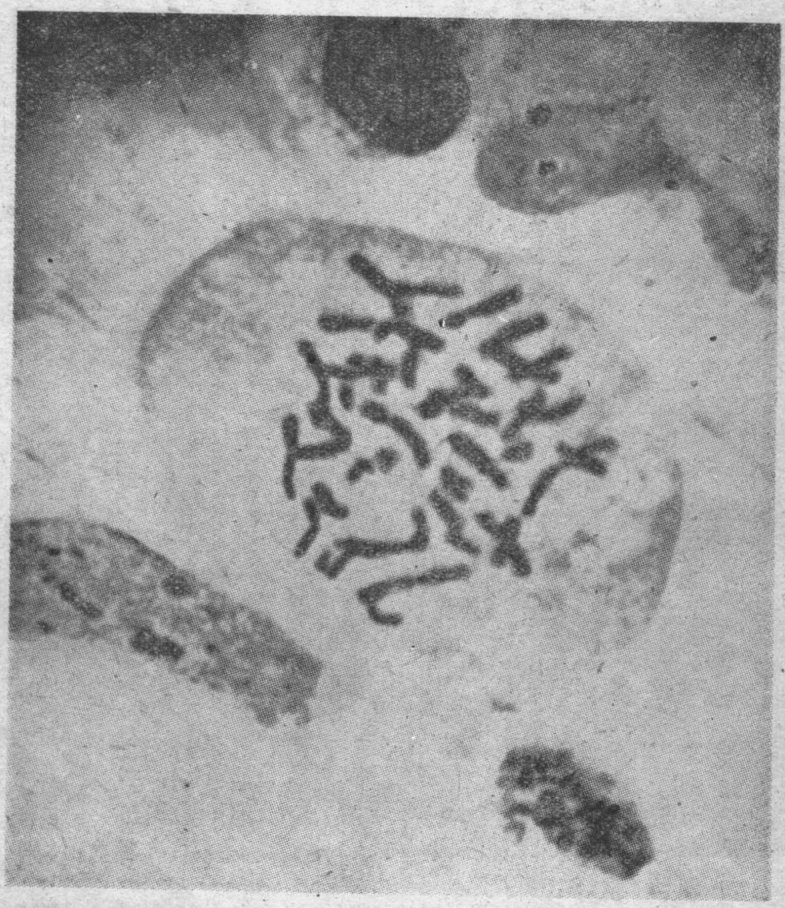

FIG. 2-3.—The chromosomes of man as they appear at mid-cell division (metaphase). (Photograph courtesy of Dr. T. C. Hsu.)

chromosome is still poorly understood. It is composed of special proteins, termed "nucleoproteins"; but how these are arranged is not known.

2.6. *Sex determination.*—The members of each of the 24 pairs of chromosomes are generally identical in appearance. There is one exception to this finding. Males possess one unequal pair of chromosomes, termed the "XY-pair." Females, on the other hand, possess two X-chromosomes. The X-

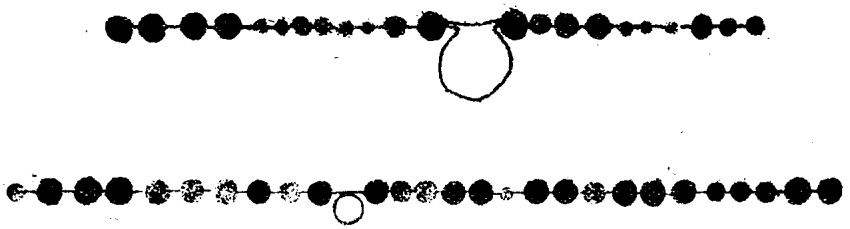

FIG. 2-4.—A semidiagrammatic representation of the appearance of chromosomes 1 and 2 of man (the two nucleolar-bearing chromosomes) as they appear in the early stages of meiosis. (Chromosome 1 by permission of Dr. Jack Schultz and the Journal of Heredity; chromosome 2 by courtesy of Dr. Masuo Kodani.)

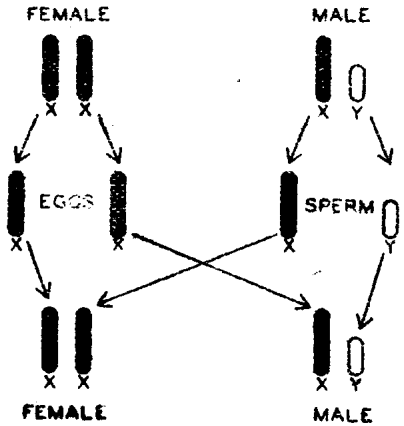

FIG. 2-5.—The chromosomal basis for the determination of sex in man. Further explanation in text.

chromosome is considerably larger than the Y. The sperm cells of a male are of two types, half containing an X-chromosome, and half a Y. All the egg cells, on the other hand, are X-bearing. Random union of the two types of sperm with eggs gives rise to two kinds of zygotes in equal numbers—those with an X- and a Y-chromosome, and those with two X's. The former develop into males, the latter into females. This is a self-perpetuating mechanism. The situation is as depicted in Figure 2-5.

2.7. *The number of genes.*—Considerable effort has been expended in estimating the probable number of genes present in Drosophila. The most reliable estimates thus far available suggest that the (diploid) nucleus of a female Drosophila contains a minimum of 10,000–20,000 genes. The nucleus of a male Drosophila—because of the presence of a Y-chromosome, which is, for the most part, genetically inert, rather than a second X-chromosome—would, of course, contain somewhat fewer genes. The single attempt thus far made to estimate the number of genes present in man has yielded a (diploid) figure of 40,000–80,000, with the difference between males and females relatively less than in Drosophila because of the larger number of autosomes[1] in man (Spuhler, 1948). These estimates are very approximate, the evidence that man has a greater number of genes than Drosophila being especially circumstantial. However, even if man possesses no more genes than Drosophila, the enormity of the task involved in the development of a detailed familiarity with the kinds and functions of human genes is obvious.

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1. All the chromosomes which are not sex chromosomes are referred to as "autosomes."

CHAPTER 3

Man's Genetic Diversity

IT IS difficult for those unfamiliar with genetic concepts to appreciate the enormous possibilities for genetic diversity which exist within the human species. Lack of appreciation of these possibilities lies behind some of the misunderstandings, to be discussed later, concerning human inheritance. A consideration of what is now known concerning the genetics of the human red blood cell will illustrate the extent of the possible genetic differences between men.

3.1. *The number of possible different genotypes with respect to the inherited anemias.*—Roughly speaking, the inherited characteristics of the red blood cells are of two types. We recognize, on the one hand, a series of inherited defects in the red cell which often result in an anemia and, on the other hand, a series of inherited serological reactions. The hereditary anemias with a simple genetic basis include hereditary spherocytosis, thalassemia, sickle-cell anemia, ovalocytosis, and Fanconi's syndrome. Each of these anemias is due to an abnormal gene situated at some particular point on a chromosome ("genetic locus"). With respect to any particular one of the five different genetic loci involved in these anemias, an individual may have received the abnormal gene from both parents or from only one parent, or, as is much more likely, he may have received the corresponding normal gene from both parents. If as regards a particular genetic locus an individual has received from both parents an identical form of the gene occupying that locus, we refer to him as "homozygous" at that genetic locus. Where, on the other hand, the members of a gene pair differ with respect to their characteristics, we speak of the individual as "heterozygous" at that locus. The alternative forms of a gene which may occur at any genetic locus are termed "allelomorphs" or, more simply, "alleles." With reference to each of the inherited anemias, an individual may be homozygous with respect to the normal gene, heterozygous for the abnormal gene, or homozygous for the abnormal gene. There are thus three genetic alternatives. Assuming that the findings at one locus are not related to those at another, the number of theoretically possible different genetic combinations as regards these five anemias is $3^5 = 243$.

3.2. *The number of possible different genotypes with respect to serological traits.*—In addition to the inherited anemias, there are inherited serological differences between red cells. These differences determine the manner in which the red cells react with certain test sera. They will be discussed at some length in subsequent chapters. These serological differences appear for the most part to have a rather simple genetic basis, the presence of a particular reaction corresponding to the presence of a particular gene and the absence of the reaction to the absence of that gene. For some of these serological reactions there are multiple forms which the reaction may take, corresponding to multiple alternative forms of the responsible gene, i.e., "multiple alleles." The occurrence of multiple alleles greatly increases the possibilities for genetic differences between individuals. Thus, where there are three alternative forms of the gene (only two of which can be represented in an individual at one time), the number of possible genetic constitutions ("genotypes") is six. Where there are four alleles, the number of genotypes is ten. The general formula for the number of possible genotypes where a series of multiple alleles exists is $n + (n-1) + (n-2) + (n-3) + \ldots + 1 = n(n+1)/2$, where n = the number of alleles. This corresponds to $n(n-1)/2$ heterozygotes and n homozygotes.

There are now recognized at least seventeen apparently independently inherited types of serological differences between individuals. Eight of these differences are quite rare, and the positive type is very seldom encountered. One of the seventeen, the so-called "Rh reaction," is represented by at least eight different alleles (or closely linked gene complexes; see Sec. 8.6, p. 86). There are thirty-six combinations in which these eight alleles may occur in any one individual. Another difference, upon which the common A_1, A_2, B, and O blood groups are based, may be traced to four alleles, which may occur in ten different combinations. The remaining fifteen differences depend, so far as is now known, on a single pair of alleles; but it is quite possible that further studies will reveal multiple alleles at some of these loci. Even if only a single pair of genes were postulated at each genetic locus associated with a serological reaction, the total number of genetic combinations possible with reference to the genes responsible for the already recognized serological reactions would be $3^{17} = 129{,}140{,}163$.

3.3. *The total number of possible genotypes with respect to the red blood cell.*—If we now consider the number of possible genotypes with respect both to serology and to anemia, we must recognize well in excess of $129{,}140{,}163 \times 243 = 31{,}381{,}059{,}609$. *It is obvious that very many of these possible combinations have never been realized.* Some of the anemias have restricted racial distributions, being more common in one part of the world than in another. Thus individuals homozygous for the thalassemia gene occur about once in