

ELEMENTS OF GENETICS

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GENETICS

MENDEL'S LAWS OF HEREDITY WITH SPECIAL APPLICATION TO MAN

By
EDWARD C. COLIN, Ph.D.
Chicago Teachers College

Second Edition



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SECOND EDITION
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To My Mother

PREFACE TO SECOND EDITION

AMONG the reasons for presenting a revised edition of this book, the following are of chief importance. During the past five years investigators in genetics have discovered new principles and made new applications of established laws. An up-to-date textbook should include the most significant of these advances. The writer's experience as well as the suggestions of other users of the book have shown the desirability of broadening the discussion of certain topics, of adding new illustrative material, and of making a few changes in the sequence of subject matter. However, the original plan and purpose of the book as a beginning text in genetics, as outlined in the Preface to the First Edition, have met with favor and are retained. The principal additions and changes will be mentioned briefly.

The treatment of probability has been strengthened by a description in Chapters 2 and 3 of the application of the binomial theorem and of the Chi Square Test to problems in genetics. The chapter on Linkage and Crossing-over has been clarified by the addition of new illustrations and examples. An exchange in position has been made between this chapter and that on the Factor Principle, so that Linkage (one of the most difficult principles for students) now comes later in the book. New illustrations and examples of the Factor Principle have been added.

A number of changes have been made in the chapters on Heredity in Man, where the most important new material relates to differences in human blood. The discussion of the major blood groups has been brought up to date by the inclusion of the subgroups of groups A and AB. Newly added is the description of the M-N Types and the recently discovered Rh blood factor. The subjects of Sex Determination, Sex Differentiation, and Sex Linkage have been thoroughly revised. Among the additions to these chapters are several new and original illustrations.

The chapter on Heredity and Environment has been improved by the introduction of several new examples and original figures.

The discussion of the Gene and Mutation has been revised in the light of some of the recent significant work on the nature and physiology of viruses and their relation to genes. Under the head of Chromosome Changes, polyploids receive increased attention in line with their established importance in the origin of new types of plants. There is a brief discussion of the Position Effect. New illustrations and examples add much to the interest and effectiveness of the chapter on Inbreeding and Crossbreeding. The chapter on Heredity and Evolution has been critically revised and notice taken of recent research on population genetics.

To the reader, perhaps the most noticeable change in the book as a whole will be the many new and attractive illustrations. The number of illustrations has been practically doubled in this edition; each one has been carefully selected to illuminate some particular point and thus to facilitate its understanding and retention by the student. The lists of problems have been revised, and new problems added for most of the chapters. It is hoped that this revised edition will merit the same generous and favorable response accorded the first.

I wish to thank both authors and publishers for their permission to reproduce illustrations from their various publications; full credit for all borrowed figures is given in the legends thereto. I am indebted to Prof. R. A. Fisher, also to Messrs. Oliver and Boyd, Ltd., of Edinburgh, for permission to reprint Table No. 2 from their book, "Statistical Methods for Research Workers." I am greatly indebted to Professor Sewall Wright for checking Fig. 77. My thanks are due to my son Edward for making the drawings for the new figures and to my son Galen for typing the new material in the book. To the efficient staff of The Blakiston Company I acknowledge sincere thanks for their part of the job of seeing the book through the press.

The author assumes full responsibility for all text material, and he will be grateful as in the past to readers who may suggest, either to him or to the publisher, changes or inclusions which they deem necessary.

E. C. C.

PREFACE TO FIRST EDITION

THIS BOOK is designed especially for college students in genetics. It is the outgrowth of study on the part of the writer in connection with teaching the subject over a considerable period of years. Although written primarily for use as a text and reference work it is hoped that the large amount of material on man will make it of interest and value to the general reader.

The aim has been to present a clear and readable account of the elements of the science of genetics, with special emphasis upon the applications to man. In addition to a full explanation of the classic laws of Mendel and of the supplementary principles of heredity discovered since Mendel's time there is included a thorough discussion of the rôles of heredity and environment in the development of the individual.

The historical approach has been adopted as the one most likely to gain the interest of the reader. Numerous historical references are included in each chapter: it is felt that a knowledge of the development of a science is of particular interest and importance to the beginning student. A separate chapter on the rediscovery of Mendel's work has been introduced because of the human interest and cultural value of the facts surrounding this episode. Similar reasons have prompted the inclusion of two rather long chapters on the heredity of human traits.

There is as yet no standardized order for the treatment of topics in genetics. The present arrangement has been found logical and workable in college classes; various shifts in the sequence of chapters are possible, however, without sacrificing the unity and coherence of the discussion as a whole.

Special care has been taken to select attractive and appropriate figures and to integrate these with the body of the text. The problems at the ends of the chapters have been tried out with numerous students. They represent considerable range in difficulty; in general the easier problems are placed at the head of the

list and the more difficult ones near the end. Since good definitions of terms used in genetics are not always easy to find, a *Glossary* has been appended.

I am deeply indebted to Professor Sewall Wright for reading the entire manuscript and for making valuable suggestions. Special thanks are due to my wife, Alta R. Colin, who made some of the drawings and read the text at several stages in its development, giving much assistance in the clarification of the language. Most of the drawings are the work of Virgil Vogel, to whom I express my sincere appreciation. It is with pleasure that I record my gratitude to The Blakiston Company, Publishers, and to their highly efficient editorial and advisory staff. Finally, I wish to thank the numerous authors and publishers who have generously granted permission to use copyrighted figures and quotations from their various publications. Individual credit is given to each author and publisher in the appropriate place in the text.

In spite of all efforts to eliminate errors it is realized that these may still exist. For any errors that may be found the author is entirely responsible and he will be grateful to anyone who will be kind enough to call them to his attention.

E. C. C.

CHICAGO, ILLINOIS.
February, 1941

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I

MENDEL: STUDENT, PRIEST, TEACHER, INVESTIGATOR

IN THE HISTORY of man's progress toward an understanding of the laws of nature, no story has higher dramatic interest than that of the discovery of the laws of heredity. This story centers about the life of a great man, Gregor Johann Mendel,¹ born July 22, 1822, in Heinzendorf, a village in the Sudeten region of Silesia, at that time a part of the Austro-Hungarian Empire.

Mendel was the second child of a successful farmer and fruit grower. His ancestry was probably a mixture of German and Czech. He went through high school, being forced during a part of the time to earn his own living. Although he was not a brilliant student, his industry enabled him to make an excellent record.

After graduating from high school, Mendel attended the Philosophical Institute at Olmütz. Here again he was compelled to earn a part of his expenses: this he did by private tutoring. Outside work added to study proved so strenuous that he became ill. Consequently, after finishing at the institute, he decided to enter a profession which would relieve him of the worry of earning a living: on September 7, 1843, he joined the order of Augustinian monks at Brünn in Moravia. Of himself he wrote later that his private circumstances determined his choice of profession. After Olmütz, there followed four years spent in the study of theology.

Mendel's life as a parish priest was brief. Obviously he was not fitted for the work, since the necessity of visiting the sick made him seriously ill. In 1849 he was appointed supply teacher in the

¹ As authority for most of the facts on the life of Mendel I am indebted to the excellent biography, "Life of Mendel," by HUGO ILTIS, published originally in German, 1924, under the title, "Gregor Johann Mendel, Leben, Werk, und Wirkung," and translated into English by EDEN and CEDAR PAUL, 1932, W. W. Norton & Co.

high school at Znaim, a town about forty-eight miles northwest of Vienna. According to Mendel's biographer, the illnesses which he had frequently experienced up to this time appeared to be of a somewhat neurotic character.

MENDEL AS TEACHER

In his high school position Mendel taught Greek and elementary mathematics. In 1850, at the urging of his chief and

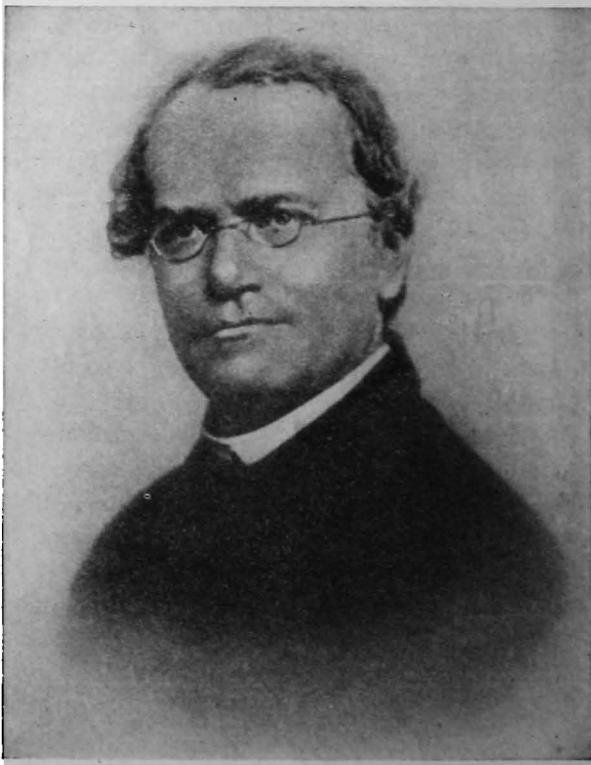


FIG. 1. Mendel as a young man. (From ILTIS: "Life of Mendel," courtesy, W. W. Norton & Co.)

colleagues, he took the examination for a teaching certificate. The examination was conducted by professors at the University of Vienna. In spite of the fact that the young teacher had studied little science in school and had never studied at a university, he suc-

ceeded in passing the examination in physics, but failed in geology and in the classification of mammals.

The chairman of the examining committee, recognizing Mendel's native ability, recommended that he be given more training. As a result of this recommendation, the abbot of the monastery permitted him to enter the University of Vienna as a student. Here he studied from 1851 to 1853, taking courses in zoology, systematic botany, paleontology, physics, and mathematics.

In 1854 Mendel began his career as a supply teacher of science in the Brünn Modern School. In 1856 he came up for a second trial at the examinations, but again he failed to win a certificate. The record is not clear as to why he failed. Iltis believes that he was in some way offended in the oral part of the examination and voluntarily withdrew. Whether this is true or not, it agrees with what we might expect from one of Mendel's sensitive and independent nature. The events in his later life show clearly that when he believed himself to be in the right he could be one of the most stubborn of men. Apparently his own school authorities did not regard him as incompetent, for he remained as supply teacher for 12 more years, and then was elected abbot. With his students and colleagues he was a popular and successful teacher.

MENDEL AS INVESTIGATOR

According to one of his colleagues, Mendel was stimulated to begin his experiments on artificial crossing of plants by the dispute with an examiner already referred to. Iltis does not accept this theory, but believes that he entered upon the experiments for their own sake. However this may be, it is well known that in those of tough mental fiber a failure in one line of endeavor merely spurs the will to succeed in some other line. Mendel's brilliant success as an investigator in succeeding years proved beyond all doubt the superior quality of his mind.

Mendel states in the introduction to his paper describing the famous experiments with peas that these experiments were suggested by results obtained in artificially fertilizing ornamental plants in order to produce new color varieties. The striking regularity with which the same hybrid forms appeared when fertilization took place between the same species led him to follow

up the development of the hybrids in their own offspring. This principle is illustrated in the well-known case of the mule, a hybrid between the horse and the ass. Mules are no more variable than the parent species from which they are derived.

As the son of a farmer and fruit grower Mendel had grown up in an atmosphere of plant and animal breeding and he maintained his interest in plants and animals throughout life. Fruits, flowers, and bees were of special interest to him. In his study of botany and paleontology at the University of Vienna he must have gone into the technical classification of plants as well as into their past history, and there had, no doubt, developed in him a thirst for a more adequate philosophical explanation of what he saw in living nature.

A number of reports of experiments on plant hybridization, including one on a hybrid between the pea and the vetch, had recently been published. Mendel may have been influenced by them. It is possible also that his interest in evolution and the origin of species was instrumental in directing the line of his researches.

MENDEL AND EVOLUTION

We do not know at what time Mendel first became interested in the growing discussion of evolution which, in 1859, burst with explosive force in the publication of Charles Darwin's book, "The Origin of Species," shaking the intellectual world to its foundations. We learn from Iltis that Mendel, during his own researches, became a thorough student of Darwin's work; that he bought all of Darwin's books; and that almost all of the Darwinian literature of the 1860's and 1870's is in the library of the monastery at Brunn. In a copy of "The Origin of Species" and also in a copy of "The Variation of Animals and Plants under Domestication" by Darwin, belonging to the library, there are many notes in Mendel's handwriting.

With characteristic independence of mind, Mendel did not accept Darwin's theories as adequate, although he was not opposed to evolution. And, interestingly enough, the very field in which Darwin's theories later proved to be inadequate (the field of heredity) is the one in which Mendel was to make his own great contribution. According to one of his fellow teachers Mendel

frequently tried to produce permanent variations by the transplantation of plants from their natural habitat, but the results were always negative. These experiments seem to have convinced him that nature did not work in any such way, and that, contrary to Darwin's belief, the inheritance of acquired characters was not a factor in evolution. It is certain, however, that Mendel realized the important relationship of his own discoveries to the principle of evolution, for we find this point specifically emphasized in his paper.

By the irony of fate, Darwin never knew of Mendel and his work. A search through Darwin's extensive library, made by his son following the scientist's death, failed to disclose a copy of the paper on peas, and no reference to Mendel has ever been found in any of Darwin's writings. In the sixth edition of "The Origin of Species"² published in 1872, six years after Mendel made known the laws of heredity, we still find the following statement:

The laws governing inheritance are for the most part unknown. No one can say why the same peculiarity in different individuals of the same species, or in different species, is sometimes inherited and sometimes not so; why the child often reverts in certain characteristics to its grandfather or grandmother or more remote ancestor . . .

These were exactly the questions which Mendel's experiments had answered. Had Darwin come in contact with Mendel's work the history of biology during the last third of the nineteenth century would have been quite different. Darwin's extensive knowledge of hybridization, based in part on his own experiments, would no doubt have led him to appreciate at once the importance of Mendel's work. As a result, Mendel would surely have received during his lifetime the recognition due him. This, however, was not to be.

MENDEL'S EXPERIMENTS WITH PEAS

In 1856, soon after his second failure in the examination, Mendel began his experiments in crossing the edible pea. On February 8, 1865, after eight years' work, he first gave to the world the results of his investigations. His breeding experiments were carried on each summer in a garden plot measuring only

² "The Origin of Species," by CHARLES DARWIN, D. Appleton-Century Co.

20 feet by 120 feet alongside the building of the monastery (Fig. 2). Again and again he writes in his letters how cramped he is in his researches. During the winter months when he could not continue his experiments out-of-doors, it is easy to imagine him going over and over his results until he had finally formulated the laws by which his name, years after his death, was to become famous.



FIG. 2. Garden of the Augustinian Monastery at Brunn, Moravia, in which Mendel carried on his experiments with peas. (From G. H. SHULL: *J. Heredity*, Sept., 1935.)

Mendel delivered the first report of his work before the Brunn Society for the Study of Natural Science on February 8, 1865. At a second meeting one month later he concluded his discussion. In 1866 the paper was published in the proceedings of the society. The proceedings were exchanged with more than 120 other societies, universities, and academies at home and abroad.³

Mendel's report fell on deaf ears. In his lectures before the society there were no questions and no discussion. The same silence enveloped the publication of his article. During the following 34

³ Mendel's original paper, "Versuche über Pflanzenhybriden" (Experiments in Plant-Hybridization), was published in *Verhandlungen des Naturforschenden Vereins in Brunn*, Vol. IV, 1866. A reprint of an English translation by the Royal Horticultural Society of London is published and sold by Harvard University Press, Cambridge, Mass:

years not one person, so far as the records show, realized that here in the compass of 40 pages was revealed one of the most important laws of nature ever discovered by man. How are we to explain this apparent blindness of other scientists? An attempt to answer this question had best be deferred until after an examination of the nature of the discoveries themselves.

Mendel's choice of peas as experimental material was not an accident. He tells how important he regards the right material to the success of any experiment, and gives his reasons for selecting peas: first, he found that peas were obtainable in many pure-

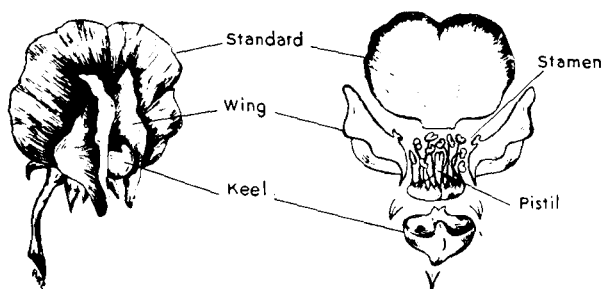


FIG. 3. (Left) Mature pea blossom. (Right) Diagram of pea blossom showing perals, consisting of the standard, wings, and keel, separated to expose the pistil and stamens. The boat-shaped keel and the wings close tightly around the pistil and stamens insuring self-pollination.

breeding varieties; second, the flowers were well protected from the influence of foreign pollen, owing to the close encasement of the reproductive organs inside the petals of the flower (Fig. 3); and last, the hybrids resulting from crossing two varieties were perfectly fertile. The last fact had been demonstrated many times by other experimenters.

Having decided upon peas, Mendel obtained seeds of 34 varieties from several seedsmen. These he tested out by planting over a period of two years, in order to be sure that they were pure-breeding varieties. From the list of 34 he selected 22 varieties which he cultivated during the entire eight-year period of the experiments. Without exception they remained constant, indicating that they were pure varieties.

Mendel's primary object was to cross one variety with another and to observe the resulting hybrids⁴ in the first and succeeding generations in order to discover the law which controlled the appearance of contrasting characteristics in successive generations. Peas are normally self-fertilizing, but the production of hybrids is not difficult: all that is necessary is to open the bud before the flower is fully developed, and with forceps to extract the pollen-

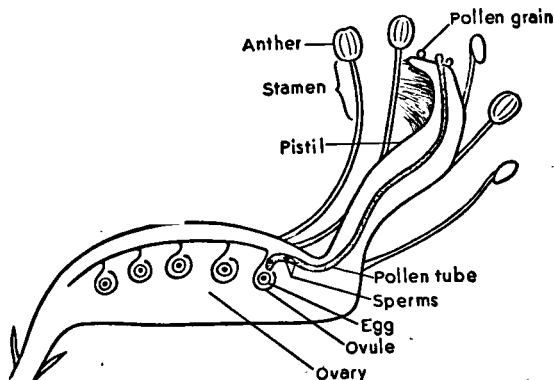


FIG. 4. Diagram of pistil and stamens of the pea showing pollen tube growing down carrying the sperm to fertilize the egg. The second sperm unites with two other nuclei (not shown) in the ovule to produce the endosperm of the seed.

producing organs (stamens); then the pollen, containing the male fertilizing cells or sperms from a plant of another variety, is at once dusted upon the upper end of the egg-producing organ (pistil). This was the technique followed by Mendel.

The wall of the pollen grain soon breaks, and a pollen tube containing the sperm cell grows down, eating its way through the pistil until it finally reaches the egg in the ovary (expanded lower end of the pistil). This is shown in Fig. 4. Here the sperm fertilizes the egg just as it does when the pollen comes from the stamen of the same flower. The seed which develops after cross-fertilization is a hybrid for the same reason that an animal whose parents are of different varieties is a hybrid.

⁴ Although the term hybrid is often used in a popular sense to mean the offspring of two distinct species, it is used properly also, as pointed out by Mendel, for offspring of two different varieties.

REASONS FOR MENDEL'S SUCCESS

Mendel was keenly aware of the basic problems which had to be solved in order to gain an understanding of the mechanism of heredity. He has been credited by the leading contemporary British cytologist, Darlington,⁵ with the successful conduct of two of "the three vital experiments" on which modern genetic principles are founded. The best known of these experiments, his work with peas, is described in the next two chapters. The second experiment, which is not widely known and is not often mentioned, led to the proof that a single pollen grain is sufficient to bring about the fertilization of the egg of a plant. The results were reported in 1879 in a letter to the German botanist Nägeli.

On the basis of experiments of leading investigators of the time it had become generally accepted that several pollen grains were necessary for a single fertilization. If true, this would have been irreconcilable with Mendel's deductions regarding the laws of heredity obtained in his experiments with peas. Accordingly, he considered it necessary to repeat the pollination experiments. He used the same plant, the four-o'clock (*Mirabilis*), as the previous workers had used. In this plant the pollen grains are extraordinarily large. His results were directly contrary to those of previous workers. He obtained from fertilization with single pollen grains, eighteen well-developed seeds and from them as many plants, the majority of which were just as fully developed as those derived from free pollination.

Mendel correctly explains the advantage in using a number of pollen grains. He concludes that pollen grains are not all alike in their fertilizing capacity. With a number of grains there is a chance that one at least will be successful in effecting fertilization. Where several compete, he says, we may assume that always the strongest succeeds in alone effectuating the fertilization. Differences in viability and in growth rate in pollen have been abundantly confirmed in many different species of plants since Mendel's time.

Like all great discoverers, Mendel had predecessors from

⁵ "The Evolution of Genetic Systems," by C. D. DARLINGTON, 1939, Cambridge University Press.

whom he got ideas and by whose mistakes he profited. Hybridization experiments had been done many times before with both animals and plants, including peas, but not one of the earlier experimenters had succeeded in discovering the law by which one could predict what sort of offspring a given hybrid would produce, and the relative numbers of each kind to expect. Mendel clearly saw the reasons for such failures and took every precaution to avoid them.

First, he recognized the necessity of keeping adequate records. A good experimenter must first of all be a good bookkeeper. He saw that he must keep separately the records for each generation and that he must carefully divide the offspring in each generation into classes according to their visible characteristics and record the exact numbers of each class. Finally, he recognized that a law of cause and effect cannot be deduced from a few instances, but that the numbers must be large enough to insure that merely chance occurrences will cancel one another, leaving the underlying law free to assert itself. A failure to recognize the necessity of adequate numbers is the statistical rock on which countless otherwise promising experiments have foundered.

DOMINANCE AND THE LAW OF SEGREGATION

MENDEL, unlike most of his predecessors, perceived that the laws of heredity in a complex organism must be discovered by concentration on one characteristic of the organism at a time. Other investigators had failed, partly because of their attempt to experiment with the organism as a whole. Having chosen peas as his experimental material, Mendel reduced the problem to its simplest terms by selecting for study a single pair of easily recognizable, contrasting characteristics. Other pairs were in turn selected until at the conclusion of his experiments he had thoroughly analyzed seven pairs of such characteristics. These seven pairs are as follows:

1. Differences in the shape of the ripe seeds: either smoothly rounded or deeply wrinkled and irregular in shape.
2. Differences in the color of the cotyledons: either yellow or green.
3. Differences in the color of the seed-coat: either grey-brown or white.
4. Differences in the form of the ripe pods: either simply inflated, not constricted in places, or deeply constricted between the seeds.
5. Differences in the color of the unripe pods: either green or yellow.
6. Differences in the position of the flowers: either axial, that is, distributed along the main stem; or terminal, that is, bunched at the top of the stem.
7. Differences in the length of the stem: either tall, from 6 to 7 ft.; or short, from $\frac{3}{4}$ to $1\frac{1}{2}$ ft.

Between varieties showing sharp contrasts in the characteristics selected he made crosses in the manner previously described. The offspring from the hybrids were in turn studied through successive generations.

ROUND PEAS AND WRINKLED PEAS

Let us now examine one of Mendel's experiments—an experiment that will illustrate perfectly the results he obtained in all. A variety of peas having smoothly rounded seeds was crossed with a variety having deeply wrinkled seeds. The hybrid seeds resulting from this cross were all round, like the round-seeded parent. This was true regardless of which variety was used to furnish the pollen and which the eggs.

The following season Mendel planted the hybrid round seeds. From these at harvest time he obtained 5,474 round seeds and 1,850 wrinkled seeds, or a ratio of 2.96 round to 1 wrinkled (almost a perfect 3:1 ratio).

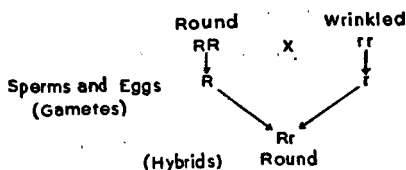
Although the hybrids had all been visibly indistinguishable from their round parent, they were evidently not pure round, since one-fourth of their offspring were wrinkled. The wrinkled character, he concluded, must in some way have been carried over in a latent form in the hybrid. Round had dominated in the hybrid and therefore Mendel called this the *dominant* character; wrinkled had receded from view, therefore he called this the *recessive*.

What is the explanation of the ratio of 3 to 1 in the third generation? Mendel's correct answer to this question deserves the highest credit, for in his day little had yet been discovered about what goes on inside of plants during reproduction, save that there was the formation of two sorts of reproductive cells (eggs and pollen cells); that the pollen cell fused with the egg in the process of fertilization; and that the fertilized egg then developed into a tiny embryo contained within the seed.

Mendel assumed the existence in each pollen cell and egg of a "formative element" capable of determining a character in the offspring. (More accurately, a single nucleus from the pollen grain, Fig. 4, functions as a sperm in fertilization. Hereafter we shall refer to this nucleus as the sperm.) Upon fertilization, these

“elements” or determiners are brought together in pairs; they continue to reside in pairs throughout the life of the organism until the time again comes to produce sperms and eggs; then they separate. In a pure-bred variety the determiners occur in identical pairs, which may be represented by two capital letters, as RR , for round. In the contrasting variety, wrinkled, the determiners are different from those for round, and the symbols chosen must therefore be different, as for example rr . (Following Mendel’s lead, there has grown up a universal custom of representing dominant determiners by capital letters and recessive determiners by lower case letters. This method of symbolism is the simplest yet devised. It has many uses in dealing with problems in heredity.) As a matter of economy, the single term *gamete* is often used to denote either a sperm or an egg.

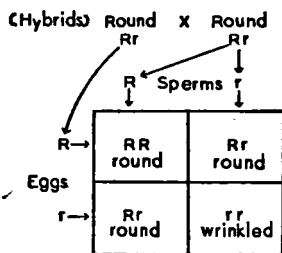
A cross mating of round peas and wrinkled peas is therefore represented as follows:



The dominant determiner is able in some unknown way to override completely the recessive determiner so that all of the hybrid seeds are round like the round parent.

The term *hybrid* can now be defined more exactly as an individual resulting from the union of a sperm and an egg which differ in one or more determiners. The word hybrid is used as an adjective in exactly the same sense. Thus we have hybrid corn, hybrid roses, etc. Another term commonly used for hybrid is *heterozygote* (*hetero*, different; *zygote*, egg); the word *homozygote* (*homo*, same; *zygote*, egg) is used to denote an individual in which both determiners are identical. The terms *heterozygous* and *homozygous* serve as adjectives in corresponding senses.

The union of the determiners in hybrids is, however, only temporary, and when the hybrid seeds in turn are planted and eventually produce sperms and eggs, the determiners R and r liberate themselves from the union, as shown below:



Having liberated themselves from the union, the determiners are now free to combine either with a determiner like themselves or with one of the contrasting kind. Obviously, the hybrid produces two kinds of eggs and two kinds of sperms with respect to the determiner under consideration, and these occur in equal numbers. Each kind of egg has exactly the same chance of functioning in fertilization as the other, and the same rule holds true for the sperms. The hybrids, therefore, produce offspring represented by four combinations of letters: RR , Rr , rR , and rr ; and these occur in equal numbers. Rr and rR are identical, making the true ratio 1 RR to 2 Rr to 1 rr . Since R is dominant over r the first three look alike, and the visible ratio is therefore 3 round to 1 wrinkled.

The principle illustrated by the round and wrinkled peas is known as the *Law of Segregation*.

OTHER CHARACTERS FOLLOW THE SAME LAW

In like manner with all his other six pairs of contrasting characteristics, Mendel found that one member of each pair was fully dominant and the other was recessive. Which one was to be dominant and which one was to be recessive could not be predicted; it could be discovered only by making the cross. Mendel had no theory as to why one determiner dominates over the other, and even today in only a few cases have we an adequate theory of dominance. Undoubtedly in all cases dominance is bound up in some way with the physiology of development of the organism.

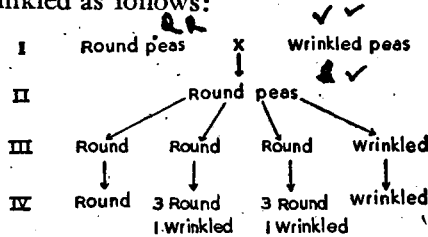
Just as with the characters round and wrinkled, the hybrids for every other pair of determiners produced offspring consisting of dominants and recessives, always approximately in a ratio of 3 dominants to 1 recessive.

LATER GENERATIONS OF HYBRIDS.

A less critical investigator might have stopped his experiments at this point, but Mendel was not yet satisfied. His next step was to plant the seeds of the third generation to see what happened. The reader may now safely risk a prediction as to the outcome.

Mendel found in every case that the recessives, when self-fertilized, produced only pure recessives. We can see why this should be. A wrinkled seed always contains both determiners *rr*; it cannot be a hybrid since the hybrid *Rr* is always round. A recessive must therefore always breed true.

With the round seeds of generation III, however, Mendel found that one-third produced nothing but round seeds; the other two-thirds produced round and wrinkled seeds in the ratio of 3 round to 1 wrinkled as follows:



Mendel continued this testing process through six generations of descendants of the first hybrids, and in each generation the round seeds produced by hybrid round peas continued to appear in the ratio of one pure-breeding round to two hybrid round. It is obvious from the preceding diagram that if self-fertilization of all the offspring occurs in each generation, the proportion of hybrids in the entire population diminishes rapidly from generation to generation, while the proportion of pure types steadily increases. This, Mendel writes, confirms the observations made by other investigators that hybrids tend to revert to the parental types. Theoretically, however, the hybrids will never disappear entirely.

MENDEL'S DETERMINERS: CHROMOSOMES AND GENES

In Mendel's day modern methods of staining cells in order to make visible their differentiated structures had not been perfected; and, as far as we can learn from his paper, Mendel was unaware of

any visible structure in the cells of living things capable of serving as the determiners. Determiners remained for the time being as purely hypothetical "elements." Not long after Mendel had published his results, however, visible structures (now known as *chromosomes*¹) were observed regularly in cells. Some years later it was found that the chromosomes occur in pairs in all the body cells of organisms, including the reproductive organs, and that during the formation of the eggs and sperms the chromosomes constituting each pair in the early reproductive cells separate so that each egg and sperm receives only one member of each pair. At fertilization they again come together in pairs. There is thus a perfect parallelism between the behavior and distribution of the chromosomes as we know them today and of the determiners mentioned by Mendel. Since Mendel's time, by methods ever growing in refinement, it has been proved beyond doubt that the chromosomes contain the "formative elements" or determiners which Mendel assumed to exist. The shorter name *gene* has now been adopted everywhere to designate the determiners. The chromosomes and genes are considered in detail in later chapters.

THE BACK-CROSS: PURITY OF THE GENE

The core of Mendel's discovery, as just described, is that individuals which are hybrid (heterozygous) with respect to one pair of determiners (genes) always produce two kinds of eggs and two kinds of sperms, while those which are pure (homozygous) produce only one kind. Moreover, Mendel's ratios show that the two kinds of eggs and sperms occur in equal numbers, and that at fertilization the union is as likely to take place between identical genes as between unlike genes. The specific genes contained in a sperm usually have nothing to do with its ability to reach and fertilize the egg; nor do the specific genes of the egg determine its capacity for fertilization.

In the experiment in which the hybrids were tested out through six successive generations there was found no contamination of one

¹ The word chromosome (*chroma*, color; *soma*, body) was coined by Waldeyer, 1888, and alludes to the ready capacity of these cellular bodies to absorb basic dyes. Although chromosomes had been seen before Mendel's time, it was not until the 1870's and 1880's that their significance in cell division was finally established.

gene by another, in spite of their close association in the same cells of the hybrid, for at the end of the experiment the hybrids were still producing pure dominants and pure recessives in the same ratio as at the beginning. The purity of the gene is a point of fundamental importance. Evidently the gene behaves almost as an autonomous body within the cell, being affected neither by other genes in the same cell nor by the cells of the organism as a whole. The genes remain pure indefinitely.

Many experiments to test this conception of the purity of the gene have been performed since Mendel's time. The most extensive of these, extending over a period of more than 15 years, carried on at Johns Hopkins University under the direction of Professor Raymond Pearl,² fully confirms Mendel's results. Using the fruit fly *Drosophila* (Fig. 5), as the experimental animal, more than 300 successive generations of descendants of a particular individual were reared. Converted into human generations and allowing four generations to the century, this would carry us back farther than 5500 B.C. Such an experiment is made possible by the fact that under favorable conditions the life cycle of this fly is completed within ten days.

The gene chosen for testing in this experiment was one affecting the development of the wings, a recessive gene known as vestigial, the effect of which is to reduce the wings to useless stubs. The experiment was begun with a normal male mated to a female with vestigial wings. The hybrids all had normal wings. From these hybrids and from the hybrids in each succeeding generation males were bred back to vestigial females, making what is known as *back-cross matings*. From each back-cross mating the ratio of normal-winged offspring to vestigial-winged offspring was always 1:1. Consequently, the normal gene in the hybrids was exposed for more than 300 generations to the influence of the contrasting recessive gene—and this without showing any effect whatever of the vestigial gene on the normal gene.

The method of the back-cross mating has important applications to plant and animal breeding, as well as to human heredity. It is being used on a large scale to develop disease and insect

² PEARL, RAYMOND: *Biology and social trends, J. Washington Acad. Sci.*, 25: No. 6, 1935.

resistant varieties of plants such as wheat.³ In the development of pure breeds of animals one often wishes to know whether a certain

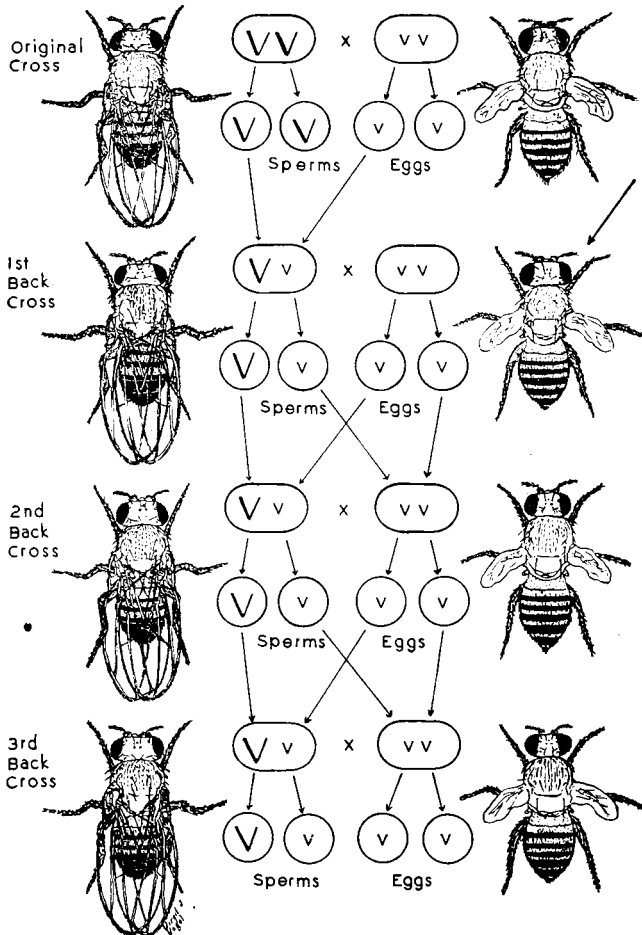


FIG. 5. Diagram illustrating a back-cross mating in the fruit fly *Drosophila*. A normal-winged fly is mated to a vestigial-winged fly; the hybrid is then mated to a vestigial-winged fly, and this cross is repeated in each generation. The ratio in each back-cross generation is 1 normal to 1 vestigial.

individual is hybrid or pure with respect to a dominant character. The back-cross mating is the simplest and quickest way of finding

³ BRIGGS, FRED N.: The use of the backcross in crop improvement, *Am. Naturalist*, May-June, 1938

out. The suspected hybrid, say a colored guinea pig, is mated with a recessive white one, as illustrated in Fig. 6. Since the colored guinea pig represented in the figure is a hybrid, the offspring will appear in the ratio of 1 colored to 1 white. If the colored animal had been pure, all the offspring would of course have been colored, since colored is dominant. Obviously the back-cross method of testing is simpler than the method of mating the suspected hybrid

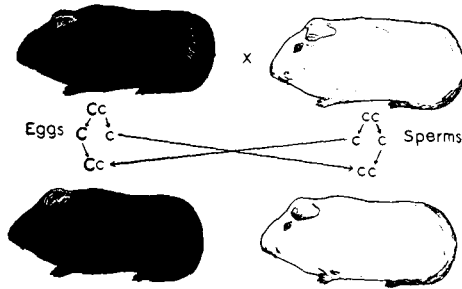


FIG. 6. A back-cross mating between a hybrid colored guinea pig and a recessive white guinea pig, resulting in a ratio of 1 colored to 1 white.

to another hybrid, since the ratio from the latter mating would be 3 dominants to 1 recessive and, in order to obtain one recessive, would therefore necessitate the raising of a larger number of animals than is necessary in the back-cross mating.

THE LAW OF PROBABILITY

Suppose that in testing out a colored guinea pig suspected of being a hybrid by the back-cross method just described, one obtains five offspring, all colored. Does this prove that the colored animal is pure? If not, how many colored offspring is it necessary to get before one can say that his animal is homozygous? The answer to these questions is given in the following simple analysis.

The prediction of the color of the young guinea pigs is like predicting heads or tails in the fair flip of a coin. The causes favoring a sperm with large C in fertilizing a given egg are balanced exactly by those favoring a sperm with small c , just as the causes in favor of heads are balanced by those in favor of tails. What is the chance of obtaining a straight run of five heads? On the first

flip the chance of heads is one in two. On the second flip the chance is also one in two. Therefore, the chance of obtaining heads on the first two flips is one-half of one-half or one in four. In like manner the chance of obtaining a run of two black guinea pigs from a hybrid back-crossed to a white is one in four.

If there is any doubt in the reader's mind about the last statement it can be settled by a simple experiment. Let heads stand for black guinea pigs and tails stand for white. Toss a coin twice and record the results. Repeat 100 times. It will be found that on approximately 25 throws out of 100 there will be a run of two heads, on 25 throws a run of two tails, and on 50 throws one head and one tail, or *vice versa*.

What is the chance of obtaining a run of three heads, or three black guinea pigs? There has already been a run of two heads in one trial out of four ($\frac{1}{4}$). On the third flip the chance of getting a head is one in two ($\frac{1}{2}$). Therefore in $\frac{1}{2} \times \frac{1}{4}$, or $\frac{1}{8}$ of the times we will get a run of three heads. This also can be proved experimentally by tossing three coins.

The rule is now evident. Each time the length of the run is increased by one the chance of obtaining it, expressed as a fraction, is divided by two, as shown in Table 1.

If the chance of an event occurring is one in six (as would be the case in an attempt to throw a given number with a die) the chance of obtaining any two desired numbers, say two five spots, with two dice will be $\frac{1}{6} \times \frac{1}{6}$ or one in 36. We can generalize this law of probability a step further by saying that the chance of two or more wholly independent events occurring simultaneously is equal to the product of the chances of the events occurring separately.

Table 1

Run of 1 head.....	1 chance in	2
Run of 2 heads.....	1 chance in	4
Run of 3 heads.....	1 chance in	8
Run of 4 heads.....	1 chance in	16
Run of 5 heads.....	1 chance in	32
Run of 6 heads.....	1 chance in	64
Run of 7 heads.....	1 chance in	128
Run of 8 heads.....	1 chance in	256
Run of 9 heads.....	1 chance in	512
Run of 10 heads.....	1 chance in	1,024

the nearer he approaches certainty that the parent is pure-bred or homozygous, but he can never arrive at absolute certainty. The point at which the breeder stops his test will depend on practical considerations, such as time and expense involved. He may decide after the first ten, all colored, that for his purpose he is reasonably certain of the purity of the animal. Nevertheless, he runs the risk of being wrong once in about a thousand times.

To some minds this element of uncertainty in certain problems involving Mendel's laws may appear as a decided weakness, making the application of the laws to man of doubtful value. But such a view has no justification in fact. At last analysis, many—if not all—of the so-called laws of nature are statistical laws, i.e., laws involving probability. Through reliance on these laws, the affairs of men are conducted with a reasonable degree of success. Most of our decisions and activities as individuals are controlled by considerations of probability. If men waited for absolute certainty of the success of their enterprises before acting, little would be accomplished.

From the foregoing examples it is evident that by probability we mean simply the chance of occurrence of any particular form of an event expressed as a fraction of the total number of ways in which the event might occur—assuming always that all forms of the event are equally likely of occurrence.

Thus, since there are only two possible ways for a tossed coin to fall, each being equally likely, the probability of heads coming up is $\frac{1}{2}$; or, since a heterozygous organism such as *Aa* produces only two forms of gamete, and these in equal numbers, the probability of *A* occurring in any given fertilization is $\frac{1}{2}$.

Since the law of probability is always at work in sexual reproduction, there must be offspring in reasonable numbers before conclusions as to ratios and modes of inheritance can be drawn. In a single human family the number of children is usually too small for the observed ratio alone to have great significance. For this reason we require many similar consistent pedigrees before we conclude that a given human trait is inherited in accordance with Mendel's laws. This is especially true of recessive traits. Albinism, for example, was diagnosed as a recessive single gene difference only upon the basis of numerous consistent pedigrees.

As we have seen, the law of probability applies to the occurrence of combinations of primary events as well as to the events themselves. Thus in flipping a coin the calculation of the probability of obtaining a run of three heads was found to be $\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} = \frac{1}{8}$. The run of three is itself an event of a higher order than the flip of a single coin.

Suppose we wish to know the chance of obtaining any particular combination of heads and tails, such as two heads and one tail in three flips. We may find the answer by writing down all the possible forms of the event and noting what fraction of the total consists of two heads and one tail. The following eight runs alone are possible, and each is equally likely of occurrence.

<i>1st flip</i>	<i>2nd flip</i>	<i>3rd flip</i>	<i>Run</i>	
head $\frac{1}{2}$	head $\frac{1}{2}$	head $\frac{1}{2}$	$\frac{1}{8}$	} $\frac{3}{8}$ 2 heads: 1 tail
head $\frac{1}{2}$	head $\frac{1}{2}$	tail $\frac{1}{2}$	$\frac{1}{8}$	
head $\frac{1}{2}$	tail $\frac{1}{2}$	head $\frac{1}{2}$	$\frac{1}{8}$	
tail $\frac{1}{2}$	head $\frac{1}{2}$	head $\frac{1}{2}$	$\frac{1}{8}$	} $\frac{3}{8}$ 2 tails: 1 head
tail $\frac{1}{2}$	tail $\frac{1}{2}$	head $\frac{1}{2}$	$\frac{1}{8}$	
tail $\frac{1}{2}$	head $\frac{1}{2}$	tail $\frac{1}{2}$	$\frac{1}{8}$	
head $\frac{1}{2}$	tail $\frac{1}{2}$	tail $\frac{1}{2}$	$\frac{1}{8}$	
tail $\frac{1}{2}$	tail $\frac{1}{2}$	tail $\frac{1}{2}$	$\frac{1}{8}$	

We were interested merely in the chance of obtaining the combination two heads and 1 tail and not in the order in which heads and tails came up. Evidently three of the runs out of eight are of this constitution and the answer to our problem is three times in eight.

With increase in numbers the labor involved in calculating probability by the above method soon becomes excessive. An alternative method, which gives all possible combinations with less labor; consists of the algebraic expansion of the binomial. The binomial $(x + y)$ is raised to the power corresponding to the total number of individuals. In our problem, this being three, we have $(x + y)^3 = x^3 + 3x^2y + 3xy^2 + y^3$.

If we let x stand for the chance of obtaining heads and y stand for the chance of obtaining tails we obtain for the second term, which is the combination desired, $3 \cdot \frac{1}{2} \cdot \frac{1}{2} \cdot \frac{1}{2} = \frac{3}{8}$.

Where small numbers of individuals only are involved the use of the binomial theorem is of great practical value in giving the probability of obtaining by chance a particular ratio among two

classes of individuals. For larger numbers and for problems dealing with more than two classes of individuals other statistical methods have been developed. One of these is described in the next chapter.

ALBINISM, A MENDELIAN TRAIT IN MAN

In human heredity two questions often arise: (1) Does a given characteristic follow Mendel's laws? (2) What are the probabilities that a given Mendelian characteristic will appear in the offspring of a particular mating?



FIG. 7. An albino boy and his normally pigmented twin, offspring of normally pigmented Mexican parents. The eyes of the albino have a pinkish cast. Three other children in the same family are normal. (From WINDLE: *J. Heredity*, Jan., 1935.)

In attempting to answer the first question with respect to man, Mendel's technique of controlled breeding experiments obviously is not practical. We must study the pedigrees of human families as we find them. For example, take the case of albinism in man. In albinism there is almost total lack of pigment in the skin, hair, and eyes. The eyes appear pink as a result of the reflection of light from the blood vessels of the eye. The vision is very defective, not only because of the extreme sensitiveness to light (note squinting of albino child in Fig. 7), but also due to the imperfect development of the retina itself. The skin of albinos also appears pink where the blood vessels approach the surface. Albinos occur

in all races of man and probably in all species of domesticated mammals, as well as in wild species. Practically every large museum of natural history displays mounted specimens of albinos representing various wild species, such as woodchucks, porcupines, skunks, opossums, squirrels, etc.

In laboratory mammals such as white mice, white rats, white rabbits, white guinea pigs, and so on, albinism is invariably inherited as a recessive. It is, therefore, probably inherited in the same manner in wild animals. In man, a study of hundreds of pedigrees points to the same conclusion. When both parents are albinos, the children are all albinos.⁴ Most human albinos, however, as in wild animal species, come from normally pigmented parents (Fig. 7). This is true whether the parents are Caucasians, Negroes, or Mongolians. The occurrence of an albino under such circumstances depends upon the chance mating of two individuals both hybrid (heterozygous) with respect to the albino gene. A typical pedigree taken from an extensive monograph on albinism is shown in Fig. 8. In this pedigree the gene for albinism probably had been carried for a good many generations without making its presence known. The marriage of cousins merely increased the chance that each parent would carry the gene. The monograph also includes many pedigrees showing albino children from marriages of unrelated persons.⁵ From all the evidence at hand, we are justified in concluding that albinism in man, like that in other mammals, is a recessive character.

Knowing that a given human trait is Mendelian, its appearance in the offspring can be predicted with the same degree of certainty as in other organisms. For example, since the parents of the pigmented child shown in Fig. 7 must both be heterozygous for albinism, the child himself has a chance of one in three of being entirely free from the gene for that character. This leaves two chances out of three that he is heterozygous for the gene. If later he should marry a woman who also had an albino brother or sister (she like himself would have a chance of two in three of

⁴ A few exceptional cases have been reported. If authentic, these are possibly the result of a mutation of the albino gene back to normal. Such reverse mutations are occasionally observed in *Drosophila*.

⁵ For a discussion of the relationship of cousin marriages to the expression of recessive traits, see Chapter 14.

being heterozygous for the albino gene), the chances of both partners in marriage being simultaneously heterozygous for the albino gene would be $\frac{2}{3} \times \frac{2}{3} = \frac{4}{9}$ (four out of nine). If both parents should happen to be heterozygous for the albino gene the chance of their first child being an albino would of course be one in four. Putting these two probabilities together we can say that the chance of an albino as the first child of two normally pigmented persons, both from families in which there is an albino brother or sister, is $\frac{4}{9} \times \frac{1}{4} = \frac{1}{9}$ (one in nine).

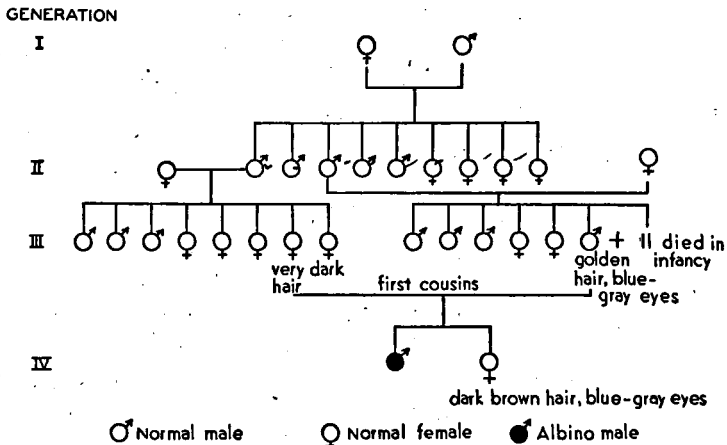


FIG. 8. Pedigree showing an albino boy born to normal parents who are first cousins. (From "A monograph on albinism in man," Part IV, by K. PEARSON, E. NETTLESHIP, and C. H. USHER, Dulau & Co., London, 1913.)

The principle stated above applies in the case of any other recessive gene; therefore, where questionable genes are concerned, it becomes plainly a matter in which the prospective partners in marriage may decide for themselves whether the risk of an undesirable recessive character appearing in their children is too great to be run.

LACK OF DOMINANCE

Although Mendel chose for his final experiments contrasting pairs of characters in which essentially complete dominance of one character prevailed over the other, he observed that dominance was not a universal law in peas. In his preliminary experiments he

The difference between cases of dominance and lack of dominance evidently relates to the physiological effect of the genes in the hybrid. Where dominance exists a single dose of the dominant gene completely masks any effect of the recessive gene, while in lack of dominance the two genes co-operate in development to produce a character more or less intermediate between the two original characters. The expression incomplete dominance or partial dominance is sometimes used to cover cases such as the one described, especially where the hybrids tend to resemble one parent much more than the other.

During the years since the rediscovery of Mendel's laws, many cases of lack of dominance have been discovered in plants and animals as well as in man. In all such cases Mendel's conclusion that the law of segregation applies just as in the case of dominance has been fully confirmed.

AN EXAMPLE OF LACK OF DOMINANCE IN MAN

The form of the hair, with reference to curly and straight as found in Caucasians of European descent, illustrates a Mendelian trait showing lack of dominance. The hybrid is intermediate, having wavy hair. The extent of waviness is variable, however, and some hybrids may be classed as curly-haired. Curly hair is therefore sometimes called an incomplete dominant.

Two straight-haired parents have only straight-haired children, and two pure-bred curly-haired parents have only curly-haired children; but to avoid mistakes in classification it should be remembered that wavy hair has a tendency to straighten out with advancing age, and that a wavy-haired person may appear straight-haired if the hair is cut short.

A marriage between a straight-haired person and a wavy-haired person gives children with straight hair and wavy hair in the ratio of one to one. Actual figures for such matings, as cited by Cockayne,⁶ are straight hair 61 to wavy hair 52. This author also gives figures for children both of whose parents had wavy hair as follows: 27 straight to 51 wavy to 22 curly. This ratio is

⁶ COCKAYNE, E. A.: "Inherited Abnormalities of the Skin and Its Appendages," Oxford University Press, 1933.

very close to 1:2:1, and therefore agrees with what we should expect from hybrids where dominance is lacking.

The inheritance of hair form in the Mongoloid and Negroid divisions of mankind does not follow this simple plan. Its consideration, therefore, is deferred to a later chapter.

PROBLEMS

1. In the plant known as the four-o'clock, there is lack of dominance between the flower colors red (RR) and white (rr). The hybrid (Rr) is pink. Give the ratios of the colors expected from the following cross-pollinations:

- (a) Red \times pink.
- (b) Pink \times white.
- (c) Pink \times pink.

2. In peas, tall (TT) is dominant over short (tt). Four experiments in cross-pollination gave the results shown below. In each case give the most probable gene formula of the parents, as indicated by the ratio among their offspring:

- (a) Tall \times tall produced 95 tall, 29 short.
- (b) Tall \times short produced 50 tall, 0 short.
- (c) Tall \times tall produced 75 tall, 0 short.
- (d) Tall \times short produced 12 tall, 5 short.

3. Starting with a hybrid from two pure varieties of peas, round (RR) and wrinkled (rr), find the percentage of hybrids in each of the next four generations (F_2 , F_3 , F_4 , and F_5) resulting from self-fertilization of all individuals in each generation. (Assume that all individuals are equally productive.)

4. The brightly colored petals of flowers are usually explained as devices for the attraction of insects since insects carry pollen on their bodies from flower to flower and thus effect cross-pollination. How do you explain the color of the flowers of peas, which normally are not insect pollinated, but are self-pollinated?

5. Assume that one person out of 70 in the population as a whole is heterozygous (carrier) with respect to the recessive gene for albinism (according to calculations this is somewhere near the actual figure). Assume also that marriages are purely at random with respect to persons who are carriers (Aa) and those who are not (AA). Disregarding marriages of albinos, what is the expected proportion of all births that are albinos?

6. A normal person whose parents are normal has a grandparent who is an albino. Assume that all the other grandparents are free from

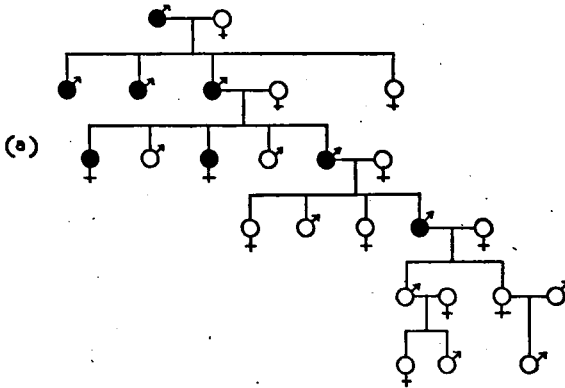
the gene for albinism. What is the chance that this person is a carrier of the albino gene?

7. If the person mentioned in problem 6 marries an individual with a similar pedigree, what chance is there that their first child will be an albino?

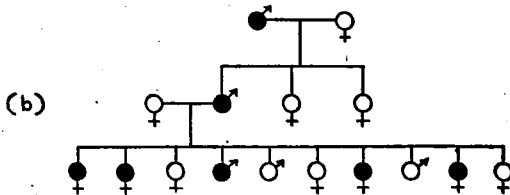
8. A normal person, whose parents are normal, has a grandparent who carries the gene for albinism. Assume that all the other grandparents are free from the gene for albinism. What is the chance that this person is a carrier of the albino gene?

9. Explain the fact that defective traits due to dominant genes are more easily eliminated from a population than are defective traits due to recessive genes.

10. In the following human pedigrees the characteristic mentioned beneath the pedigree is indicated by a solid black circle. The normal condition is indicated by an open circle. Assume for each trait that the difference between the normal and the affected individuals is due to a single gene. Determine in each case whether the characteristic is recessive or probably dominant. Some of the characteristics are very rare. The others are found in a small minority of the population.

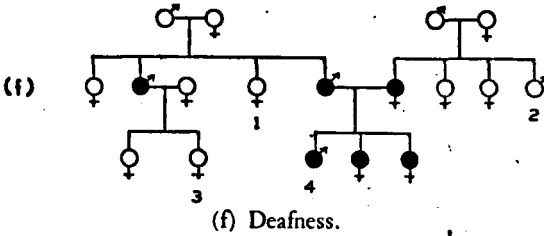
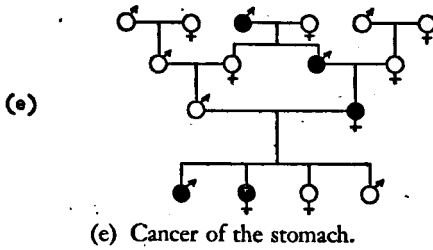
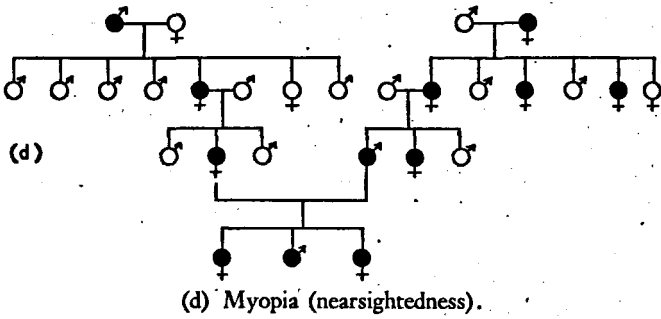
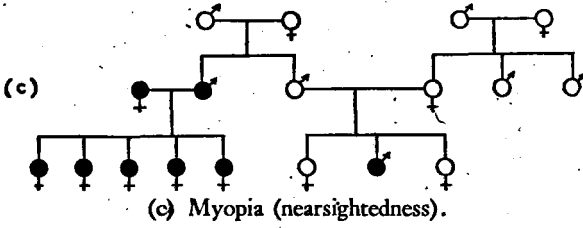


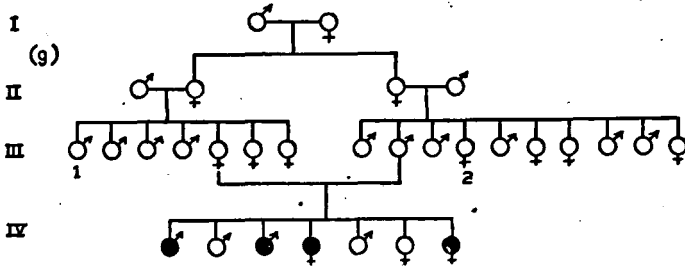
(a) Pick's disease (atrophy of the brain).



(b) Aniridia (absence of the iris).

Problems





(g) Spastic paraplegia (paralysis of the legs).

11. In a marriage between individuals 1 and 2 in the pedigree for deafness (*f*), what is the chance of the first child's being deaf? What is the chance of a deaf child from a marriage between 3 and 4?

12. In a marriage between individuals 1 and 2 in the pedigree for spastic paraplegia (*g*), what is the chance that the first child will develop the disease? (Assume that the mothers of 1 and 2 are both carriers of the gene and that their fathers are both free from it.) What is the chance that one of the normal children in generation IV is a carrier of the gene?

13. Give two possible explanations for the fact that in human beings it is much easier to discover pedigrees of dominant characteristics than pedigrees of recessive characteristics.

14. From a mating of two wavy-haired persons what is the chance that the first four children will be straight-haired?

15. In a mating between a wavy-haired person and a straight-haired mate what is the chance that the first child will be straight-haired and the next three wavy-haired?

16. What is the chance that in the mating indicated in problem 15, two of the four children will be straight-haired and two wavy-haired?

17. In corn, a recessive gene known as albino (*aa*) prevents the development of the green pigment, chlorophyll, in the leaves and stem. After reaching a few inches in height an albino plant dies of starvation. Corn is normally cross-pollinated. Given an ear of corn guaranteed to produce a ratio of three green plants to one albino, show by diagram the steps which you would follow in producing another ear of corn like the first. (Corn may be readily self-pollinated by hand.)

18. Toss three coins simultaneously for 40 throws and record at each throw the combination of heads and tails. Compare your experimental result with the combined ratio obtained by the class as a whole. Why should you expect the larger number of trials to give the better ratio?

3

DIHYBRIDS: THE LAW OF INDEPENDENT ASSORTMENT

THE DISCOVERY of the law of heredity just described (The Law of Segregation) was no small accomplishment, but Mendel did not stop at that point. He recognized that a complex organism contains many determiners (genes), and that if we are to gain an understanding of the organism as a whole, we must be able to put two or more pairs of genes together and interpret the results. His solution of this problem proved to be as brilliant as that of the simpler one. Let us now examine the method of solution of the more complex problem.

Using the seven pairs of contrasting characters previously mentioned, Mendel had found that the dominant and the recessive in each pair were as follows:

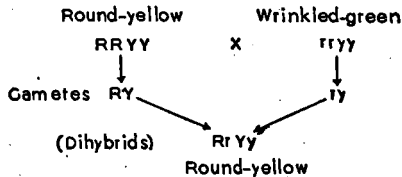
<i>Dominant</i>		<i>Recessive</i>	
1. Round seeds	(RR)	Wrinkled seeds	(rr)
2. Yellow cotyledons	(YY)	Green cotyledons	(yy)
3. Grey-brown seed coats and violet-red flowers	(BB)	White seed coats and white flowers	(bb)
4. Inflated pods	(II)	Constricted pods	(ii)
5. Green unripe pods	(GG)	Yellow unripe pods	(gg)
6. Axial flowers	(AA)	Terminal flowers	(aa)
7. Tall plant	(TT)	Dwarf plant	(tt)

By a series of carefully planned experiments he demonstrated that these characters could be sorted out and recombined in the same free manner as though they were cards shuffled and dealt by a player. One of his experiments, which is typical in its methods and results, is described below.

A DIHYBRID MATING

Mendel crossed a variety combining the seed characters round and yellow with a variety combining the characters wrinkled and green. He does not tell us how he obtained the two pure varieties, but since the shape of peas is commonly either round or wrinkled and the color either yellow or green, he may have been able to select two which suited his purpose from his 22 varieties. He could have produced them easily by making the proper crosses.

The hybrid offspring from this cross were all round-yellow, as shown below:



Mendel planted the dihybrids and obtained from them as a result of self-fertilization four sorts of seeds, the actual numbers of which were as follows:

$$\begin{array}{c}
 \text{Dihybrids } (RrYy) \times (RrYy)^1 \\
 \downarrow \\
 \begin{array}{l}
 (9) \ 315 \text{ Round and yellow} \\
 (3) \ 101 \text{ Wrinkled and yellow} \\
 (3) \ 108 \text{ Round and green} \\
 (1) \ 32 \text{ Wrinkled and green}
 \end{array}
 \end{array}$$

Frequently all four sorts were in the same seed pod. It is obvious that the ratio of the four kinds is almost a perfect 9:3:3:1.

Mendel's explanation of this result, which proved to be entirely correct, is based upon the assumption that there is a separate determiner (gene) for each character; that the gene for each character occurs in pairs in the cells of the plant; that each gamete receives one member only of each pair of genes; that as many sorts of gametes are formed as there are possible combinations of genes, and that these are formed in equal numbers; and finally that all

¹ The "×" is used ordinarily to indicate a mating of two separate individuals. In the case of self-fertilizing organisms such as peas, however, it indicates a mating between the male and female parts of the same individual.

four sorts of sperms have an equal opportunity of fertilizing the four kinds of eggs.

These various assumptions are all represented diagrammatically in Fig. 10. It is perfectly clear that if each gamete is to carry but one gene for each character there can be only the four kinds of

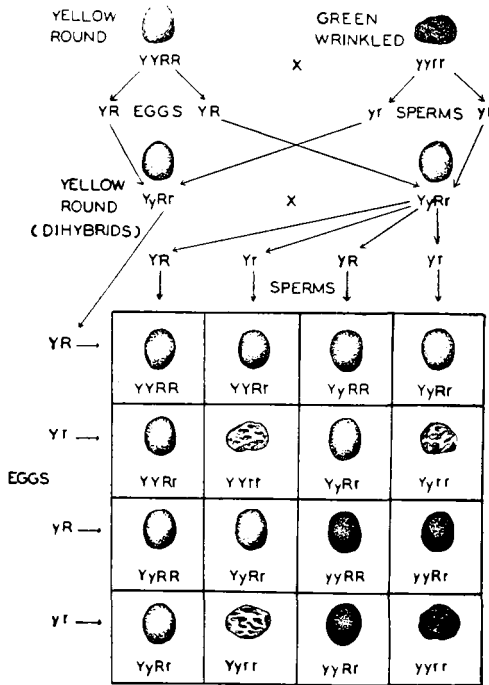


FIG. 10. Diagram showing Mendel's results from crossing two varieties of peas differing in two independent characteristics. The offspring of the dihybrids are represented in the squares of the checkerboard in their actual numerical ratios: 9 yellow round; 3 yellow wrinkled; 3 green round; 1 green wrinkled.

gametes, since these are the only possible combinations of the letters used to represent the genes. The combination of these eggs and sperms at fertilization is merely an extension of the law of probability previously discussed. For example, since one-fourth of all the eggs carry *ry* and one-fourth of all the sperms carry *ry*, the chance of a union between the two (*rryy*) is $\frac{1}{4} \times \frac{1}{4}$ or $\frac{1}{16}$

(one in 16); because, as previously explained, the chance of the simultaneous occurrence of two independent events is equal to the product of their chances of occurring separately.

In the same way, the chance of any other one of the 16 possible combinations taking place is $\frac{1}{4} \times \frac{1}{4}$ or $\frac{1}{16}$ (one in 16). Each of these combinations is represented by a square on the checkerboard.

TESTING THE OFFSPRING OF THE DIHYBRIDS

The rule just disclosed was of far-reaching importance if it could be proved to be of general application, since it showed that an organism was like a mosaic, consisting of many characters, and that by the proper matings the various characters could be sorted out and recombined at will.

In order to establish this principle beyond doubt, Mendel went to great trouble. The following year he planted all 556 seeds obtained from the dihybrids. With painstaking care he tells us exactly how many seeds of each group either failed to develop or did not produce seeds. Altogether there were only 27 nonproductive seeds. The remaining 529 seeds proved by the progeny which they produced that they belonged to the following nine genetic types (*genotypes*):

<i>RrYy</i>	(Round-yellow)	138	} 301 (9)
<i>RRYy</i>	(Round-yellow)	65	
<i>RrYY</i>	(Round-yellow)	60	
<i>RRYY</i>	(Round-yellow)	38	
<i>Rryy</i>	(Round-green)	67	} 102 (3)
<i>RRyy</i>	(Round-green)	35	
<i>rrYy</i>	(Wrinkled-yellow)	68	} 96 (3)
<i>rrYY</i>	(Wrinkled-yellow)	28	
<i>rryy</i>	(Wrinkled-green)	30	30 (1)

An inspection of the checkerboard (Fig. 10) shows that theoretically these nine genotypes are expected in the same ratio as found by Mendel.

Obviously the round-yellow peas are of four genotypes, while the round-green peas and wrinkled-yellow peas are each of two

genotypes. There is only one type of wrinkled-green, since this is the double recessive.

In addition to the foregoing experiment, Mendel performed others in which he united the remaining characters by two's as hybrids, and in all cases obtained the same results.

On the basis of these several experiments it is now possible to predict that dihybrids will produce nine genetically different types of offspring, and that these will appear in the definite ratio indicated above. If dominance is complete for both pairs of characters, these nine genotypes will group themselves under four visible types (*phenotypes*) in the ratio of 9:3:3:1. The law illustrated by the experiment just described is known as the *Law of Independent Assortment*.

LACK OF DOMINANCE IN DIHYBRIDS

In all of Mendel's experiments with dihybrids dominance was present. The law of independent assortment holds good, however, whether there is dominance or not, just as does the law of segregation. It should be emphasized that dominance relates to the physiological effects of genes, while the law of independent assortment concerns the distribution of the genes.

To illustrate independent assortment without dominance we may choose a well known case in cattle. In hair color, red is due to a pair of genes, *RR*. White may be designated *rr*. The hybrid, *Rr*, is not red, but roan (red hairs intermingled with white hairs, producing a brindled effect). The three colors, red, roan, and white, are all found in the shorthorn breed of cattle (See Fig. 11). Since roan is always a heterozygote roans never breed true, but when two roans are mated they yield reds, roans, and whites in the ratio of 1:2:1. It is of course possible to obtain pure-breeding races of reds and whites simply by mating them with their own color exclusively.

Hereditary lack of horns (known as polled) is due to a simple dominant gene, *H*. Horns are due to a recessive, *h*. Among the shorthorns there are hornless as well as horned animals (Fig. 11). Since the character *horns* is independent of color it is easy to produce pure races of reds or whites, with or without horns, as desired.

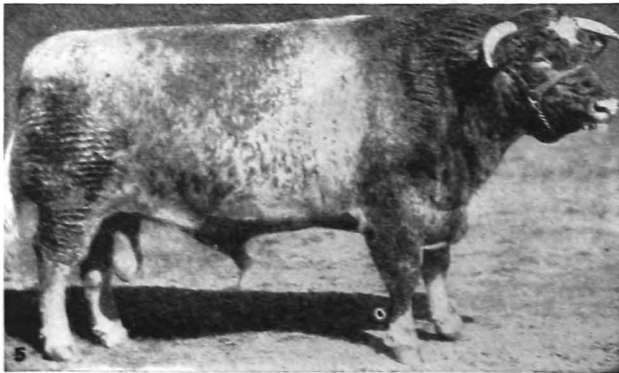
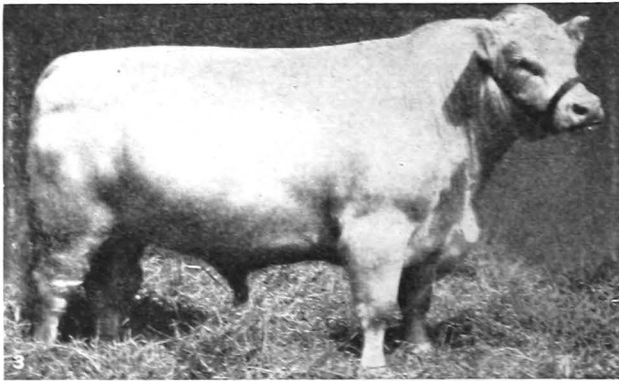
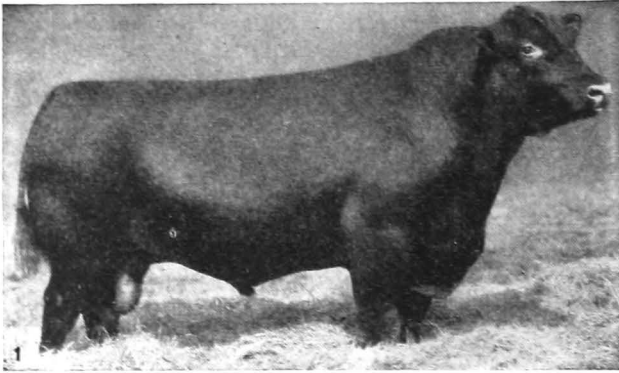
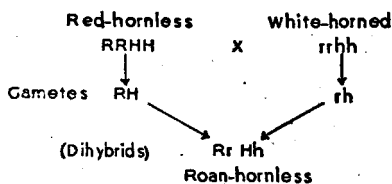


FIG. 11. Prize shorthorn cattle. 1. Red polled bull. 3. White polled bull. 5. Roan horned bull. (1 and 3 from photographs by Robert F. Hildebrand; 5 from a photograph by H. A. Strohmeyer, Jr.) (Courtesy, Encyclopaedia Britannica, V. 5, plate 1, at p. 48, U.S. edition, 1945.)

If a mating is made between a red-hornless animal and a white-horned animal, the offspring will all be roan-hornless, regardless of which one is the male and which the female, as follows:



If two of these roan-hornless hybrids are mated the offspring are as shown in Fig. 12.

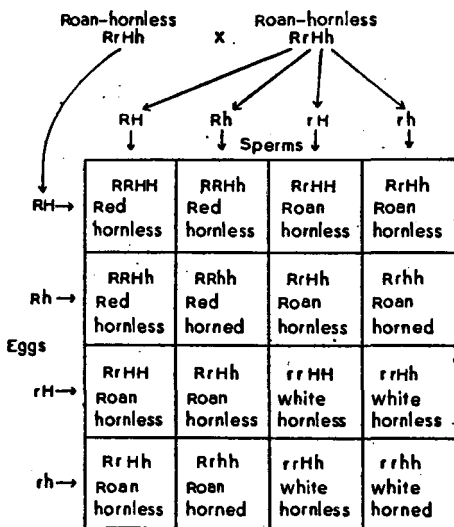


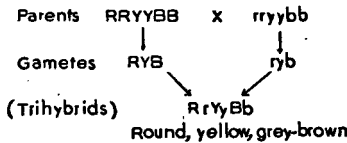
FIG. 12. Diagram showing the results of mating two roan cattle each of which is hybrid with respect to hornless. The visible ratio is 3 red hornless:6 roan hornless:3 white hornless:1 red horned:2 roan horned:1 white horned.

The number of visible types (phenotypes) here obtained is six instead of four as it would have been with dominance in both pairs of genes. The number of genotypes, however, remains the same, i.e., nine. If dominance had been lacking with respect to horns as well as color, the number of visible types would have

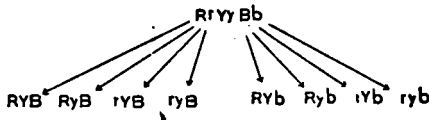
been increased to nine and there would then have been the same number of phenotypes as genotypes.

TRIHYBRIDS SHOW INDEPENDENT ASSORTMENT

Having demonstrated the law of independent assortment for two pairs of characters, Mendel next performed an experiment in precisely the same manner except that he used three pairs of characters. Of all his experiments he states that this one demanded the most time and trouble. The cross is represented as follows:



Mendel planted all the seeds which he obtained from the trihybrids and found that each of the three characters segregated independently of the other two characters. The principle governing trihybrids was found to be identical with the principle governing dihybrids. It is easy to see why this should be so if we look for a moment at the constitution of the trihybrids. Since they are hybrid in three separate respects they will produce gametes of the following eight types:



Note that the combinations on the left are identical with those on the right except that those on the left have a large *B* instead of a small *b*. The addition of a third pair of genes has obviously doubled the number of possible combinations.

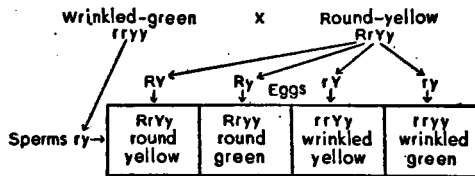
The union at fertilization of eight kinds of eggs with eight corresponding kinds of sperms, in a purely fortuitous manner, produces a population consisting of 27 different genotypes instead of the nine genotypes produced by dihybrids. In order to work out this problem in detail by the checkerboard method as we did for the dihybrid (Fig. 10) we must use a checkerboard having eight squares each way instead of four.

In cases of complete dominance, the 27 different genotypes from trihybrids fall into eight visibly different types as compared with the nine genotypes and four visibly distinct types obtained from dihybrids.

On a smaller scale Mendel performed similar experiments, combining other characters by two's and three's, until he had convinced himself that all seven of the characters chosen for study in his experiments followed the same law; that is, that each of the characters was independent of the other characters. All possible combinations of the seven differentiating characters (128 combinations in all) were actually obtained by Mendel through repeated crossing. This, also, must have involved a great amount of labor.

BACK-CROSSING DIHYBRIDS

As a final test of his theory of independent assortment, Mendel performed a back-cross experiment using one of his dihybrids and the double recessive as follows:



Mendel reasoned that if his theory was correct the dihybrid should form four kinds of eggs as shown above. The double recessive should form but one kind of sperm (ry). If all four kinds of eggs are produced in equal numbers there should result at fertilization four kinds of offspring in equal numbers as follows: 1 round-yellow: 1 round-green: 1 wrinkled-yellow: 1 wrinkled-green. This ratio was actually obtained: there were 31 round-yellow, 26 round-green, 27 wrinkled-yellow, 26 wrinkled-green seeds.

In order to test his theory for both eggs and sperms, Mendel made the reciprocal back-cross, i.e., he used a dihybrid for the sperms and a double recessive for the eggs. From this mating he obtained 24 round-yellow, 25 round-green, 22 wrinkled-yellow, 26 wrinkled green seeds. The results in both crosses confirmed his theory.

All of these seeds were tested by planting the next year, and their genetic make-up proved to be as demanded by the theory.

Similar back-cross experiments were performed with the other five pairs of characters; the results agreed perfectly with those of the foregoing experiments.

Thus, step by step, Mendel had built up an overwhelming mass of evidence, consistent within itself, and proving beyond reasonable doubt the truth of the Law of Independent Assortment.

TESTING THE CLOSENESS OF FIT OF AN OBSERVED RATIO

Statisticians have developed a number of statistical tests by means of which the investigator can determine how well the results of his experiment fit a particular theory of heredity. One of the most valuable of these is known as the *Chi Square Test*, so named because of the use of the Greek letter Chi (χ) as a symbol (Table 2). It may be applied not only to ratios involving two classes of individuals, such as a 3:1, but to those with three, four, and in fact, an indefinitely large number of classes. The test answers the question: what is the probability of obtaining merely by chance a deviation from the expected ratio greater than that shown by our observed data? For example, in an actual experiment with *Drosophila* by students the sex ratio obtained was 419 males to 466 females. The expected ratio in this species is 1:1. Does the observed deviation from a 1:1 ratio here indicate some experimental error or some systematic factor favoring females or is the result merely such a deviation as one might reasonably expect as a result of chance? The steps in the application of the χ^2 test to this case, with the result, are shown in Table 3 (p. 44).

According to the formula for χ^2 it is obvious that the larger the deviation from expectancy the larger will be χ^2 . A definite numerical relationship exists between the size of χ^2 as calculated by this formula and the chance of the deviation being exceeded in either direction merely as the result of chance. This relationship is a complex one algebraically and it is therefore not practicable to calculate the probability for each case. Instead, a table of χ^2 (Table 2) showing χ^2 for a series of probabilities, provided for us by Dr. Fisher, is used. Referring to Table 2 we note that probabilities (P), shown as decimal fractions, are written along the top

Table 2
TABLE OF χ^2

N = \ P =	.99	.98	.95	.90	.80	.70	.50	.30	.20	.10	.05	.02	.01
1	.0002	.0006	.004	.016	.064	.148	.455	1.074	1.642	2.706	3.841	5.412	6.635
2	.0201	.0404	.103	.211	.446	.713	1.386	2.408	3.219	4.605	5.991	7.824	9.210
3	.115	.185	.352	.584	1.005	1.424	2.366	3.665	4.642	6.251	7.815	9.837	11.341
4	.297	.429	.711	1.064	1.649	2.195	3.357	4.878	5.989	7.779	9.488	11.668	13.277
5	.554	.752	1.145	1.610	2.343	3.000	4.351	6.064	7.289	9.236	11.070	13.388	15.086
6	.872	1.134	1.635	2.204	3.070	3.828	5.348	7.231	8.558	10.645	12.592	15.033	16.812
7	1.239	1.564	2.167	2.833	3.822	4.671	6.346	8.383	9.803	12.017	14.067	16.622	18.475
8	1.646	2.032	2.733	3.490	4.594	5.527	7.344	9.524	11.030	13.362	15.507	18.168	20.090
9	2.088	2.532	3.325	4.168	5.380	6.393	8.343	10.656	12.242	14.684	16.919	19.679	21.666
10	2.558	3.059	3.940	4.865	6.179	7.267	9.342	11.781	13.442	15.987	18.307	21.161	23.209

N is equal to the number of "degrees of freedom" in which the observed ratio may differ from the expected, that is, it is equal to the number of classes the frequencies of which may be filled in arbitrarily. With Mendelian ratios, the expected values are calculated from the observed total, so that the four classes in a 9:3:3:1 ratio, for example, must agree in their sum. If three classes are filled in arbitrarily the fourth is determined; hence $N = 3$.

The numbers opposite P (top line) give the probability that χ^2 (in vertical columns) shall exceed the indicated value. For example, with $N = 3$ the probability of exceeding by chance a χ^2 of 7.815 is 5 per cent, or one in 20.

(From "Statistical Methods for Research Workers," by R. A. FISHER, Edinburgh, Oliver and Boyd.)

Table 3

	<i>Males</i>	<i>Females</i>
Observed numbers.....	419	466
Expected numbers on 1:1 (e).....	442.5	442.5
Deviation from expectancy (d).....	23.5	23.5
Deviation squared (d^2).....	552.25	552.25
d^2/e	1.25	1.25

$$\chi^2 = \text{Sum of } d^2/e = 2.50$$

line of the table, and under each probability figure is a vertical column of χ^2 values. The column headed N must now be consulted and the value of N chosen which represents the number of classes in our ratio. With Mendelian ratios such as 1:1, 3:1, 9:3:3:1, etc., we must choose the N which is one less than our number of classes. In our problem therefore, since there are two classes, it will be the number 1. Scanning the χ^2 values opposite N 1 we come to 2.706. This is not far from our calculated χ^2 value of 2.50 and we note that the probability of getting a larger χ^2 than this or, in other words, the chance of obtaining a greater deviation upon repetition of the experiment is approximately 0.10, or one in ten.

Statisticians have arbitrarily chosen to consider a probability greater than 0.05 (one in 20) as not statistically significant. This means that such a deviation from expectancy is not great enough to indicate the operation of any modifying factor, but is probably merely a deviation due to chance. Since ours is twice as great we conclude that the sex ratio actually obtained is well within the range of chance deviation, and hence that we are not justified in regarding the deviation as proof of the operation of some other factor. The deviation here, however, may well be the result of systematic causes rather than of chance. Our calculations cannot answer this question. All our statistical test can do is to give the probability of an observed deviation from expectancy being exceeded as the result of chance.

Let us now apply the χ^2 test to an actual student experiment involving two pairs of genes, in which the expected ratio was 9:3:3:1. The animal used was *Drosophila*. A recessive mutant known as brown eye was crossed with a recessive known as

scarlet eye. The genes show independent assortment. The F_1 hybrids are normal red-eyed. F_1 matings were made and the F_2 's observed. The expected F_2 ratio is 9 red:3 brown:3 scarlet:1 white. In this case the double recessive results in absence of pigment. The results and the calculated χ^2 are shown in Table 4.

Table 4

	Red	Brown	Scarlet	White
Observed numbers.....	1134	430	465	133
Expected on 9:3:3:1 (e).....	1217	405	405	135
Deviation from expectancy (d).....	83	25	60	2
Deviation squared (d^2).....	6889	625	3600	4
d^2/e	5.7	1.5	8.9	.03

$$\chi^2 = \text{Sum of } d^2/e = 16.13$$

Choosing the values of χ^2 opposite $N = 3$, in accordance with the rule mentioned above, we find that our table does not show values of χ^2 larger than 11.341. Interpolating from the table, however, it appears that the probability in our case is somewhere near 0.001. Evidently a result which could occur by chance only once in a thousand times strongly indicates that some explanation other than chance is to be sought. Whether the deviation from expectancy in this experiment is due to experimental error, differential viability, differential rate of development of the flies, or to some other factor or combination of factors, must be sought by further study and experiment.

PROBLEMS

1. In guinea pigs, the gene C for black color is dominant over the gene c for albino. The gene R for rough fur is dominant over the gene r for smooth fur. In the table below, the results are given for five separate matings. Give the most probable genetic formulas for the parents in each mating.

	Black Rough	Black Smooth	Albino Rough	Albino Smooth
(a) Black smooth \times albino smooth.....	0	18	0	14
(b) Black smooth \times albino rough.....	25	0	0	0
(c) Black smooth \times albino rough.....	10	8	6	9
(d) Black rough \times albino rough.....	15	7	16	3
(e) Albino rough \times albino rough.....	0	0	32	12

2. If a pure variety of peas showing the character tall (TT), and terminal flowers (aa) is crossed with a dwarf variety (tt) having axial flowers (AA), and the hybrids are allowed to self-fertilize, what will be the visible ratio among the offspring?

3. What is the chance that the tall axial plants produced by the hybrids in the preceding problem are homozygous for both genes? What is the chance that the tall terminal plants are homozygous for both genes?

4. Show the result of crossing a dihybrid from problem 2 with a double recessive (short terminal) plant.

5. If a pure variety of peas showing the dominant characters tall (TT), axial flowers (AA), violet flowers (BB), is crossed with a variety showing the recessive characters dwarf (tt), terminal (aa), white flowers (bb) and the trihybrids are allowed to self-fertilize, what is the expected visible ratio among the offspring of the trihybrids?

6. Show the results of a back-cross of one of the trihybrids in the preceding problem to a dwarf, terminal, white-flowered plant.

7. In packages of seeds of supposedly pure varieties of peas purchased at seed stores, it is common to find both yellow and green peas in the same package, whereas the seeds in a given package are usually all round or all wrinkled. How may these facts best be explained?

8. Write out the formulae for the gametes produced by an organism hybrid with respect to four genes, as $AaBbCcDd$. What chance have the offspring of two such hybrids to be $aabbccdd$? Assuming that dominance is complete in all four genes, what proportion of the offspring of two such hybrids will show all four dominant effects?

9. Starting with two pure-breeding varieties of peas—round green ($RRyy$) and wrinkled yellow ($rrYY$)—show how you might develop, in the fewest possible generations, a pure-breeding round yellow variety.

10. In cats, solid black fur (aa) is recessive to wild, tiger pattern (AA). With the genes affecting tail length, dominance is lacking: TT stands for the tailless (Manx) cat; tt stands for the normal long-tailed cat; the hybrid, Tt , is bob-tailed. What will be the visible ratios among the offspring of the following matings:

(a) $aaTt \times Aatt$.

(b) $aatt \times AaTt$.

(c) $AaTt \times AaTt$.

11. In Mendel's monohybrid experiments with his seven pairs of characters two, those involving flower color and pod color, showed the largest deviations from the expected 3:1 ratio in the F_2 . With flower color he obtained 705 violet-reds to 224 white. Calculate χ^2 and determine from the χ^2 Table whether this is a statistically significant deviation.

12. With pod color differences Mendel obtained in F_2 428 greens to 152 yellows. Calculate χ^2 and determine the significance of the deviation.

13. Calculate χ^2 for Mendel's F_2 ratio obtained from round-yellow dihybrids, as given on page 34.

14. In his experiments Mendel frequently found a single plant which gave extreme deviations from the expected ratio. For example, in the cross between yellow-seeded and green-seeded varieties one F_1 plant produced 32 yellow and only one green seed, while another gave 29 yellows and 19 greens. Calculate the χ^2 in each of these cases. What can you say of the ratio when the seeds from both plants are combined?

15. In one of Mendel's test experiments theory demanded a ratio of 2:1. From 100 plants he obtained a ratio of 60:40. In order to check the significance of this departure he repeated the experiment, obtaining on the second trial 65:35. Would you have considered it necessary to repeat the experiment? If not, why?

CHROMOSOMES AND MENDEL'S LAWS

AT THE TIME of Mendel's experiments on peas the existence of chromosomes as constant cellular bodies had not been discovered. Mendel therefore made no reference to chromosomes. It remained for an American biologist, W. S. Sutton (1902, 1903), to explain in full the operation of Mendel's laws in the light of chromosome behavior.

During the 1870's and 1880's chromosomes received gradually more and more attention from biologists. The cells of many species of plants and animals were examined, and in all cases, except in some of the simplest one-celled forms, chromosomes were found. Each species was observed to have a definite number of these bodies, appearing always in pairs (an exception in the case of sex chromosomes is noted in Chapter 10), the members of each pair having come from the parental sperm and egg respectively. In a given species the pairs were frequently distinguishable from one another in size and shape.

Rapid progress in their study was made possible by improvement in the methods of studying cells, especially the technique of staining for the purpose of bringing into visibility the various components of the cell. One of the characteristics common to all chromosomes is the special ability to take up basic dyes, a characteristic which makes easy their sharp differentiation from other cellular structures.

MITOSIS

In the period mentioned above, observations on the behavior of the chromosomes at cell division pointed unmistakably to their having some function in heredity: thus it was soon established that the usual method of cell division was not a simple division of

the cell nucleus into two parts, followed by a similar division of the cytoplasm, as had been supposed, but that the chromosomes passed through a definite series of changes and movements adapted to insure the transmission to each of the two daughter cells of a set of chromosomes identical with that of the mother cell. This process, known as *mitosis* (*mitos*, thread) was named by Flemming, one of the discoverers of mitosis, in 1882, in reference to the fact

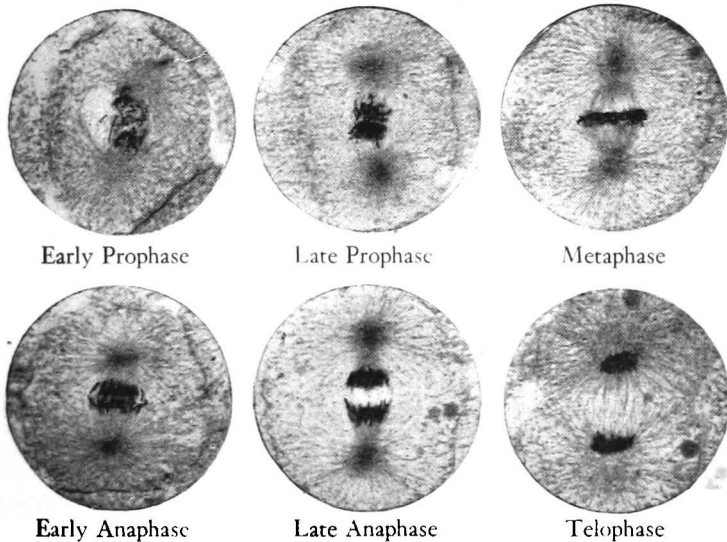


FIG. 13. Mitosis in the early embryo of the whitefish. (Photomicrographs, courtesy of The General Biological Supply House, Chicago.)

that at one stage the chromosomes appear as slender threads. As we know today, the primary function of mitosis is the equal distribution of the genes, which are on the chromosomes, to the two daughter cells.

The most favorable material for the observation of mitosis is tissue in which rapid cell division is taking place, such as the growing root tips of plants and the early embryonic stages of animals (Fig. 13). The process can be observed, however, in any growing tissue, even in that of mature animals, for instance, in the skin of mammals.

In studying mitosis the tissues are usually placed in chemicals which rapidly kill them and fix the cells and cell components in

their normal relations; thin slices are then cut and stained. In numerous instances, however, mitosis has been observed and photographed in living cells. For the photographing of living chromosomes ultraviolet rays are most effective (see Fig. 18).

Mitosis always exhibits a typical succession of stages but the process is a continuous one, each stage merging into the next. The entire process may require from one to several hours. Let us

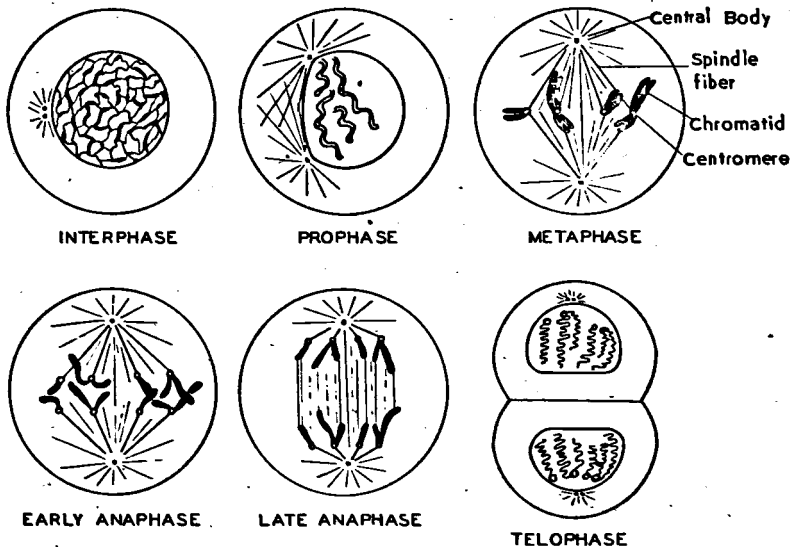


FIG. 14. Diagram of the successive stages of mitosis in a species having two pairs of chromosomes.

now examine briefly the successive stages, making use of the photomicrographs of the whitefish embryo (Fig. 13) and of the diagram (Fig. 14) in order to visualize the process.

1. **THE INTERPHASE.** This is the stage characteristic of non-growing tissue. The term resting stage is also applied to it since no visible changes are taking place, although, of course, the cell may be very active in the metabolic sense. Note in Fig. 14 that the nucleus appears as a rounded body, filled with chromatin granules apparently held in place by a fine network of fibers. In reality it is probably filled with a mass of tenuous coiled threads, representing the chromosomes. Surrounding the nucleus lies a

delicate membrane. The chromosomes, as such, ordinarily cannot be identified, owing to their finely dispersed condition.

2. THE PROPHASES. As an indication that the cell is preparing to divide, the chromatin of the resting cell gradually condenses into visible threads. At its first appearance each thread is seen to be made up of two identical strands or *chromatids* lying close together side by side. The threads gradually condense and shorten into typical chromosomes. Each chromosome bears a constriction at a definite point along its length, the locus of a tiny body known as the *centromere*,¹ which is regarded as the dynamic center of the chromosome. During this period the double nature of the chromosomes disappears. The shortening is apparently due to the spiraling of the threads in the form of corkscrews.

In the meantime, on one side of the nucleus a spindle-shaped mass of viscid cytoplasm is forming, appearing in stained cells to be made up of fibers. The nuclear membrane soon breaks down and the *spindle* comes to occupy the center of the cell, the thickest part of it lying on the equator or future division plane of the cell. The chromosomes move to take up their position on the spindle at the equator.

3. THE METAPHASE. In this stage the chromosomes lie in the equatorial region of the cell. The centromeres are lined up on the exact equator of the spindle, while the remaining portions, or bodies, of the chromosomes may lie off the equator.

In the equatorial view of the metaphase (Fig. 13) the chromosomes appear as a single row of objects. In the polar view (Fig. 15) they appear spread out in plate-like formation. The latter view is the preferred one for the counting of chromosomes.

In animal cells, unlike most plant cells, small bodies known as *central bodies* are seen at the poles of the spindle, and from these, fibers radiate in all directions, forming the so-called *asters* (*aster*, star).

4. THE ANAPHASES. Each centromere divides equally and the halves move apart, each half apparently pulling the body of the

¹ In works on cytology in the United States the term *kinetochore* seems to be superseding *centromere*. In order to show the length to which biological nomenclature may go, Professor FRANZ SCHRADER in his book "Mitosis: The Movements of Chromosomes in Cell Division," 1944, Columbia University Press, lists 27 terms that have been applied as names for the centromere since its discovery in 1894.

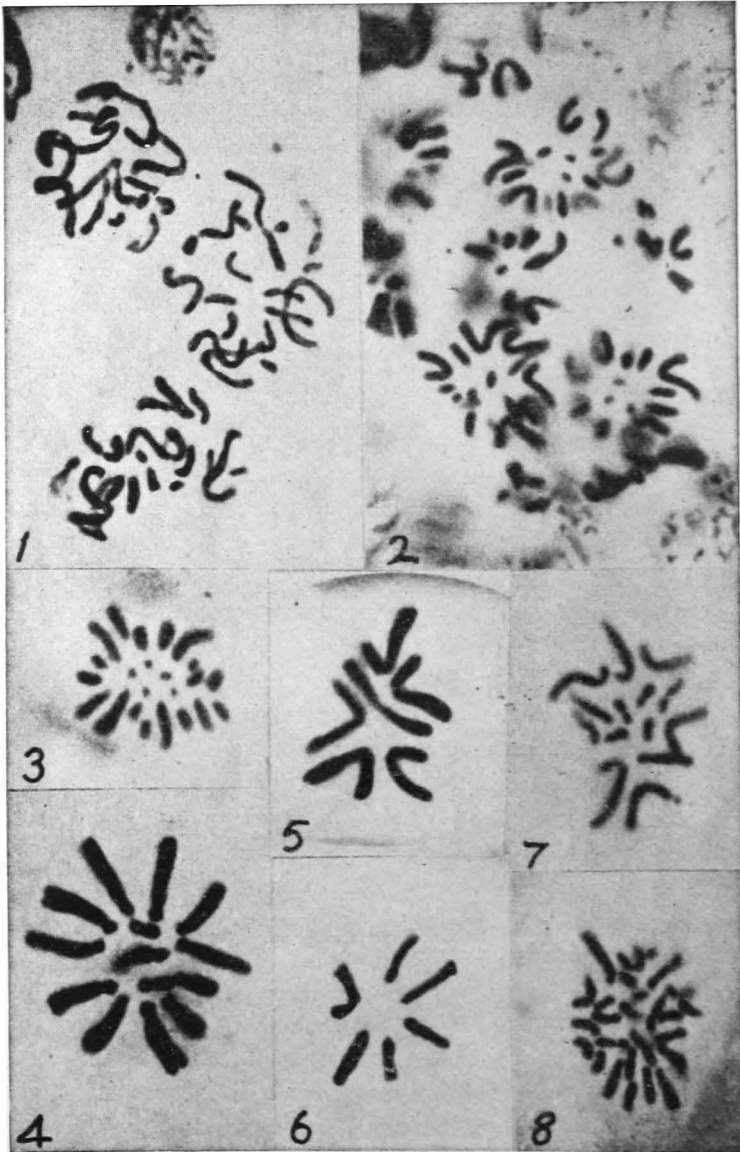


FIG. 15. Polar views of metaphase of mitosis in animals and plants (except 1, which is late prophase). 1 and 2. A grasshopper, *Chorthippus parallelus*, ♂, $2n = 16 + X$. Smear of spermatogonia. (La Cour and

(For remainder of legend see opposite page.)

half-chromosome or chromatid. The identical sets of chromatids continue to move apart toward the opposite poles of the spindle. The forces which cause this movement are probably complex; they have not been satisfactorily explained in chemico-physical terms.

5. THE TELOPHASES. Upon reaching the poles of the spindle, each group of chromatids—now known as chromosomes—enters into the formation of an interphase nucleus, the chromosomes losing, in most species, their visible identity but retaining, it is supposed, their fundamental organization.

The division of the cytoplasm into two parts is accomplished in animal cells by constriction at the equator; in plant cells with rigid cell walls it is brought about by the formation of a new cell wall in the equatorial plane.

As a consequence of the process of mitosis, repeated again and again, every cell in the body comes to have a full complement of chromosomes identical with that of every other cell. There is good evidence that each chromosome is functionally a chain of genes arranged in a definite linear order (Chapter 13), and that prior to the visible splitting of the chromosomes each gene in the chain is duplicated. The details of this process of duplication are as yet undiscovered.

The regularity, orderliness, and apparent efficiency of the process of mitosis make it one of the most interesting activities displayed by cells. Its importance in the development of the organism can hardly be overestimated, for, as we know now, it is the process that insures that the individual shall develop as an orderly and symmetrical unit. If, as sometimes happens, there is an abnormal mitosis, such as the failure of one chromosome to go into the nucleus that would normally receive it, an abnormality results in the particular part of the developing individual derived from that

Osterstock.) 3. A grasshopper, *Locusta migratoria*, ♂, $2n = 22 + X$. (Koller, unpublished.) 4. A plant, *Eremurus spectabilis*, root-tip, $2n = 14$. $\times 2000$. (Upcott, 1936.) 5. A plant, *Tradescantia bracteata*, pollen-grain, $n = 6$. 6. A plant, *Brodiaea uniflora*, pollen-grain, $n = 6$. (La Cour.) 7. A plant, *Puschkinia libanotica*, root-tip, $2n = 10 + 4 \text{ ff.}$ $\times 1500$. (Darlington, 1936.) 8. A plant, *Tricyrtis hista*, root-tip, $2n = 26$. (La Cour.) (Courtesy, C. D. DARLINGTON: "Recent Advances in Cytology," 2d ed., Philadelphia, The Blakiston Company, 1937.)

cell. If the abnormal mitosis occurs at a critical stage of development, death of the individual may be the result.

MEIOSIS

At one stage—and one stage only—in the life cycle of sexually reproducing organisms a peculiar modification of the process of mitosis described above takes place. This modification is known as *meiosis* (*meiosis*, reduction). In animals it occurs in those cells which are undergoing maturation into sperms and eggs; in plants it takes place during the formation of the spores. Essentially, the process consists of two successive cell divisions accompanied by only one splitting of the chromosomes, resulting in a reduction in the number of chromosomes from the double set found in the body cells, to a single set.

An obvious function of meiosis is the maintenance of a constant chromosome number in the species, for without it, as a consequence of fertilization, there would be a doubling of the chromosome sets in each generation. This of course would produce an impossible situation if continued for many generations, since the cells would soon be unable to contain the chromosomes. A second function of meiosis is to serve as the physical mechanism for the segregation, assortment, and recombination of the genes.

The typical steps in the process of meiosis will be described by considering in chronological order the events in the formation of the sperms and eggs in animals (Fig. 16).

SPERMATOGENESIS. During the period of sexual maturity in animals, the sperm (*spermatozoa*) are formed in the testes from reproductive cells known as *spermatogonia*. These cells, along with all other cells in the body, have come from the fertilized egg through a series of mitotic divisions. They therefore contain the double set of chromosomes characteristic of the species. The final spermatogonial divisions result in cells known as *primary spermatocytes*, which in preparation for meiosis enter upon a period of growth.

In the early prophase of the spermatocyte, the chromosomes make their appearance as fine single threads, in contrast to their appearance as double threads in ordinary mitosis. The threads soon come together side by side in pairs (*synapsis*). One thread of each

pair is maternal in origin, the other paternal. At this stage the threads frequently show granules (*chromomeres*) of varying sizes and shapes along their length, giving them the appearance of

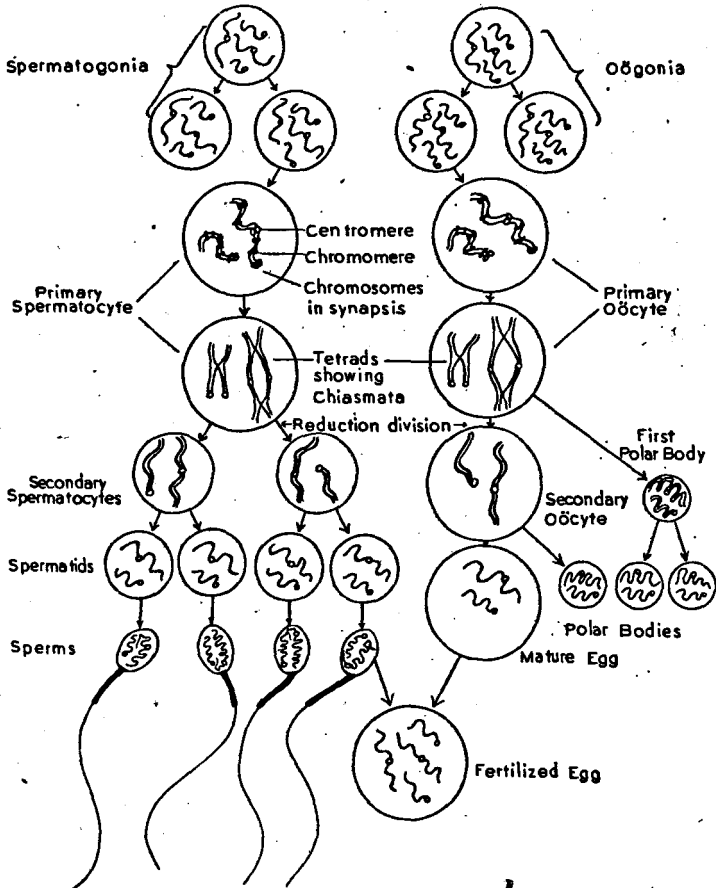


FIG. 16. Diagram of spermatogenesis, oögenesis, and fertilization in animals, designed especially to show the process of meiosis.

strings of beads. The pattern of the granules on the members of a synaptic pair is identical. Pairing takes place between identical chromomeres.

The paired chromosomes shorten and thicken, each chromosome bearing one *centromere*, as described under mitosis. After a time each pair is seen to be made up of four half-chromosomes or

chromatids, the result of the splitting of each chromosome into two chromatids. The two original centromeres, however, remain undivided. Groups of four chromatids are known as *tetrads*. The chromatids in the tetrad stage usually form a characteristic figure known as a *chiasma*, from the Greek, meaning two crossed lines. The tetrad stage is of special interest because it is at this time that the genes on the paternal and maternal chromatids are in position to exchange places with one another. This exchange, which is known to be a regular occurrence, results in a recombination of paternal and maternal genes. It is discussed in a later chapter under the head of *crossing-over*.

The tetrads line up on the metaphase plate. The undivided centromeres, each with two chromatids, move apart and proceed to the opposite poles of the spindle. The two resulting cells, known as *secondary spermatocytes*, undergo in some species a short resting stage; in others they enter at once upon the second division. In either case, this second division is like an ordinary mitosis in that each centromere divides into two; then each one of the two moves to an opposite pole, taking with it the rest of the chromatid.

The cells resulting from the second division are known as *spermatids*. As a consequence of the two cell divisions of meiosis, accompanied by only a single chromosome division, each spermatid obviously possesses just half the number of chromosomes characteristic of the species. Furthermore, this single set of chromosomes consists of a sample of every chromosome pair, and hence of every gene pair, characteristic of the species (an exception will be noted in the discussion of the sex chromosomes, Chapter 10).

Reduction now being complete, the spermatids have only to undergo a process of cytoplasmic differentiation to become the highly specialized cells known as sperms. This differentiation consists in the condensation of the nucleus into a streamlined head, and the development of a whip-like locomotor organ (tail) adapted for propelling the sperm head, with its contained chromosomes, to the egg.

OÖGENESIS. From the standpoint of chromosome behavior, the maturing of the egg follows a pattern similar to that of the sperms. The differences that exist have to do with the special rôle of the

sperm and the egg in fertilization and development. In the ovary, the immature egg, or *primary oöcyte*, grows to a relatively huge size in preparation for the cell divisions of early embryonic development. Even in mammals the egg may attain a mass one thousand or more times that of an ordinary cell. The difference in size of the egg and the sperm is still greater (Fig. 17). The characteristic growth of the oöcyte is due largely to an accumulation of stored food.

In mammals the first meiotic division commonly takes place before the oöcyte is released from the ovary. The spindle forms

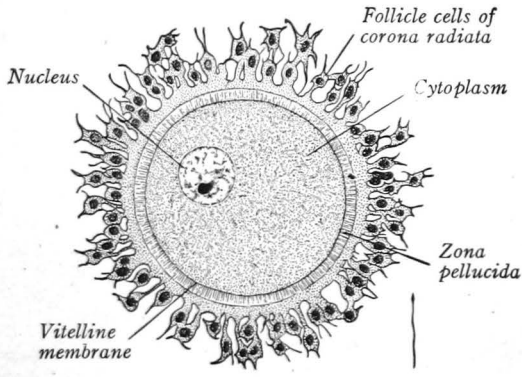


FIG. 17. A human egg approaching maturity. At the lower right is a human sperm drawn to the same scale. (Courtesy, AREY: "Developmental Anatomy," Philadelphia, W. B. Saunders Co.)

near the surface and at right angles to it, so that when the oöcyte divides one of the cells (*polar body*) receives very little of the cytoplasm, most of it being retained by the other cell, the *secondary oöcyte*. The second division usually takes place only after the entrance of a sperm at fertilization. Again as in the first division, the partition of the chromatin is equal but that of the cytoplasm is very unequal, resulting in the formation of a second polar body. In some species the first polar body may divide. The three polar bodies should be thought of as vestigial eggs; being deficient in cytoplasm, they eventually disintegrate. The functional egg and the polar bodies together are homologous with the four sperms.

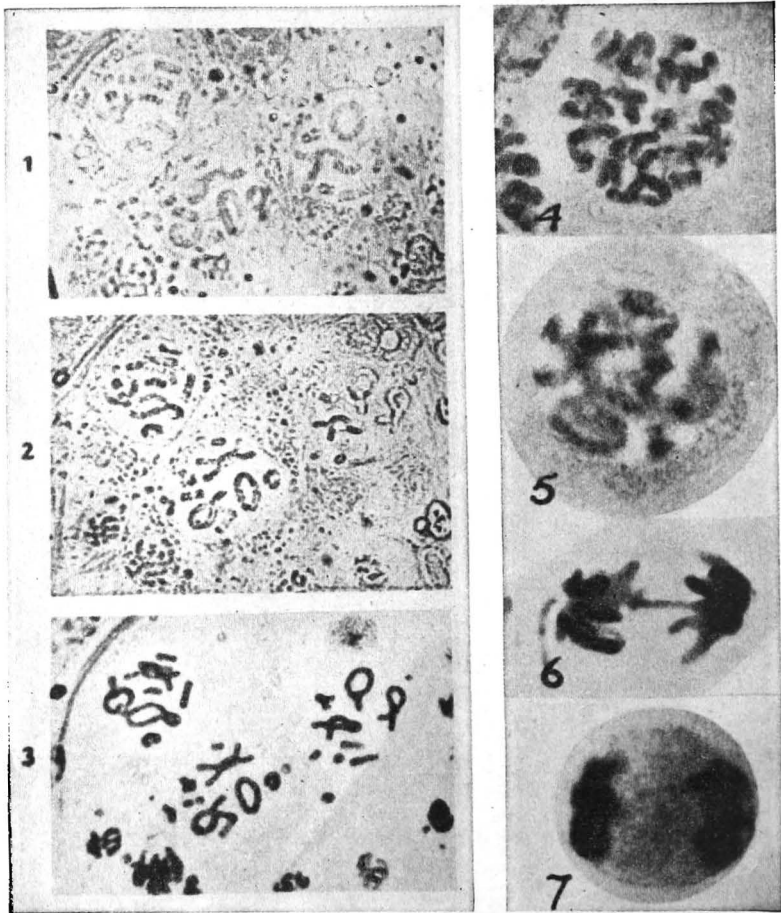


FIG. 18. Photographs of certain stages in meiosis in living cells of two species of grasshoppers. 1 to 3. Late prophase in *Stenobothrus lineatus*. (Belar, 1927.) 1. Living cells. 2. The same cells after fixation with osmium tetroxide vapor and Flemming solution. 3. The same cells after staining. 4 to 7. Living chromosomes of *Melanoplus femur rubrum*, taken by ultraviolet light. (After Lucas and Stark, 1931.) 4. Late telophase before meiosis. $\times 1800$. 5. Early prophase. $\times 1800$. 6. First anaphase. $\times 1200$. 7. First telophase. $\times 1200$. (Courtesy, F. W. SANSOME and J. PHILP: "Recent Advances in Plant Genetics," 2d ed., Philadelphia, The Blakiston Company, 1939.)

In Fig. 18 are reproduced photographs, taken under high powers of the microscope, of certain stages in meiosis of two species of grasshoppers: 1 to 3 show that the form of the chromosomes is not altered by the treatment given them in fixation and staining as practiced by cytologists, other than to produce a slight shrinkage and enhance greatly the distinctness of the chromosomes.

FERTILIZATION. Fertilization consists of the penetration of the egg by the sperm, and the fusion of the egg and sperm nuclei into one. Obviously, the fusion nucleus contains a double set of chromosomes, since each gamete brings into the union a single set. Throughout development and growth the double set is carried along by mitosis to all of the cells of the body.

The German biologist O. Hertwig, in 1875, observed for the first time all of the steps in fertilization, including the union of the chromosomes of the egg and the sperm in a single nucleus. The species he observed was an invertebrate animal known as a sea urchin. The discovery of the reduction division, for both the sperm and the egg in animals, was made by the Belgian biologist van Beneden, in 1883.

Fertilization serves two functions: first, it initiates embryonic development; second, it is the means of uniting two diverse streams of heredity, with all the possibilities of new and favorable combinations of genes that this entails. Because of its possibilities in the origination of something new and superior to that possessed by either parent, as well as something deleterious not shown by either, it is of supreme significance to the student of heredity.

There can be little doubt that the facility with which new combinations of genes can be produced by meiosis and fertilization has been a leading factor in the evolution of the higher plants and animals in which this form of reproduction is so nearly universal.

CHROMOSOMES AND INDEPENDENT ASSORTMENT

At the first division of meiosis, as the chromosomes line up on the metaphase plate, it is purely a matter of chance whether one member of a chromosome pair faces toward a given pole of the cell or toward the opposite pole. Furthermore, the orientation of one pair of chromosomes is not affected by that of another pair.

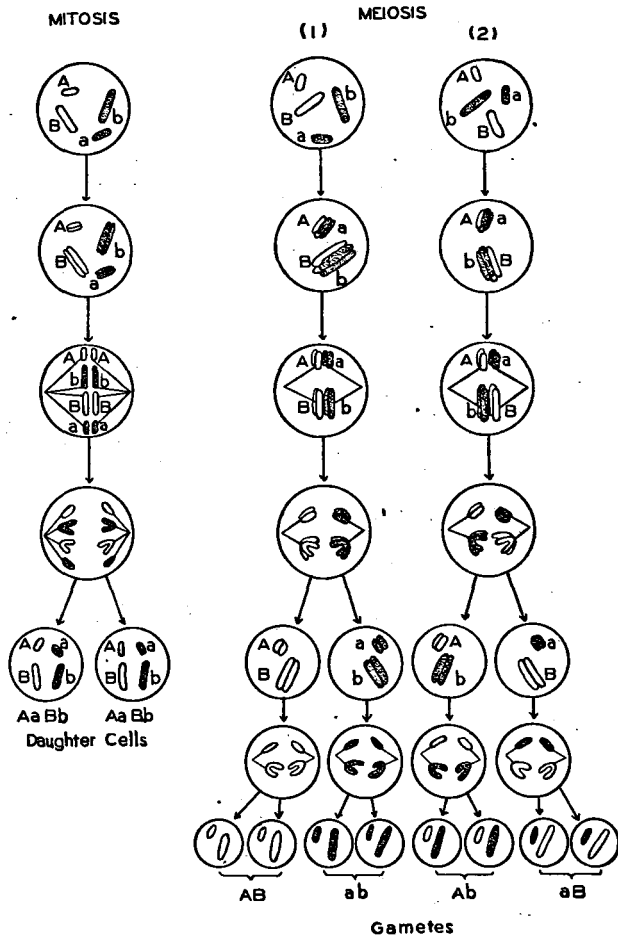


FIG. 19. Diagram comparing mitosis with meiosis in an organism having two pairs of chromosomes. The chromosomes derived from one parental gamete are indicated by stippling; those derived from the other are unshaded. Two cells are shown undergoing meiosis, resulting in gametes of four types with respect to possible combinations of paternal and maternal chromosomes. (Modified after Sharp: "Introduction to Cytology," New York, McGraw-Hill Book Co.)

Since orientations may take place in all possible combinations, meiosis becomes a mechanism perfectly adapted to accomplish the independent assortment of gene pairs lying on separate chromosomes. The relation between chromosome alignment and independent assortment in an organism having two pairs of chromosomes is shown diagrammatically in Fig. 19. It is apparent that the chromosomes may orient themselves for the reduction division in one of two possible ways (1 or 2). The result is four possible combinations in the gametes.

As already mentioned, the number of chromosomes is normally constant for each species, but varies among species. This variation is well illustrated in Table 5, a list which has been compiled from several sources, showing the chromosome numbers from familiar plants and animals. Note that the organisms are arranged to show a continuous numerical series, with a species to illustrate every chromosome number from the smallest possible (one pair) up to a fairly large one. A few additional organisms having more than 40 pairs have been reported; there would be more but for the difficulty of making accurate counts when the chromosomes are numerous. The highest numbers are found in certain plants and crustaceans. Man, with 24 pairs, stands fairly well up on the list. This number, moreover, seems to be a rather popular one: among other organisms which have 24 pairs are the rhesus monkey, the chimpanzee, a species of bat, the European hedgehog, a species of wild mouse, and ordinary tobacco.

Numerous complex organisms, for instance fruit flies, have few chromosomes, while others equally complex, for example butterflies, and moths, have many. There seems to be a tendency for the higher vertebrates to have more chromosomes than the lower vertebrates. Taken as a whole, however, the list shows no obvious correlation between chromosome number and the complexity of the organism.

Within a genus, as illustrated in *Drosophila* and *Carex*, chromosome numbers undoubtedly throw light on genetic relationships among the species. In *Drosophila* more than 35 species are known to possess six pairs of chromosomes. Fusions of these six in various combinations have resulted in species with three, four, or

Table 5

CHROMOSOME NUMBERS IN COMMON PLANTS AND ANIMALS*

(The total number of chromosomes in a body cell in each species is found by multiplying the number in the table by two)

Common Name	Scientific Name	Pairs of Chromosomes (Haploid No., n)
Intestinal worm.....	<i>Ascaris megalcephala</i>	1
Small crustacean.....	<i>Cyclops viridis</i>	2
Fruit fly.....	<i>Drosophila willistoni</i>	3
Fruit fly.....	<i>Drosophila melanogaster</i>	4
Fruit fly.....	<i>Drosophila obscura</i>	5
Fruit fly.....	<i>Drosophila virilis</i>	6
Pea.....	<i>Pisum sativum</i>	7
Onion.....	<i>Allium cepa</i>	8
Primrose.....	<i>Primula sinensis</i>	9
Corn.....	<i>Zea mays</i>	10
Opossum.....	<i>Didelphis virginiana</i>	11
Water bug.....	<i>Notonecta irrorata</i>	12
Bullfrog.....	<i>Rana catesbiana</i>	13
Salamander.....	<i>Ambystoma tigrinum</i>	14
Beetle.....	<i>Trirhabda canadense</i>	15
Honeybee.....	<i>Apis mellifera</i>	16
Lizard.....	<i>Anolis carolinensis</i>	17
Minnow.....	<i>Fundulus heteroclitus</i>	18
Pig.....	<i>Sus scrofa</i>	19
Mouse.....	<i>Mus musculus</i>	20
Rat (albino).....	<i>Rattus norvegicus</i>	21
Cottontail rabbit.....	<i>Sylvilagus floridanus</i>	22
Moth.....	<i>Pygaera pigra</i>	23
Man.....	<i>Homo sapiens</i>	24
Meadow mouse.....	<i>Microtus townsendii</i>	25
Wood rat.....	<i>Neotoma floridanus</i>	26
Monkey.....	<i>Cebus, sp.</i>	27
Silkworm moth.....	<i>Bombyx mori</i>	28
Moth.....	<i>Pygaera curtula</i>	29
Horse.....	<i>Equus caballus</i>	30
Gypsy moth.....	<i>Lymantria dispar</i>	31
Sedge.....	<i>Carex pallescens</i>	32
Moth.....	<i>Antheraea pernyi</i>	33
Sedge.....	<i>Carex vulpina</i>	34
Sedge.....	<i>Carex flava</i>	35
Sedge.....	<i>Carex riparia</i>	36
Sedge.....	<i>Carex aquatilis</i>	37
Sedge.....	<i>Carex rostrata</i>	38
Sedge.....	<i>Carex lanuginosa</i>	39
Sedge.....	<i>Carex foenea</i>	40
Fern.....	<i>Dryopteris pseudo-mas</i>	72
Crayfish.....	<i>Cambarus virilis</i>	100

* For more extensive lists, see WILSON, D. B.: "The Cell in Development and Heredity."

five pairs. According to a recent report,² in *Carex* the chromosome numbers at present known range from six pairs to 56 pairs, with every number from 12 to 43 represented in one or more species. The numbers 28, 42, and 56 occur with maximum frequency. Since these numbers are all multiples of 7 it is concluded that the basic number in this genus is seven pairs. In this genus of plants, which consists of more than 1000 species, changes in chromosome number probably have come about chiefly by the duplication of entire chromosomes or chromosome sets—a process known as *polyploidy*, discussed in Chapter 13. Polyploidy is widespread in plants but relatively rare in animals.

In no case do we know how many genes any organism possesses, but in the higher plants and animals the total must be very great. In the common fruit fly, *Drosophila melanogaster*, which has been studied more intensively than any other organism, the number of genes has been estimated by various investigators at several thousand. In this fly there are only four pairs of chromosomes. It follows that many genes must be found on one chromosome.

In peas there are seven pairs of chromosomes, as shown diagrammatically in Fig. 20. Here each gene of the seven characters studied by Mendel (see p. 33) is represented on a separate chromosome. It is obvious that if independent assortment is to take place at the reduction division each gene must be on a separate chromosome, for if two genes were on the same chromosome, wherever one went the other would necessarily go, and there would be no independent assortment between them. Mendel reported that his seven pairs of characters assorted independently. If true, this indicates that each gene was on a separate chromosome. From Mendel's statement in his paper, however, it is not certain that he obtained progeny from every possible combination

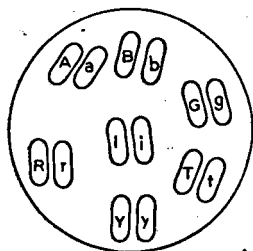


FIG. 20. Diagram showing a cell of the pea, hybrid with respect to all seven of the characteristics studied by Mendel. Each of the seven pairs of chromosomes is represented as carrying a different pair of genes.

² WAHL, HERBERT A.: Chromosome numbers and meiosis in the genus *Carex*, *Am. J. Botany*, July, 1940.

among his seven pairs of characters after he had obtained all of these combinations by crossing. Without breeding all of the combinations it could not be proved that independent assortment existed among all seven. Mendel's own statement on this point follows: "In addition, further experiments were made with a smaller number of experimental plants in which the remaining characters by two's and three's were united as hybrids; all yielded approximately the same results." It seems improbable, however, that one with Mendel's good statistical sense would have failed to produce all possible combinations of hybrids. It is significant that since Mendel's time other experimenters with peas have found that at least five of the seven characters described by Mendel do assort independently and hence must be represented by genes in five different chromosomes.

It must have been purely by chance that Mendel selected exactly the same number of contrasting characters as there were chromosomes in his plant, since there is no indication that he knew of the existence of chromosomes. A much more remarkable coincidence was his selection of seven characters whose genes were, presumably, all on separate chromosomes, for, as can be shown by applying the law of probability developed in Chapter 2, if all of the genes in peas are distributed equally on the seven pairs and if we select at random seven genes, only one time in 163 will each of the seven be found on a separate chromosome.

CHROMOSOMES AND INDEPENDENT ASSORTMENT IN MAN

Independent assortment of genes has been found to take place in all plants and animals which have been bred extensively. There is no reason why it should not occur also in man. But the presentation of actual cases in man showing numerical ratios among the offspring (9:3:3:1, etc.) as the theory demands, is not easy. This is because of the peculiar difficulties attending the study of human heredity. In man we are limited to the observation of matings already made, and it is hard to find an adequate number of pedigrees of the right sort for critical study. Casual observation of human families, however, reveals facts consistent with independent assortment in man. In large families it is usual to find the children displaying in all sorts of combinations characteristics found in

the parents, grandparents, and more remote ancestors. For example, a child may show the ear shape of one parent, the eye color of the other, the hair form of a grandparent, and so on. Characteristics which are known to be Mendelian seem in many cases to be dealt out at random to the children.

No two human individuals have ever been found who are really alike in all respects (with the exception of identical twins, identical triplets, etc., discussed in a later chapter), and we can see now why the chances of this happening are so remote as to be practically impossible. Modern man, in most localities in countries such as ours, does not inbreed extensively; instead, wide cross-breeding is the general rule. As a consequence, in comparison with our domesticated animals, man is not pure-bred. The number of genes in which the average person is heterozygous is probably great.

In order to illustrate the effect of random assortment in producing variation among people, let us suppose that in each of the 24 pairs of chromosomes an individual parent is heterozygous with respect to one pair of genes. Using letters to stand for genes, as heretofore, we will represent his or her genetic constitution with twenty-four pairs of letters as follows: *AaBbCcDdEeFfGgHhIiJjKkLlMmNnOoPpQqRrSsTtUuVvWwXx*. Since each pair of genes in the assumed case is on a separate chromosome there will be independent assortment among all of them. We can readily calculate the number of kinds of eggs or sperms such an individual will produce by applying the principle already considered in Chapter 3. We have seen that with an individual heterozygous for one pair of genes (*Aa*) two kinds of eggs or sperms are produced; with an individual heterozygous for two pairs of genes (*AaBb*) four kinds are produced; with one heterozygous for three pairs of genes (*AaBbCc*) eight kinds are produced, etc. Each time a pair is added the number of kinds of eggs or sperms is doubled, as shown in Table 6.

The eggs or sperms produced by such a person will accordingly be a sample from 16,777,216 kinds. Assuming for the sake of the example that the other partner in marriage is heterozygous for the same 24 pairs of genes (a highly improbable assumption) he or she likewise will produce a similar diverse array of gametes. At fertilization the possible different combinations of these genes will

reach the enormous total of 282,429,536,481. This number is easily calculated by applying the rule that with one pair of genes there are three genotypes, with two pairs nine genotypes, with three pairs 27 genotypes, and so on. The actual number of visible types will depend upon the presence or absence of dominance in

Table 6

<i>Pairs of Genes</i>	<i>Kinds of Eggs or Sperms</i>
1	2
2	4
3	8
4	16
5	32
6	64
7	128
8	256
9	512
10	1,024
11	2,048
12	4,096
13	8,192
14	16,384
15	32,768
16	65,536
17	131,072
18	262,144
19	524,288
20	1,048,576
21	2,097,152
22	4,194,304
23	8,388,608
24	16,777,216

the various gene pairs, and upon the interaction taking place among the genes. The question of the interaction of genes is considered in the next chapter. With complete dominance in all 24, the maximum number of visible types will be 16,777,216, since with complete dominance the maximum number of visible types in matings such as the one we are considering is exactly the same as the number of kinds of eggs or sperms. With dominance present for some genes and lacking for others the maximum number of visible types lies somewhere between the number of genotypes and the number

of visible types in cases of complete dominance. The exact number (which can be calculated) depends upon the proportion of genes showing dominance.

In the preceding example we have considered the consequences when only one pair of genes on each chromosome is heterozygous. But each chromosome in man (judging by the fact that the number of Mendelian traits is many times the number of chromosomes) may contain not merely one gene but many; and if such "linked" genes frequently change places with their mates on the other chromosome of the pair—as they are known to do in lower animals—the possible number of kinds of eggs and sperms is much greater than indicated in the preceding paragraph. Hence the number of possible genotypes is correspondingly greater. (The mechanism of exchange of genes is discussed in Chapter 7 under the head of *crossing-over*.)

From the foregoing it is evident that the gene-chromosome mechanism is admirably adapted to produce an almost unlimited variety of offspring. It seems probable that among all of the billions of human beings who have been born since man first appeared on the earth, there have never been two with identical sets of genes, unless they happened to develop from a single fertilized egg, as occurs regularly in identical twins, identical triplets, and so forth.

PROBLEMS

1. In many animals an unfertilized egg carrying only a single set of chromosomes may develop into a mature individual, but if in a fertilized egg one pair of chromosomes is missing the individual will not develop. How can these facts be explained?
2. How can one account for the fact that in several species of *Drosophila* and *Carex* shown in Table 5 there is a continuous series of chromosome numbers?
3. Make a list of all the parental dihybrid combinations which Mendel would have had to produce, using his seven characters in peas, in order to demonstrate independent assortment among all seven characters.
4. In peas, with seven pairs of chromosomes, show the method of calculating the chance that seven genes chosen at random will each be on a different chromosome, i.e., that there will be no linkage.

5. In man, brown eyes are dominant over blue. Suggest several theories that may account for the rare occurrence of one brown eye and one blue eye in the same person.
6. Why is a sperm alone not able to develop into an individual, while eggs of numerous species of plants and animals are able to develop parthenogenetically without fertilization?

THE FACTOR PRINCIPLE: ACTION AND INTERACTION OF GENES

IN THE EXAMPLES of Mendelian heredity considered thus far each character was "determined" by a single gene. Such characters frequently have been called unit characters because the change of a single gene completely changes the character. Not long, however, after the rediscovery of Mendel's paper in 1900, results of breeding experiments began to be reported which did not fit into this simple scheme. Ratios diverging widely from simple Mendelian ratios were sometimes obtained. As a matter of fact Mendel himself had reported briefly such a case in beans. We shall return to this case presently.

The first reported experiments, following Mendel's, involving what is known as the *factor principle*, were made by the British biologists, W. Bateson and R. C. Punnett. Bateson was one of the leaders in the study of heredity and variation during the latter part of the nineteenth century. He was among the first to recognize the importance of Mendel's work, and was the first to translate the paper on peas into English. Their earliest case concerned the heredity of comb shape in chickens. Another one of their early experiments dealt with the color of sweet peas. Since the sweet pea case illustrates perfectly the factor principle it will be used as our first example.

COLOR IN SWEET PEAS

There are many pure-breeding varieties of sweet peas, all supposedly derived from the wild pea of Sicily which has purple flowers. While investigating the heredity of flower color in these plants, Bateson and Punnett found that red was inherited as a

simple dominant, white being recessive. When the hybrid—produced by crossing red and white—was allowed to self-fertilize, there appeared the typical ratio of 3 red to 1 white.

In one experiment they crossed two different white-flowered plants, and were surprised to find that the resulting hybrids had red flowers. When these hybrid red plants were allowed to self-fertilize they produced red flowers and white flowers in the ratio of 9 red to 7 white.



FIG. 21. William Bateson (1861–1926). Famous British biologist and pioneer in founding the science of genetics. (Courtesy, *Genetics*, frontispiece, 1927.)

The explanation of this wholly unexpected result is as follows. The red color requires for its development the combined influence of two separate dominant genes which we may designate as R and C . A change of either one (R to r or C to c) prevents the development of red pigment and thus causes the plant to be white. The two white plants used in the original cross were genetically different,

one being $rrCC$ and the other $RRcc$. As long as each was bred by itself it remained constant, but when the two were crossed each brought in a different dominant gene, R and C respectively, both of which were necessary for the production of red pigment. Red pigment accordingly developed in the hybrid $RrCc$.

When the red hybrids self-fertilize, their genes sort out and recombine independently in all possible combinations, as indicated in the checkerboard (Fig. 22), exactly as in cases of independent assortment previously described (Chapter 3). The only difference between this case and independent assortment in Mendel's experiments with edible peas is that in sweet peas both pairs of genes produce their effect on one and the same characteristic, namely color. The mechanism of distribution of the genes is exactly the same. Obviously, we are here dealing with nothing contradictory to Mendel's laws, but with a new principle supplementary thereto. Furthermore, this result in sweet peas is just what one might have

expected from what we know of the nature of chemical reactions in general. A specific chemical reaction, such as the production of a pigment, might be expected to require two different substances, one substance depending upon the presence of one gene and another substance depending upon another gene. Since, however, the

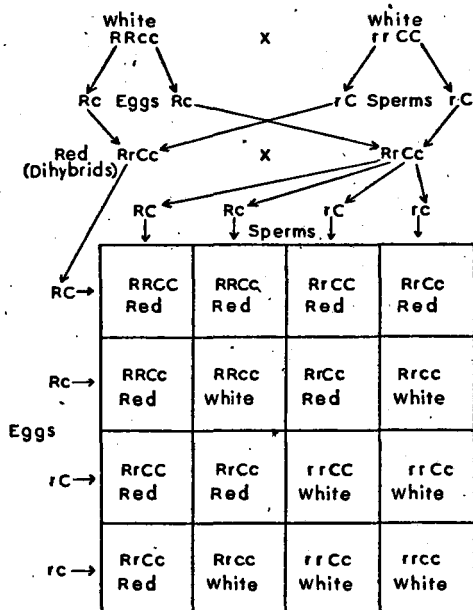


FIG. 22. Diagram showing the production of red sweet peas from a cross between two varieties of white sweet peas, and the production of a ratio of 9 red to 7 white in the offspring of the hybrid reds.

precise chemical nature of genes, as well as the way in which the genes work in the production of the pigment, is still unknown, our chemical analogy is at present hypothetical.

An inspection of the checkerboard reveals that there are three whites due to the presence of rr , three due to cc , and one due to the presence of both ($rrcc$) in the same individual. These seven whites are visibly indistinguishable, with the result that the visible ratio is 9 red to 7 white.

This example illustrates perfectly the fact that the gene rather than the character is the unit of heredity. We can now see that a

difference between two contrasting characters may rest upon a single gene difference as in most of Mendel's cases, but does not necessarily do so; two or more genes may be involved. It is therefore best to avoid the use of the term unit character. The appearance of the red color in sweet peas is obviously dependent upon two different genes, *R* and *C* (incidentally, known to be located in separate chromosomes, since they assort independently). It is therefore incorrect to say that red is "determined" by either one or the other. *R* and *C* are merely factors whose combined effect is pigment formation. The word "determiner" is a misleading term and should be dropped in favor of the word "gene" or "hereditary factor."

In succeeding years many other examples involving the factor principle, similar to that of the sweet peas just described, have been discovered both in plants and animals. In corn, for example, the colors red and white are inherited in exactly the same way as red and white in peas. Several other examples will be given presently.

The discovery of the factor principle has served to clear up a long-standing puzzle which goes under the name of reversion or atavism. These terms are applied to all those cases in which an individual suddenly appears that differs from its parents, but resembles some more distant ancestor. Before the discovery of Mendel's laws such "throw-backs" could not be satisfactorily explained, but now we see how simply they fall into order merely by assuming that each parent comes from a distinct hereditary line in each of which there is present some gene or genes lacking in the other. In matings between the two lines, the long separated genes recombine and restore the character which may have disappeared countless generations previously.

MENDEL'S CASE IN BEANS

As mentioned above, Mendel encountered a case which seemed to illustrate the factor principle. This involved the color of the flower in beans. He crossed a plant having white flowers with one having purple-red flowers. The resulting hybrids resembled the purple-red parent in color, except that the color was less intense. Dominance was apparently lacking, the case in this respect differ-

ing from the example just cited for sweet peas. Unfortunately, the hybrids were not very fertile and Mendel was able to obtain only 31 offspring from them. These 31 offspring ranged in color from purple-red to pale violet, with one pure white. This generation was likewise not very fertile though sufficiently so to show that some individuals of intermediate violet color bred true, while others of this same color produced both violet flowers and white flowers.

Mendel realized that his numbers were insufficient to establish a law, but suggested as an hypothesis that the purple-red color was the resultant of two or more independent factors which may be designated as *A* and *B* (simplifying slightly Mendel's symbols). He pointed out that if white depended upon two independent factors, which we will call *a* and *b*, only one white would be expected out of 16 offspring of the dihybrid; and since, as we have seen (p. 36), a dihybrid produces nine genotypes, the remaining 15 offspring should fall into a series of eight colors corresponding to the remaining eight genotypes, as follows: *AABB* (purple-red), *AABb*, *AaBB*, *AAbb*, *AaBb*, *aaBB*, *Aabb*, *aaBb*, (seven shades of violet). Mendel does not say how many color grades he actually observed, but obviously his hypothesis of eight grades of colored flowers would hold true only in case of lack of dominance in both pairs of genes, and only when there is a visibly distinguishable effect of *A* and *B* in all eight combinations as listed above. To show how this color variability would work out let us go a step beyond Mendel and arbitrarily assign numbers. For instance, let 6 represent the grade of color produced by the gene *A*, and 4 the grade of color produced by *B*. Then let us substitute the numbers for letters in the above series of nine genotypes. We get the following results:

Grade:	20	16	14	12	10	8	6	4	0
	<i>AABB</i> ,	<i>AABb</i> ,	<i>AaBB</i> ,	<i>AAbb</i> ,	<i>AaBb</i> ,	<i>aaBB</i> ,	<i>Aabb</i> ,	<i>aaBb</i> ,	<i>aabb</i>
Ratio:	1	: 2	: 2	: 1	: 4	: 1	: 2	: 2	: 1

Mendel thought enough of his hypothesis to suggest that it would be

well worth while to follow up the development of color in hybrids by similar experiments, since it is probable that in this way we might learn the significance of the extraordinary variety in the coloring of our ornamental flowers.

THE FACTOR PRINCIPLE APPLIED TO MAN

We may now mention a case in man which some investigators think follows exactly the rule suggested by Mendel for beans. The case is that of skin color, which has been studied especially by Dr. C. B. Davenport, a leading American student of human heredity. According to this investigator, who made extensive observations of Negro-White crosses¹ and their offspring in succeeding generations, the difference in the amount of black pigment between the full-blooded Negro native to West Africa and the Caucasian rests upon two major pairs of genes operating in essentially the same manner as the genes in the case of Mendel's beans just described. Davenport's hypothesis has not been confirmed by independent investigators, and there is still an interesting field here for further research.

A full-blooded Negro, according to Davenport, may be represented by *AABB* and a Caucasian by *aabb*. Dominance is lacking, the hybrid being intermediate in color. Each pair of genes segregates independently so that all possible combinations occur in the offspring of the hybrids. Davenport concluded that each gene mentioned was responsible for approximately the following proportion of black: *A* 19 per cent, *B* 16 per cent, *a* 2 per cent, *b* 1 per cent. The full-blooded Negro (*AABB*) is therefore 70 per cent black in color and the Caucasian 6 per cent black; the full color in each race is due to a mixture of black and yellow pigments plus red from the blood, diluted with the natural white color of unpigmented skin. The hybrid or Mulatto (*AaBb*) is 38 per cent black.

The children of two such hybrids will therefore represent a series of colors in which the expected ratio, with the percentage of black in each class, is as follows: 1 (70 per cent):2 (55 per cent):2 (53 per cent):1 (40 per cent):4 (38 per cent):1 (36 per cent):2 (23 per cent):2 (21 per cent):1 (6 per cent). It is noted that one out of 16 should be as dark as the full-blooded Negro grandparent, and that one out of 16 should be as light as the white grandparent. The other 14 will be intermediate

¹ "Heredity of Skin Color in Negro-White Crosses," by CHARLES B. DAVENPORT, Carnegie Institution of Washington, Publication No. 188, 1913.

(four the same shade as the hybrid parents, two others nearly the same, four considerably darker, and four considerably lighter).

It should be pointed out, however, that the foregoing facts do not imply that either a pure Caucasian or a pure Negro is likely to result from a mating of the two hybrids under discussion.

The chance of this happening is extremely remote, since there are many differences between the two races other than skin color (shape of nose, thickness of lips, hair form, numerous skeletal differences, etc.), each depending upon its own peculiar genes. It is not likely with so many genes involved that they will be recombined in exactly the same manner as in either of the two original races. Occasionally, however, a child from hybrid parents should receive the proper assortment of genes to enable it to pass readily as a pure-blooded individual either of one race or of the other.

Several other characters are known in man which can best be explained by means of the factor principle. Some of these are described in later chapters.

Although the discovery of the factor principle has added nothing new to the mechanism of gene distribution as discovered by Mendel, it has broadened our knowledge of the physiology of development of the organism. We no longer look upon a character as the product of a single gene. Perhaps all characters depend upon the co-operation of several genes. Even though the difference between two contrasting characters—as yellow and green in peas—may depend upon a single gene difference, this does not mean that only one gene is involved in the production of color in the pea. Both yellow and green peas probably have other genes necessary to pigment production. But as long as both varieties possess these other genes we have no way of demonstrating their existence.

THE FACTOR PRINCIPLE IN GUINEA PIGS

Guinea pigs offer a striking example of the interaction of several genes in the production of hair and eye color in mammals. The case will be presented in some detail because the principles involved have a broad application. The wild rodent of South America from which the guinea pig was derived is colored some-

what like the North American red squirrel.² When examined closely each hair is seen to be dull black at the base, with a reddish band near the tip, and with a black tip. This banding of the individual hairs is known as agouti, named after another South American rodent (the agouti), which shows the same pattern to a pronounced degree. The pattern is common also in North American rodents such as rabbits, rats, mice, woodchucks, and squirrels, as well as in some other mammals, including raccoons, cats, and foxes. The color of the band varies in different mammals, ranging from red, through yellow and cream to white. There is often more than one band in a single hair, especially if the hair is long. The writer has counted as many as three distinct reddish bands in the long tail hairs of a fox squirrel.

The agouti pattern is probably an advantage to many wild animals in that it tends to give them a neutral color which blends with their environment, thus affording protection against enemies. Anyone who has observed wild rabbits in the field can vouch for the concealing effect of their coloration. In the case of predatory animals it may be an advantage in enabling them to approach the prey without detection.

In guinea pigs the agouti is a common color variety, but like all animals that have been under domestication for centuries, the guinea pig shows many color variations, including solid black, sepia, white, chocolate brown, red, yellow, black and white spotted, black and red spotted, black-red-white spotted, and so on. The individual colors are not very different from those found in the hair of man, but in man spotting is rare, with the exception of dark and white spotting. The numerous color variations of domesticated guinea pigs undoubtedly came either from the wild type or from other color varieties by sudden mutations occurring from time to time. In nature most of these colors would be disadvantageous to their possessor by making it more conspicuous and a ready prey to predatory animals. This fact explains the scarcity of such colors among wild animals.

The heredity of the color varieties of the guinea pig has been

² The guinea pig is thought to have been domesticated from the wild Peruvian cavy (*Cavia cutleri*). At the time the Spaniards first visited Peru they found Indians raising guinea pigs for food, a practice which is still followed.

studied by many investigators, and most exhaustively by Professor Sewall Wright of the University of Chicago. In all known cases in guinea pigs the color mutations from the wild type are inherited as recessives. Among the best known of these mutations are the following:

<i>Dominant</i>	<i>Recessive</i>
SS, No white spots.....	ss, White spots
(Dominance irregular)	
(S and s are so nicely balanced in their effect that the amount and pattern of the white areas is quite variable. Sometimes S behaves as a complete dominant; rather more frequently the hybrid (Ss) has a little white on nose and feet.)	
EE, No red spots	ee, Red spots ³ (Size and pattern of red spots variable)
AA, Agouti pattern.....	aa, No agouti bands
CC, Intense color.....	cc, Red reduced to yellow, black slightly reduced ³
BB, Black eyes, black hair.....	bb, Brown eyes, brown hair, red unaffected
PP, Dark eyes, dark hair.....	pp, Pink eyes, pale sepia or pale brown hair, red unaffected

As regards color, the wild type guinea pig therefore has the gene formula, *SSEEAACCBBPP*. Each one of these genes is a factor, and all are necessary for the production of the typical wild color pattern. By a long continued process of crossing guinea pigs possessing the recessive mutations listed above, Wright succeeded in building up a family of animals combining all six recessive genes, *sseeaacbbpp*. In appearance they are pale brown, yellow spotted, white spotted, without agouti bands and with pink eyes. He then crossed these multiple recessives with the wild type. The hybrids were like the wild type (except that in some there was a trace of white spotting, as expected from the fact that S is not always dominant over s). The genetic formula of the hybrids was of course *SsEeAaCcBbPp*.

The hybrids were then back-crossed to the multiple recessives.⁴ As we have seen (Table 6, page 66) hybrids in six respects

³ In order to distinguish them from other genes in a series of alleles Wright uses the symbol *e²* to represent the gene for red spotting and *e⁴* for the gene *c* above. For the sake of simplicity I have dropped these superscripts in the present discussion.

⁴ WRIGHT, SEWALL: An eight-factor cross in the guinea pig, *Genetics*, 13: 508-531, 1928. In this experiment two genes affecting hair direction (roughness) also were studied.

should produce 64 kinds of eggs and sperms. These 64 kinds should of course occur in equal numbers provided all six genes are on separate chromosomes. In Table 7 in the left hand column are listed all the possible combinations (32 in number), omitting the gene for white spotting. By combining these 32 with *S* and *s*, respectively, shown in the right hand column, we get 64 combinations. Upon fertilization, the union of these 64 kinds of eggs and sperms with eggs or sperms from the multiple recessive (all of which are *seacbp*) results in 64 gene combinations or genotypes.

Note in Table 7 under "visibly distinct types" that there are eight instances where two genotypes must be lumped together because genes *C* and *c* have practically the same effect upon black and brown. The consequent lumping reduces the number of visibly distinct types to 56, all of which were actually obtained by Wright among the 399 offspring produced by the back-cross matings. The numbers of each type he obtained are shown in the two right hand columns of Table 7. With a perfect distribution of the 399 offspring among the 56 types there should be approximately six of each type, except in the four groups which are lumped; in these there should be approximately 12. The numbers actually obtained are as near to this ratio as could be expected with so large a number of types and only 399 individuals. By various statistical tests Wright shows that the results clearly indicate independent assortment among all six genes studied. This means that each of the six genes is located on a different chromosome.

No experiment could serve better than the one just described to show that the color of an animal is not a unit character, but that the gene is the unit. Note, for example, that the pale brown (pink eyed) animals (*SsEeaaCcbppp*) resulting from *seacbp* × *SEaCbp* have pale brown color because of the co-operation of the three pairs of recessive genes: *aa*, *bb*, *pp*. The pair *aa* eliminates the agouti band from the hair; the pair *bb* changes the quality of the pigment from black to chocolate brown, and *pp* reduces the intensity of the brown to a pale brown.

Fig. 23 shows the results of a mating of guinea pigs which in the days before Mendel's experiments would have been inexplicable. Our present knowledge of the genes affecting hair and eye color and of their interactions, as described in the preceding pages,

Table 7

OFFSPRING FROM A SIX-FACTOR BACK-CROSS IN THE GUINEA PIG

(*SsEeAaCcBbPp*) × (*sseeaacbbpp*)

(After Wright)

Genotypes	Visibly Distinct Types	Offspring	
		Little or No White (Ss)	White Spotted (ss)
<i>e a c b p</i> (eggs and sperms of recessives)			
<i>E A C B P</i>	Black, red agouti	9	5
<i>E A c B P</i>	Black, yellow agouti	10	7
<i>E A C b P</i>	Brown, red agouti	4	7
<i>E A c b P</i>	Brown, yellow agouti	6	5
<i>(Eggs and sperms of hybrids)</i>			
<i>E a C B P</i>	Black	12	16
<i>E a c B P</i>	Black		
<i>E a C b P</i>	Brown	18	10
<i>E a c b P</i>	Brown		
<i>e A C B P</i>	Black, red agouti, red spots	4	8
<i>e A c B P</i>	Black, yellow agouti, yellow spots	6	7
<i>e A C b P</i>	Brown, red agouti, red spots	6	4
<i>e A c b P</i>	Brown, yellow agouti, yellow spots	9	7
<i>e a C B P</i>	Black, red spots	12	1
<i>e a c B P</i>	Black, yellow spots	2	5
<i>e a C b P</i>	Brown, red spots	9	5
<i>e a c b P</i>	Brown, yellow spots	5	5
<i>E A C B p</i>	Pale sepia, red agouti	9	6
<i>E A c B p</i>	Pale sepia, yellow agouti	6	6
<i>E A C b p</i>	Pale brown, red agouti	6	7
<i>E A c b p</i>	Pale brown, yellow agouti	3	10
<i>E a C B p</i>	Pale sepia	12	17
<i>E a c B p</i>	Pale sepia		
<i>E a C b p</i>	Pale brown	18	17
<i>E a c b p</i>	Pale brown		
<i>e A C B p</i>	Pale sepia, red agouti, red spots	5	8
<i>e A c B p</i>	Pale sepia, yellow agouti, yellow spots	5	3
<i>e A C b p</i>	Pale brown, red agouti, red spots	5	5
<i>e A c b p</i>	Pale brown, yellow agouti, yellow spots	5	3
<i>e a C B p</i>	Pale sepia, red spots	8	7
<i>e a c B p</i>	Pale sepia, yellow spots	5	6
<i>e a C b p</i>	Pale brown, red spots	3	1
<i>e a c b p</i>	Pale brown, yellow spots	2	7
Totals		204	195

however, enables us to account for the case in simple terms. The litter of five black-haired, black-eyed guinea pigs was sired by the albino male shown with them. The dam, also shown, is pale sepia, pink-eyed, with no spotting. The genotype of the albino male is $s-e^p-a-c^a c^a P-B-$. (The dashes indicate uncertainty as to heterozygosis.) The female is of genotype $SSEe^p aa C-pp B-$.

Two of the young are self black. Their genotype is $SSE-aa Cc' Pp B-$. The aa accounts for non-agouti pattern; C insures full

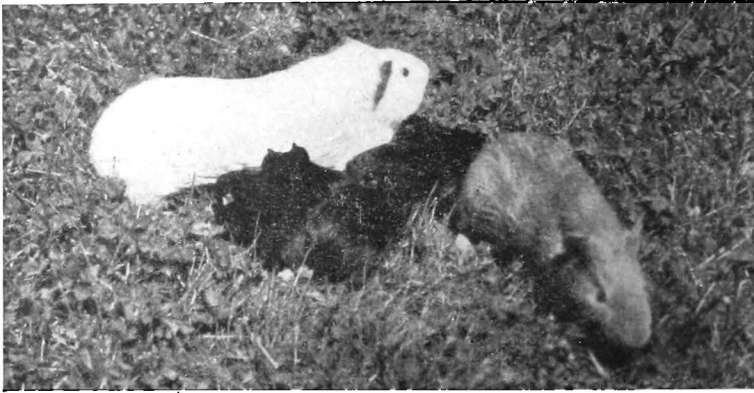


FIG. 23. A litter of five black guinea pigs, their albino sire, and pink-eyed, pale sepia dam. (Photograph by the author.)

intensity of pigmentation; P is the dominant alternative of the gene for pink eyes and pale colors; and B works to produce black pigment rather than brown.

Of the other three young, two have each a white foot and one has a small amount of red spotting. Their genotypes are therefore like those of the two self blacks except for the substitution of Ss in the white-spotted animal and $e^p e^p$ in the red-spotted one.

One may ask how we know that the albino male carries the gene B . The answer is that albino guinea pigs, like Siamese cats and Himalayan rabbits (Chap. 12), develop some pigment on feet, nose, and ears when they are exposed to low temperatures. This animal had been so exposed and had developed conspicuous black pigment in the regions mentioned. Had he been bb this pigment would have been brown in color and inconspicuous. This same temperature effect enables us also to tell that he carries at least

one gene *s*. One of his feet remained white, indicating a white spot: in white-spotted areas no pigment develops even at low temperatures.

MULTIPLE ALLELES

The word *allele* is a general term used to denote the alternative forms of a gene. Thus the gene for vestigial wing in *Drosophila* (Fig. 5, p. 18) and the alternative normal gene are alleles. An older term, *allelomorph* (*allelon*, of one another; *morph*, form), is frequently employed; introduced by Bateson in the early days of Mendelism, its usage is now yielding to the shorter term allele.

The studies of linkage and crossing-over, discussed in a later chapter, have shown that all the alleles of a given gene occupy the same locus on the chromosome. Only a single allele, of course, is present at any one time at a given locus.

For a good many years it has been known that more than two alternative forms of a gene may exist. Three or more in a set make up what is known as a series of *multiple alleles*. Multiple alleles have been discovered in many species of plants and animals.

Several series have been discovered in man. Among these are the series responsible for the human blood groups and for the recently discovered Rh blood factor, described in Chapter 9, and the alleles involved in color vision described in Chapter 11.

The principles governing the relationships of the alleles in a series have been studied thoroughly in a number of plants, in *Drosophila*, and in mammals. In *Drosophila* many series are known. There are, for example, at least eight alleles of the vestigial gene, all affecting the size, shape, and structure of the wing; and 14 alleles of the white-eye gene, all affecting eye color, producing a series of eye colors ranging from white through cream and pink to red. These two series illustrate the fact that the genes in a series usually affect the same characters or processes in the organism. Frequently the effects seem to be only quantitative, but often they are qualitative as well.

In rodents several series of multiple alleles have been demonstrated. According to Castle, at least five series are known in rabbits. One of these is a series of triple alleles responsible for blood groups similar to those in man.⁵ In another series in rabbits

(the albino series) six alleles have been identified. In the house mouse there are three series; in the Norway rat, two; in the black rat, two; and in the wood mouse (*Peromyscus*), one.

In the guinea pig three series have been found, all affecting pigmentation. Since the multiple alleles in the guinea pig illustrate the principles common to other organisms, they will be described in some detail.

The wild-type guinea pig (agouti pattern) was described on p. 75. A mutant variety has red spots; in the absence of white spots the red hairs tend to be dispersed, giving the animal a brindled or "tortoise shell" appearance. The amount of red varies from only a few red hairs to large red areas. A third allele eliminates all black from the hair, leaving the animal self red. Pigmentation of the eyes is not affected by this series. Summarizing the effects mentioned we have:

E, No red spots.

e^p, Tortoise shell (red spots).

e, Self red.

As in the example chosen, superscripts are usually added to the symbols in order to differentiate the genes of a series of multiple alleles. *E* is dominant over both of the other alleles and *e^p* is dominant over *e*. It is interesting to note that in rabbits a series apparently homologous with this one in guinea pigs contains at least four alleles.

In multiple alleles one gene of the series usually is completely dominant over the others. Ordinarily this gene is the one prevalent in the wild species, and from it the others have arisen by mutation. Dominance among the other members of the series is sometimes complete; more often it is incomplete. There is no way of representing, by means of symbols, the dominance situation of the lower alleles. As a general rule the genes may be arranged in a series showing graded effects on a character, as in the above example.

A second series of triple alleles in guinea pigs, the *agouti series*, concerns the distribution of pigment in the individual hairs. In the wild-type guinea pig the agouti band (p. 76) is wider and lighter in color on the underparts of the animal than elsewhere, causing the

⁶ KEELER, C. E., and CASTLE, W. E.: Blood group inheritance in rabbits, *J. Heredity*, Nov., 1934.

belly to appear yellow. As already noted, a recessive allele of the gene A eliminates the band, converting the agouti pattern to black.

A third allele, a^r , is intermediate, both in effect and as to dominance; a^r reduces the width of the yellow band so that the agouti pattern is more or less uniform all over the body. The agouti gene A is dominant over the other two, and a^r is dominant over a . In their effects, the alleles listed above form a graded series in which the amount of red or yellow pigment in the individual hairs is reduced in two steps, thus:

A , Agouti, light bellied.

a^r , Agouti, uniform.

a , Non-agouti (no banding of hairs).

The third series of multiple alleles found in guinea pigs is considerably more complex than the other two. Known as the *albino series*, it seems to be of general occurrence in mammals, although not identical among them. In guinea pigs five alleles make up the albino series. Assuming that the background of other genes is that found in the wild type, the effects of this series may be summarized briefly as follows:

C , "Intense": coat color black and red, eyes black.

c^k , "Dark-dilution": coat color dark sepia and yellow, eyes black.

c^d , "Light-dilution": coat color medium sepia and yellow, eyes black.

c^r , "Red-eyed dilution": coat color dark sepia, yellow reduced to white, eyes dark red.

c^a , Albinism: coat white, eyes pink.

The effects of all of the possible combinations of these five alleles have been studied exhaustively by Wright.⁶ His results are summarized in Table 8. The numbers in the columns headed *Black* and *Yellow*, respectively, represent average intensities based upon a scale in which 21.0 is black, 10.6 is red, and 0 is white in each of the two color series.

An inspection of Table 8 reveals a number of interesting facts.

⁶ WRIGHT, SEWALL: The factors of the albino series of guinea pigs and their effects on black and yellow pigmentation, *Genetics*, 10: 223-260, 1925; and The effects in combination of the major color-factors of the guinea pig, *Genetics*, 12: 530-569, 1927.

We note first the complete dominance of *C* over the other four alleles and the incomplete dominance among the four lower members. If the alleles are arranged in the order of their quantitative effect upon one process, as upon the formation of yellow pigment, they are not in similar order as to their effect upon black pigment. Note for example that *c^r* produces almost as much black pigment in the hair as the intensity gene *C*; in striking contrast is the low ability of *c^r* to produce pigment in the eye and its total inability to produce yellow pigment.

Wright's theory concerning the physiological effect of the albino series of alleles is summarized in the following quotation:

It is suggested that the factors of the albino series determine the rate of some one process fundamental to all pigmentation and that the irregularities in the order of effect on different kinds of pigment, or in different regions of the body, are due to subsequent physiological processes with which the albino series of genes has nothing to do. Among such processes one which determines a higher threshold for yellow than for black finds extensive corroboration in the albino series of other mammals. A tendency for the production of yellow to interfere

Table 8

EFFECTS OF THE ALBINO SERIES OF GENES IN GUINEA PIGS IN ALL POSSIBLE COMBINATIONS

(After Wright)

Genes	Black (Grade)		Yellow (Grade)		Eye Color
<i>C</i> —	Black	21.0	Red	10.6	Black
<i>c^bc^b</i>	Dark sepia	20.1	Yellow	7.1	Black
<i>c^bc^d</i>	Dark sepia	19.4	Yellow	7.2	Black
<i>c^bc^r</i>	Dark sepia	20.5	Yellow	4.6	Black
<i>c^bc^a</i>	Dark sepia	18.5	Yellow	4.6	Black
<i>c^dc^d</i>	Medium sepia	16.9	Yellow	7.0	Black
<i>c^dc^r</i>	Dark sepia	19.1	Cream	4.1	Black
<i>c^dc^a</i>	Light sepia	14.0	Cream	4.2	Black
<i>c^rc^r</i>	Dark sepia	20.1	White	0	Dark red
<i>c^rc^a</i>	Light sepia	15.5	White	0	Light red
<i>c^ac^a</i>	White	0	White	0	Pink

with the production of black is suggested by the guinea-pig series. The differences between intensity of black in the fur and the eye suggest that competition

from yellow is lacking in the eye, which thus shows more simply than the fur the effects of the different genes on intensity of black.

As we shall see later (p. 131), the genetic analysis of hair color and eye color in man still offers considerable difficulties. It is probable that some of these difficulties are due to the fact that in man one or more series of multiple alleles exist just as they do in other mammals. The solution of the problem in human beings must wait on the collection of more extensive pedigrees than those now available. We have no reason for thinking that the principle of multiple alleles has any peculiar relationship to hair color in animals. It has merely been easier to demonstrate it in hair-color than in most other characters.

MULTIPLE EFFECTS OF A SINGLE GENE

Although the gene is the unit of heredity, a single gene often affects more than one characteristic of the organism, sometimes in wholly unexpected ways. In chickens a well-known example of a gene with multiple effects is the gene *C*, known as "Crest." It is responsible for the long, partially erect feathers producing a distinct crest in breeds like the Polish and Houdan⁷ (Fig. 24). These breeds belong to what are regarded as ornamental varieties, and the crest has been developed for its beauty by human selection over a period of centuries. Examination discloses that the skull of crested birds is highly abnormal in many ways. Darwin, who made a thorough study of the varieties of fowls, examined fourteen skulls of Polish and other crested breeds, and gave detailed descriptions of them.⁸ One of the most conspicuous features is the large hemispherical protuberance of the frontal bones, which include the cerebrum of the brain (Fig. 25). It can be seen in Fig. 25 that the frontal bones in the Polish skull are very thin as compared to the Cochin and that there are openings where no bone has formed. These open spaces are covered with membrane only. Darwin found that the protuberance varied greatly among individuals in size and in the degree of ossification of the roof of the

⁷ FISHER, R. A.: Crest and hernia in fowls due to a single gene without dominance, *Science*, Sept. 28, 1934.

⁸ "The Variation of Animals and Plants Under Domestication," by CHARLES DARWIN, 2nd ed., 1875.

skull. Usually there were many variously shaped open spaces, the bone forming an irregular network. In one specimen there was no bone whatever over the whole protuberance, and the skull when viewed from above presented the appearance of an open



FIG. 24. White Houdan male; from a crested breed of fowl developed in France. Note well-developed crest, beard, and small V-shaped comb. (Courtesy, U.S. Department of Agriculture.)

basin. As one might expect, the brain is modified in a corresponding manner, since the frontal cavity is entirely filled with brain. Darwin investigated the question as to whether there was abnormality of behavior among these birds. He found evidence that in

some instances crested birds were stupid and abnormal in their reactions.

Other characteristics of the crested breeds are short beak, comb absent or small and of unusual shape, wattles either present or replaced by a beard-like tuft of feathers (see Fig. 24).



FIG. 25. Longitudinal sections of skull, natural size, lateral view, of two breeds of fowl. (Top) Polish cock. (Bottom) Cochin cock, selected for comparison with the above from being of nearly the same size. (Courtesy, "The Variation of Animals and Plants under Domestication," by CHARLES DARWIN, New York, D. Appleton & Co., 1887.)

Darwin made no crosses between crested and noncrested breeds, although he did cross several other breeds of chickens. During the early part of this century, however, several investigators made such matings. The most recent are those by Fisher, already cited. As a result of these studies it seems clear that the gene C , when present in a bird in double dose, CC , makes the skull so defective that the cerebrum pushes through, forming a cerebral hernia. Such birds usually die. Heterozygous birds develop no hernia and are more or less normal. From these the breed is kept

going. Matings between heterozygous crested birds produce a ratio as follows:

1 CC	2 Cc	1 cc
Crest	Crest	No Crest
Cerebral hernia	No hernia	Brain normal
(Usually die)		

The gene C obviously behaves as a dominant with respect to crest. With respect to skull and brain there is no dominance; the heterozygote is intermediate, although as to its lethal effect the gene is recessive.

Another classic case similar to the one just described is found in mice. A dominant gene Y changes the color of mice to yellow, y representing the usual grey. A mouse that receives a double dose of Y , however, always dies in a very early embryonic stage.

The double effect of Y is summarized as follows:

YY , Yellow	Yy , Yellow	yy , Grey
Dies in uterus	Normal	Normal

As in the case of the crested fowl, we here have the interesting fact of a gene being recessive in one effect and dominant in another. Since all yellow mice that live are necessarily hybrids (Yy), it is obvious that yellow mice never breed true. One-third of the offspring of two yellow mice are always non-yellow.

As the pure yellows, YY , die before birth, the size of litters from yellow mice should be one-fourth smaller than normal, provided the usual number of eggs are fertilized. This has been confirmed by observation. Yellow mice produce litters about three-fourths the size of other mice. The final link in the chain of evidence for the lethal effect of gene Y was established by an examination of pregnant females in matings between yellow mice. Operations on such females disclosed that about 29 per cent of their embryos were dying at a very early stage and undergoing disintegration and absorption, as compared with only about one per cent in white mice.⁹

In man we have a striking example of the multiple effects of a single gene in the hereditary condition known as "brittle bones."

⁹ KIRKHAM, Wm. B.: The fate of homozygous yellow mice, *J. Exp. Zool.*, 28: 125-136, 1919.

Here a single dominant gene makes the bones so fragile that they break under very ordinary circumstances. Affected persons suffer from one fracture after another. The same gene causes the whites of the eyes (sclera) to be thin, transparent, and bluish in color; the teeth to develop abnormally; and the ear bones to grow together, causing deafness.

As to the manifold effects of a single gene no clearer statement has been found than that of Professor Dobzhansky of Columbia University in his excellent book "Genetics and the Origin of Species,"¹⁰ from which we quote:

Mutant genes are named according to the most prominent characteristics produced by them. In *Drosophila*, mutations of the gene "white" turn the eye color from red to white, "vestigial" makes vestigial wings, "stubble" causes a shortening of the bristles, and so on. This system of naming is convenient, but the names are not to be taken as complete accounts of the differences between the mutants and the ancestral form, much less as indicative of the total range of the effects of the particular gene on development. Despite the inadequate descriptions of mutations customarily given in the genetic literature (attention being centered almost exclusively on a single change or on a few easily observable ones), it is well known that many mutants, in *Drosophila* as well as in other forms, differ from the ancestral types in complexes of diversified characters. The mutation white changes not only the eye color, but also that of the testicular membrane, the shape of the spermatheca, length of life, and the general viability. Vestigial reduces wing size, modifies the balancers, makes certain bristles erect instead of horizontal, changes the wing muscles, the shape of the spermatheca, the speed of growth, fecundity, and length of life. Under favorable external conditions vestigial decreases the number of ovarioles in the ovaries while it has the opposite effect under unfavorable conditions. Stubble modifies the bristles, wings, legs, antennae, and viability. . . .

Genes that produce changes in more than one character are said to be pleiotropic or to have manifold effects. The frequency of such genes is not well known at present. It is true that a majority of the mutations studied produce striking effects on a single character, and that their manifold effects, if any, involve changes which to our eyes appear trivial. Thus, the main characteristic of the mutant vestigial in *Drosophila* is a decrease of the wing size, and other characters mentioned above are secondary. But to conclude on this basis that vestigial is a "wing gene" rather than a "bristle gene" would be as naïve as to suppose that a change in the hydrogen ion concentration is a "color gene" because it produces a striking change in the color of certain chemical indicators.

In view of certain criticisms that had been raised respecting the methods of demonstrating multiple effects of a gene, Dobzhan-

¹⁰ "Genetics and the Origin of Species," by THEODOSIUS DOBZHANSKY, 1941, New York, Columbia University Press, 2d ed., p. 31.

sky and Holz¹¹ have recently performed additional experiments with *Drosophila*. New methods were used. Visible mutations were induced by means of x-rays applied to males of a long inbred wild type strain. The shapes of the spermathecae in the mutants were compared with wild type. The authors state that if they observed "repeated mutations at the same locus, and if simultaneously with the appearance of the external characters of the mutant the shape of the spermatheca undergoes a corresponding change, the probability of the external and the internal changes being due to coincidence becomes negligible."

In all, 15,820 male offspring of treated males were examined. From these, 19 mutants were preserved: four had white eyes, ten were yellow-bodied, two were ruby-eyed, one vermilion-eyed, one showed forked bristles, and one a dusky body. An examination of the spermathecae of the mutants disclosed that all of the whites, nine out of the ten yellows, and the vermilion were modified with respect to the shape of these organs. No changes of spermatheca shape were found in the two ruby, in forked, and in the dusky mutants. The authors conclude, therefore, that the genes white, yellow, and vermilion have manifold effects—they are pleiotropic genes.

PROBLEMS

1. Show the ratios expected among the progenies of the following crosses in sweet peas:

- (a) Red ($RrCc$) \times white ($rrcc$).
- (b) Red ($RRCc$) \times white ($rrcc$).
- (c) Red ($RrCC$) \times red ($RrCC$).
- (d) White ($rrCc$) \times white ($Rrcc$).

2. Assume that the difference in stature between two groups of people, one averaging 5 feet, 4 inches in height and the other averaging 6 feet in height, depends upon two independent genes ($AABB = 6$ feet; $aabb = 5$ feet, 4 inches). Assume also that there is no dominance and that the effect of gene A equals that of gene B in increasing height, each adding two inches to the height.

What is the expected ratio as to height among the offspring of two dihybrids, $AaBb \times AaBb$?

¹¹ DOBZHANSKY, THEODOSIUS, and HOLZ, A. M.: A re-examination of the problem of manifold effects of genes in *Drosophila melanogaster*, *Genetics*, 28: 295-303, 1943.

Construct a bar graph or a histogram showing the frequency of offspring of each height from the above mating. Represent the frequencies vertically, with the tallest on the right and the shortest on the left.

3. If a third gene, *C*, having the effect of increasing the stature 2 inches is added to genes *A* and *B* mentioned in problem 2 ($AABBCC = 6$ feet, 4 inches; $aabbcc = 5$ feet, 4 inches), show the expected ratio from matings between trihybrids ($AaBbCc \times AaBbCc$).

Construct a bar graph showing the distribution of heights of offspring from the above mating in the same manner as in problem 2.

Note: Using the letters for the various color mutations in guinea pigs as listed on pp. 77 and 79, show the visible ratios expected from the following crosses. Assume that all animals are *SS*, and hence are free from white spotting:

4. Brown, red spotted ($eeaaCcbbPp$) \times pale brown, yellow spotted ($eeaacbbpp$).

5. Black ($EEaaCCbPP$) \times pale sepia ($EEaaCCbpp$).

6. Brown, red agouti ($EeAaCCbbPP$) \times pale brown, yellow agouti ($EeAacbbpp$).

7. What is the chance of obtaining a pale brown guinea pig from the following cross: Black, red agouti ($EeAaCcBbPp$) \times pale sepia, yellow agouti, yellow-spotted ($eeAaccBbpp$)?

Note: In one experiment with sweet peas, Bateson and Punnett found that a dominant gene (*B*) converted the red pigment into purple. A cross between two white plants gave all purple-flowered plants, as follows: $CCrrBB$ (white) \times $ccRRbb$ (white) = $CcRrBb$ (purple).

8. Show the expected result of a cross between two white sweet peas of the following constitution: $CCrrBb \times ccRRBb$.

9. Show the expected result of a back-cross of a purple sweet pea ($CcRrBb$) to a white ($ccrrbb$).

10. Show the ratio resulting from the self-fertilization of a trihybrid ($CcRrBb$).

11. According to one theory of the nature of alleles, known as the *Presence and Absence Hypothesis*, proposed by Bateson and Punnett, a recessive character is due to the absence of a dominant gene. Morgan suggested that the occurrence of multiple alleles made this hypothesis untenable. Why does this conclusion logically follow?

Note: In the following problems show the expected ratios from the various matings in guinea pigs, using Table 8 for reference. Assume that in every case the animals are homozygous for the gene for red spotting, $e^r e^p$, and the non-agouti gene, *aa*.

12. Mate two light sepia, cream, black-eyed animals ($c^d c^a \times c^d c^a$).

13. Mate a dark sepia, white, dark red-eyed animal with a light sepia, white, light red-eyed animal ($c^r c^a \times c^r c^a$).

14. Mate two light sepia, white, light red-eyed animals ($c^r c^a \times c^r c^a$).

15. In corn the dominant genes, *A*, *C*, and *R* are all necessary for the production of red aleurone color. A plant that carries a double dose of any one of the three recessive alleles (*aa*, *cc*, or *rr*) produces white seeds only. A fourth dominant gene, *I*, inhibits the production of aleurone pigment, regardless of any other genes that may be present. A fifth dominant gene, *P*, converts any red pigment that is produced to purple. *P*, however, has no effect when acting by itself.

Show the expected phenotypic ratios from the following crosses:

- (a) $AACCRrPpii \times AACCRrPpii$
- (b) $AACcRrPPii \times AACcRrPPii$
- (c) $AACCRrPPIi \times AACCRrPPIi$
- (d) $AACCRrPpli \times AACCRrPpli$
- (e) $AaCcRrPPii \times AaCcRrPPii$
- (f) $AaCcRrPpii \times aaccrrppii$

6

THE REDISCOVERY OF MENDEL'S WORK

MENDEL's biographer, Iltis, believes that the chief reason why Mendel's work was so little noticed or understood, either by the members of the Brünn Society for the Study of Natural Science, before whom it was described orally, or by scientists in general, was the atmosphere of intense interest in Darwin's theory of the origin of species, which had been published just six years previously. Iltis writes:

The psychological law that the contents of consciousness are sharply restricted applies, not only to individuals, but to generations; and since the consciousness of the epoch was entirely filled by the flood of ideas contained in the Darwinian theory and its consequences, people would not trouble themselves to make a place in their minds for the profound and peculiar ideas of Mendel, even though these were concerned with a kindred field.

The basic notion of Darwin's doctrine was the variability of species, whereas the basic idea of Mendel's (though none of Mendel's hearers nor even the lecturer himself had clearly recognized this) was the constancy, if not of species, at least of their elements, of characters, and of the heredity factors producing these. . . . The trouble was this, and this only, that the time was not yet ripe for the understanding of Mendel's laws either in Brünn or elsewhere.¹

"BOTANICAL MATHEMATICS"

Furthermore, according to Iltis, "many of Mendel's auditors must have been repelled by the strange linking of botany with mathematics." In Mendel's day, the quantitative study of biology in its various branches had only begun. Mathematics as a necessary tool for the biologist had not yet been generally recognized. The conception of organisms as living machines which might profitably be weighed and measured in all their manifestations was only gradually gaining ground. To certain minds it is possible that Mendel's laws may have seemed too mathematical to be true for

¹ "Life of Mendel," by HUGO ILTIS, courtesy, W. W. Norton & Co.

living things. His theoretical ratios may have smacked of some of the old discredited notions involving mystical numbers and formulae. To be sure, Mendel gave the actual numbers of offspring in the different generations from which he deduced his ratios, but the idea of exact numerical ratios was so novel that Mendel may easily have aroused a suspicion that he was the victim of his own mathematical preoccupations.

A part of the difficulty in winning acceptance of the new ideas related to the nature of the laws themselves, and a part to Mendel's method of presentation. First, the laws involve the idea of probability or statistics, and among the various branches of mathematics, statistics is one of the late arrivals on the scene. Few scientists in general, and fewer biologists, were trained in those days to think in terms of probability. In fact, few biologists, except some of the younger ones, are adequately trained even today. According to Charles Galton Darwin, grandson of the evolutionist Charles R. Darwin, the subject of probability was badly neglected in schools (at least in England) until recently, and still is not what it should be. In a recent address² he stated:

The subject of probability ought to play an enormously greater part in our mathematical-physical education. I do not merely mean that every one should attend a course on the subject at the university, but that it should be made to permeate the whole of the mathematical and scientific teaching not only at the university but also at school. To the best of my recollection in my own education I first met the subject of probability at about the age of thirteen in connection with problems of drawing black and white balls out of bags, and my next encounter was not till the age of twenty-three, when I read a book—I think it was on the advice of Rutherford—on the kinetic theory of gases. Things are better now, but mathematicians are still so interested in the study of rigorous proof that all emphasis goes against the study of probability.

Its elements should be part of a general education also, as may be illustrated by an example. Every month the Ministry of Transport publishes a report giving the number of fatal road accidents. Whenever the number goes up there is an outcry against the motorists, and whenever down, of congratulation for the increased efficiency of the police. No journalist ever seems to consider what should be the natural fluctuations of this number. A statistician answers at once that the natural fluctuations will be the square root of the total number, and apart from obvious seasonal effects that is in fact about what the accidents show; the number is roughly 500 ± 25 . The proof of this does not call for any difficult mathematics, neither the error function nor even Stirling's formula, but can be done completely

² DARWIN, CHARLES GALTON: Logic and probability in physics, *Science*, Aug. 19, 1938.

by the simple use of the binomial theorem. There is no mathematical difficulty that should trouble a clever boy of 15; it is only the train of thought that is unfamiliar, and it is just this unfamiliarity that is the fault of our education.

So far as my observations extend, the schools in this country are no better off than those in England with respect to the teaching of probability. The topic usually appears near the end of the algebra text, where it is likely to be omitted in the rush at the end of the course. An experience of many years in teaching Mendel's laws to the uninitiated convinces me that to many intelligent minds there is at first contact something difficult and baffling in the ideas involved. This difficulty seems in most cases to be due to unfamiliarity with ideas of probability. Relatively few persons fully grasp the import of the laws at their first introduction. This experience is so constant that it has come to be expected as a matter of course. From the point of view of the reader who already understands the laws, Mendel's paper is a model of scientific exposition. In logic, orderliness, and accuracy it could hardly be improved. Nevertheless, its presentation is unnecessarily mathematical in the use of algebraic formulae. The geometric diagrams now widely used, as illustrated in Chapters 2 and 3, are probably easier for most persons to grasp. By eliminating entirely his algebraic formulae and substituting diagrams, Mendel might possibly have obtained a closer reading and some understanding from his colleagues.

OTHER REASONS FOR LACK OF APPRECIATION OF MENDEL'S WORK

Mendel's position as a priest and teacher in a small secondary school was probably not in his favor in certain quarters. Had he been a member of a great university, no doubt he would have had a more sympathetic hearing. Although copies of the publication in which his paper appeared were circulated to more than 120 institutions, including ten or more in the United States,³ it is natural that an obscure journal should not have received the same careful reading as did the better known scientific periodicals.

Obviously, another reason why the time was not yet ripe for

³ DORSEY, M. J.: Appearance of Mendel's paper in American libraries, *Science*, Mar. 10, 1944.

the recognition of Mendel's discovery was the lack of knowledge of what went on inside the cell. It is recalled that knowledge of the behavior of the chromosomes during mitosis, meiosis, and fertilization was still a closed book.

NÄGELI AND MENDEL

Karl W. Nägeli (1817–1891), professor of botany at Munich, Bavaria, was one man at least who from his own interests and researches should have appreciated Mendel's work. Nägeli had for years been studying hybridization in plants, and writing on heredity and evolution. Mendel had great respect for Nägeli, and in 1866 wrote him a letter enclosing a copy of the paper on peas. From Nägeli's answer and from notes he made on Mendel's work it is clear that he regarded the formation of pure eggs and sperms by a hybrid (as reported by Mendel) an impossibility. He thought that the constant forms which had segregated out of Mendel's hybrids required to be tested further, and predicted that they would sooner or later vary once more. It is well to recall that this doubt had apparently occurred to Mendel also, for he had tested out hybrids on this very point—in some cases through as many as six generations. Nevertheless, Nägeli was not satisfied, and asked that Mendel send him some of his seeds for testing at Munich. Mendel replied, sending 140 labeled packages of seeds with directions for testing them. Nägeli planted a number of the test seeds, but he never made the promised series of control experiments and, according to Iltis, neither in his letters to Mendel nor in his subsequent papers and books do we find any reference to Mendel's work on peas. It seems therefore that if one of the leading biologists in Europe could thus fail to appreciate the importance of Mendel's work or the necessity of repeating the experiments relating to a field in which that biologist was an authority, it is little wonder that other men less favorably situated should have failed to do so.

RESURRECTION OF MENDEL'S PAPER

As late as 1900 there were, according to H. F. Roberts,⁴ only two published works which referred to Mendel's paper on peas.

⁴ "Plant Hybridization before Mendel," by H. F. ROBERTS, 1929, Princeton University Press.

The first of these was a book by a German botanist, Hermann Hoffmann, published in 1869, reporting investigations on the problem of species and varieties in connection with a study of Darwin's theory of evolution. The second was a book by W. O. Focke, published in Berlin, 1881, entitled "*Die Pflanzenmischlinge*" (Plant Hybrids). In one of his references to Mendel, Focke states that Mendel's experiments on peas gave results similar to those obtained by Andrew Knight (an Englishman who about 1825 had reported experiments in hybridizing peas), but that Mendel believed he had found constant numerical ratios among the types produced by hybrids.

Apparently a third reference to Mendel's work should be added to this list, for, according to Dorsey, the American botanist L. H. Bailey included a reference to Mendel's work in a paper on cross breeding and hybridizing in 1892. De Vries, mentioned presently, learned of Mendel's work from Bailey's bibliography. None of these authors, however, seems to have realized that Mendel had discovered an important new law, and their passing references to Mendel apparently attracted no further notice to him. Iltis quotes a letter to himself from Focke as follows:

I know that my attention was drawn to Mendel's work by some reference or other in the literature of the 'seventies, but I cannot now remember when or where I first heard of him. I did not read his paper until shortly before the publication of my own book . . . You ask me as to the impression Mendel's paper made on me when I first read it. I can only say that it seemed to me his statements were well worth checking, and that I regretted not being in a position to repeat his experiments. This would have needed much more time and much more cultivable space than were at my disposal. Fluttering the pages of my book I note that on p. 492 I have included Mendel among the most trustworthy of observers.

In the years following the publication of Focke's book, rapid strides were being made in the branch of biology dealing with the cell and its behavior. The nucleus and chromosomes were receiving more and more attention, and were coming to be recognized as those parts of the cell especially adapted for the transmission of the hereditary materials. Theories of heredity were being proposed and debated. On the basis of the newer knowledge of the cell, the old belief in the inheritance of acquired characters was yielding ground.

Among the leaders in the debate on the inheritance of acquired

characters was August Weismann, who is most famous for his germ-plasm theory of heredity and development. He regarded the chromosomes as the material basis of heredity and looked upon these as passing unchanged from generation to generation, showing on theoretical grounds that there must be a reduction division at the formation of the reproductive cells. The hereditary materials were, in his view, not made up from an assemblage of particles released by the body cells into the blood and later aggregated in the reproductive cells, as Darwin had suggested, but were in each generation received as such from the parents, and were only temporarily protected and nourished by the body until the time came for them to be passed on to the next generation. The body cells, as well as the sperms and eggs, arose by cell division (mitosis) from the fertilized egg. After serving their function the body cells eventually died, while the reproductive cells, potentially immortal, were passed on to the next generation.

With biologists stimulated to take up again the study of heredity, it is perhaps not surprising that in the last decade of the nineteenth century a number of investigators should have begun an attack on the problem by crossing plants. Nevertheless, there is dramatic interest in the fact that three botanists, in three different countries, independently began such experiments, and unknown to one another, obtained within a short period of time results confirming Mendel's discovery, while not one had read Mendel's paper before beginning his own experiments.

The first botanist to report his results was Hugo de Vries of Holland. In March 1900 he published two papers, one in French and one in German, giving results of experiments begun in 1892. The former paper, appearing in the "Comptes Rendus" of the French Academy of Science was very brief, containing merely an abstract of his conclusions. It mentioned several species of plants used in the experiments. The pea was not one of them. Segregation was reported, and the ratios agreed perfectly with those of Mendel. The terms "dominant" and "recessive" were used in the same sense as used by Mendel, but Mendel's name was not mentioned.

The German paper, seven pages in length, was also little more than a summary. It was published in "Berichte der Deutschen

Botanischen Gesellschaft" (Reports of the German Botanical Society). In it de Vries lists species of plants belonging to more than a dozen genera which he had experimented with beginning in 1892, and which were found to follow Mendel's laws of dominance and segregation. In this paper he gives Mendel credit for being the original discoverer of these laws, in the following words:

These two propositions were in their essential points drawn up long ago by Mendel for a special case (peas). They were, however, not appreciated and sank into oblivion. They possess, according to my own experiments, general validity for true hybrids. This important paper is so seldom referred to that I myself first learned of it after I had finished the majority of my experiments, and had deduced the propositions mentioned.

De Vries also gives results confirming the law of independent assortment, but does not mention Mendel as having also discovered this law. In a footnote he cites the book by Focke already referred to which presumably led him to find Mendel's paper.

The implication in the use of the phrase "special case" seems hardly justified, for Mendel had also performed experiments with two species of beans (reported in the paper on peas), which were in perfect agreement with those in peas. In two other species of beans his results were only in partial agreement, but were correctly explained by him as falling under the same laws, with the addition of a supplementary principle (the factor principle), discussed in the preceding chapter.

Mendel was modest in making any claims for his laws beyond the point directly supported by the facts. In one place in his paper he states:

Whether the variable hybrids of other plant species observe an entire agreement must also be first decided experimentally. In the meantime we may assume that in material points an essential difference can scarcely occur, since the unity in the developmental plan of organic life is beyond question.

The second botanist to confirm Mendel's results was Carl Correns of Tübingen, Germany, who interestingly enough was one of Nägeli's former students. His paper was published in the same German periodical as de Vries', in April 1900, in the very next issue. It is ten pages in length and entitled "G. Mendel's Law Concerning the Behavior of the Descendants of Racial Hybrids." Correns states that the publication of de Vries' paper (the one in

French) induced him to write his own; that in his experiments with varieties of corn and peas he had come to the same conclusions as de Vries and that he also believed, as de Vries obviously did, that he had discovered something new; but that later he had found that Gregor Mendel in the 'sixties had obtained not only the same results but had given exactly the same explanation, so far as this was possible in 1866. "To bring it up to date," says Correns, "one needs merely to substitute egg and egg nucleus for germ cell and germinal vesicle, and generative nucleus for pollen cell." Correns mentions the fact that Mendel had confirmed in beans the results of his experiments with peas and that Mendel supposed that the law held in many other cases. His opinion of Mendel's work is expressed as follows:

This paper of Mendel's to which Focke refers in his "Pflanzenmischlinge," but without giving it its due, and which had received scarcely any notice, is among the best works ever written upon the subject of hybrids, in spite of numerous criticisms which can be made of it in incidental matters such as terminology.

Correns disagrees with de Vries' claim that dominance is a universal rule and cites cases in which the hybrid is intermediate. In this he followed Mendel who, as we have seen, found a similar case. Correns, however, made the mistake of regarding Mendel's laws as applicable almost exclusively to racial hybrids. Mendel had suggested that there was no essential difference in the mechanism of heredity between racial hybrids and species hybrids, and this has been found to be true.

The third man to confirm Mendel's laws of dominance and segregation was Erich Tschermak, a botanist of Vienna. His paper, consisting of seven pages, was published in June of the same year in the same periodical as the papers of de Vries and Correns. His experiments were confined to peas. Although he does not give his actual numbers, his ratios produced by monohybrids were as 3:1. No mention is made of experiments on independent assortment. Tschermak states that he was stimulated to begin his crossing experiments on peas in 1898 by Darwin's experiments on the effects of self-fertilization and cross-fertilization, and that he was especially interested in the group of plants to which peas belong since they furnish an exception to the general

rule that crossing different individuals and varieties has a beneficial effect on the offspring. His observations of dominance and segregation seem to have been incidental.

In a postscript to his paper Tschermak states: "The simultaneous discovery of Mendel by Correns, de Vries, and myself, seems to me especially gratifying. I, too, as late as the second year of my experiments, believed I had discovered something entirely new."

ILTIS' TRIBUTE TO MENDEL

I should like to conclude this chapter by quoting from the beautiful tribute to Mendel penned by his fellow countryman and biographer, Hugo Iltis:

This almost simultaneous rediscovery of the writings of Gregor Mendel by three investigators working quite independently one of another was remarkable enough to rivet the attention of biologists the world over. Mendel's time had at length come, and this to an extent far beyond anything of which he had dreamed. A mighty edifice has been erected upon what seemed, though wrongly, to be a very slender foundation. The little essay published in the "Proceedings of the Brünn Society for the Study of Natural Science" has given a stimulus to all branches of biology, with the result that the study of heredity, in its neomendelian form of genetics, has become one of the most important branches of contemporary research. . . . The progress of research since the beginning of the century has built for Mendel a monument more durable and more imposing than any monument of marble or bronze, inasmuch as, not only has "mendelism" become the name of a whole vast province of investigation, but all living creatures which follow "mendelian" laws in the hereditary transmission of their characters are said to "mendelise." In these words Mendel's name will be immortalised as long as science endures.

All the same it was felt by many that a memorial to Mendel ought to be erected in the place where he had lived and worked and died. This was when the work had already become famous throughout the world, but in Brünn most of the elders had forgotten him, and few of the young folks had ever heard of him. Brünn, in fact, was hard to move. A great many lectures had to be delivered, and much propaganda was needed in the newspaper press, before some understanding of the importance of "mendelism" could be knocked into the hard heads of the Brünners. Indeed, for those who know little and care less about biology, its importance is not obvious, and the doctrine is somewhat hard to understand. . . .

Of course it was far from easy to arouse in the minds of those whose only claim to intelligence was the possession of such "common sense" an understanding of Mendel's importance in the world of modern thought. Not a few of the influential residents of Altbrünn protested against the erection of the memorial in the Klosterplatz on the ground that this would involve the banishment of the booths and roundabouts which at fair-time amused people and brought money

into the town. Others, pluming themselves on being advanced thinkers, objected to the raising of a monument to a priest.

Still, within a few years it was found possible to reconcile Brünn to the idea of the Mendel memorial. In fact most of the money was collected locally, although part of the sum came from abroad through the instrumentality of a large international committee to which more than 150 investigators of all parts of the world belonged. Competitive designs were asked for, and that of Theodor Charlemont of Vienna was accepted. In the Charlemont statue we see the figure of Mendel as a young priest dressed in the conventual robes standing in front of a hedgerow of peas and beans (the classical objects of his investigations), and, with outstretched hands, fingering flowers and leaves. The face, finely intellectual, is looking out thoughtfully into the distant future. Charlemont had nothing better than photographs to work from, but the result is as lively and natural as could be wished. On the face of the pediment, immediately beneath the standing figure, is the inscription

TO THE INVESTIGATOR
P. GREGOR MENDEL
1822-1884

Along the lowest part of the front is a further inscription

ERECTED IN 1910 BY THE FRIENDS OF SCIENCE

Between these two inscriptions and upholding the upper one, in slight relief, are the figures of a youth and a maiden, nude and kneeling, with joined hands. This is a subtly allegorical allusion to the far-reaching importance Mendel's genetic laws are likely to have upon human life. The monument is not only a noble tribute to Mendel but an extraordinarily beautiful example of the sculptor's art.

The unveiling of the memorial took place on October 2, 1910. All honor was then paid to the life and work of the retiring investigator who in the little garden near at hand had been so happy among his flowers and his beets. To him were now applicable the somewhat crude but thoughtful verses he had himself in boyhood penned in memory of Gutenberg:

*May the might of destiny grant me
The supreme ecstasy of earthly joy,
The highest goal of earthly ecstasy,
That of seeing, when I rise from the tomb,
My art thriving peacefully
Among those who are to come after me.*

That was in the year 1910, and William Bateson, as spokesman of the British mendelians, delivered a speech extolling the power of science to bring the nations together, concluding with Schiller's words: "Alle Menschen werden Brüder."

During the years that followed, men forgot their brotherhood. In the mad days of barbarism and savagery while the war was raging and after it, those who should have been the devotees of science were devoting themselves to the cultivation of hatred and to the arts of destruction. Slowly, however, the world returned to its senses. In 1922 a century had passed since Gregor Mendel first saw the light in the little Silesian village where he was born. The scientific press throughout the world made much of this centenary, and a commemorative volume was issued.



FIG. 26. Memorial to Gregor Mendel in Brunn. Statue by Theodor Charlemont. (Courtesy, "Life of Mendel," by HUGO ILTIS, New York, W.W. Norton & Co.)

In Brünn a centenary festival was held, and for the first time in eight years men of science from all nations met together there in amity. The debates that had been raging were stilled *sub specie aeternitatis*. In front of the Mendel monument, speeches were delivered in German, Czech, English, and French. The Czechs and the Germans, the divided races who dwell in Mendel's homeland, their mutual enmity forgotten if only for a moment, joined hands beneath the statue of the dead investigator. In this matter, likewise, Gregor Mendel had worked a miracle.

That was nearly ten years ago now, and with every year his influence is more widespread. He is modifying our whole outlook on life; he has helped us amazingly to increase "the fruits of the earth in due season"; and he has opened up paths of research which seem likely to enable mankind to remould its very self. Thus his name will always live as a pioneer of research, as a pathfinder on the way to the new time; and the coming generations will never forget Gregor Mendel as one of the chief among those who have brought light into the world.

LINKAGE AND CROSSING-OVER

AS WE HAVE SEEN, the Principles of Segregation and Independent Assortment together with the Factor Principle explain the sudden appearance of many new traits and combinations of traits in living things—the larger the number of chromosomes the greater the number of possible combinations. But the effectiveness of independent assortment is limited by the fact that many genes are carried on a single chromosome, and these genes tend to remain together. The tendency of genes to persist in groups from generation to generation is known as *linkage*, a principle of general application in plants and animals.

Experience teaches that many species with a small number of chromosomes are highly variable, although their opportunities for variation as a result of independent assortment are strictly limited. For example, in *Drosophila melanogaster* (Table 5), an insect with four pairs of chromosomes, only 16 combinations of maternal and paternal chromosomes are possible in the gametes.

The limitations inherent in the linkage system are, however, largely compensated for by still another mechanism for increasing variability. This mechanism is known as *crossing-over*. Crossing-over may be defined as the mutual exchange of blocks of homologous genes located on the two members of a pair of chromosomes. As a result of crossing-over most of the combinations theoretically possible among the genes eventually occur.

The first observations leading to the discovery of linkage and crossing-over were made by Bateson and Punnett, previously mentioned as the first to demonstrate a case of the factor principle, in experiments on sweet peas. For the fullest development of the principle of linkage and crossing-over, however, we have to

thank the American biologists, T. H. Morgan and his students and associates, especially A. H. Sturtevant, H. J. Muller, and C. B. Bridges. The epoch-making experiments upon which our present conception of linkage and crossing-over is based were begun by

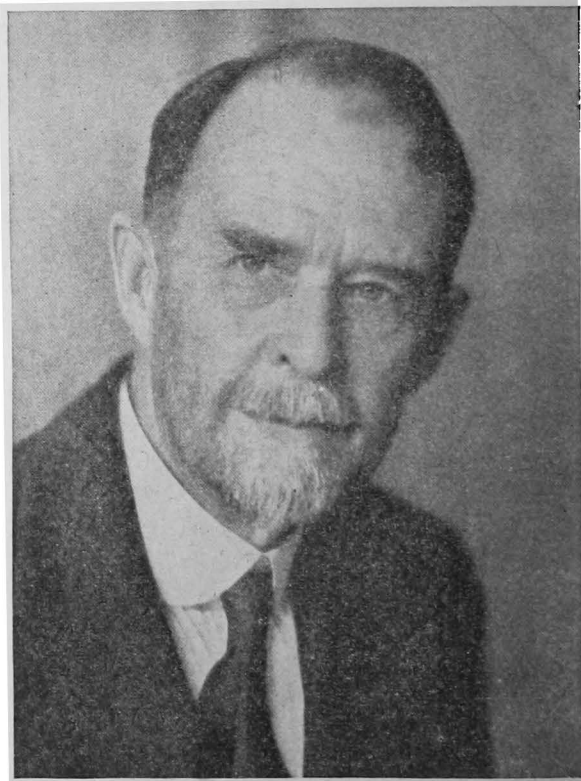


FIG. 27. Thomas Hunt Morgan (1866-1945). (Taken 1932.)

Morgan about 1910, at Columbia University. The fruit fly *Drosophila*, which has come to occupy a preeminent place in research on chromosome structure and behavior, was used in the experiments. For his contributions in this field Morgan received many honors, including the Nobel prize in medicine for 1933. In order to illustrate linkage and crossing-over we may well select a case in *Drosophila* worked out by Morgan.

LINKAGE AND CROSSING-OVER IN *DROSOPHILA*

Two recessive mutations discovered by Morgan about 1920 are shown in Fig. 28. One of these, known as "black," is much darker than the normal grey-bodied fly. The other, "vestigial," has wings which are reduced to useless stubs. In both cases, if crossed with normal flies, these mutants give the typical 3:1 ratio in the third (F_2) generation. From a cross between a pure long-winged, black fly and a pure grey-bodied, vestigial fly (Fig. 28) the offspring are all normal, since each parent gives to the offspring the normal gene lacking in the other. When one of the normal dihybrid females from this cross is back-crossed with the double recessive (black, vestigial) the resulting ratio is very different from the 1:1:1:1 ratio we have learned to expect in a back-cross mating of a dihybrid to a double recessive (p. 41). The actual results of such an experiment are shown in Fig. 28.

We note that the ratio is symmetrical in that the two combinations of traits present in the grandparents are equally numerous, as are also the two new combinations. The original combinations, however, make up 83 per cent of the total number, instead of 50 per cent, as would be the case for independent assortment. The rest of the offspring, amounting to 17 per cent, are *new combinations*. The new combinations are known as *crossovers*. As we shall see later it was purely accidental that two mutants were chosen that showed 17 per cent crossing-over. The percentage of crossing-over has direct relationship to the distance the genes lie apart on the chromosome, and two other genes chosen at random would probably show a different percentage.

Morgan showed that this unusual ratio fits perfectly into the theory that the genes *black* and *vestigial* are on the same chromosome; in other words, that they are linked, and that the dihybrid produces four types of gametes in the same ratio as that of the character combinations in its offspring, namely, in this case:

$$\begin{array}{cccc} (Bv) & (bV) & (bv) & (BV) \\ 41.5\% & : & 41.5\% & : & 8.5\% & : & 8.5\% \end{array}$$

(Symbols of genes located on a single chromosome are customarily enclosed in parentheses.)

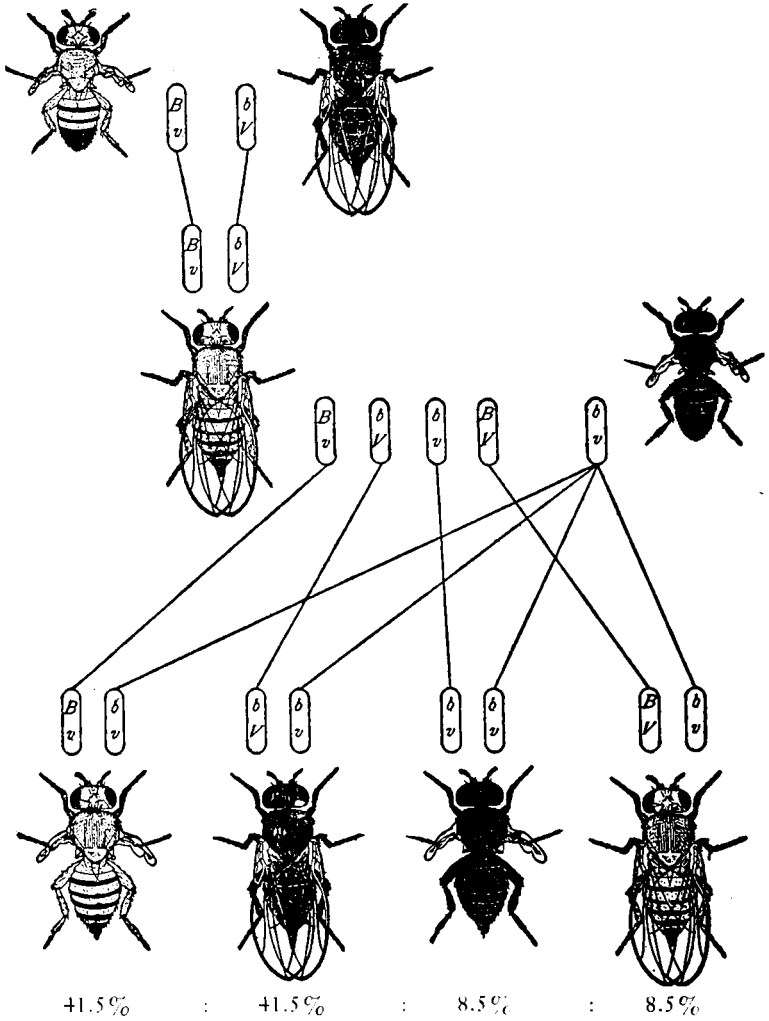


FIG. 28. Crossing-over in *Drosophila*: A grey, vestigial-winged male is crossed with a black, long-winged female. One of the female offspring is back-crossed with a black, vestigial male; the result is four types of offspring in the proportions indicated. (Courtesy, T. H. MORGAN: "The Physical Basis of Heredity," Philadelphia, J. B. Lippincott Co.)

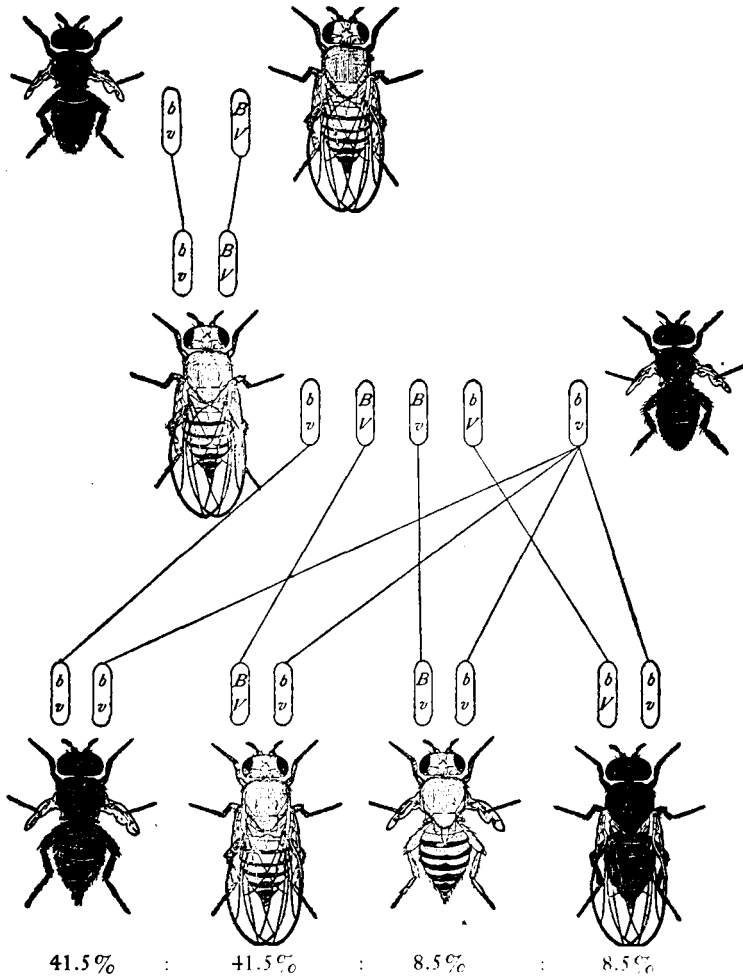


FIG. 29. Crossing-over in *Drosophila*. A black, vestigial-winged male is crossed with a grey, long-winged female. One of the female offspring is back-crossed with a black, vestigial male; the result is four types of offspring as indicated. Note that the combinations of traits shown by the crossovers are the same as those of the non-crossovers in Fig. 28. (Courtesy, T. H. MORGAN: "The Physical Basis of Heredity," Philadelphia, J. B. Lippincott Co.)

The double recessive parent produces only one kind of gamete (bv). Since both genes in this gamete are recessive, they do not affect the ratio: the characteristics of the offspring in a back-cross to the double recessive correspond in every case to the gene make-up of the gametes of the dihybrid.

The dihybrid female parent obviously received from its parents the two chromosomes (Bv) and (bV). The only way in which the gametes (bv) and (BV) could be produced by this female was through an exchange of genes between the parental chromosomes. This exchange, or crossing-over, gave rise to the two new combinations of traits in the offspring. It is highly significant that in all experiments such as the one described, both recombinations, as well as both parental combinations, occur with equal frequency.

If the above experiment is modified by using in the backcross mating a female obtained from a cross between wild-type and the double recessive and which, therefore, has both dominant genes on one chromosome and both recessive genes on the other (Fig. 29), the same percentage of recombinations among the offspring is obtained as in the previous experiment. The combinations of traits in the crossovers and the non-crossovers are, however, reversed in the two experiments, as can be seen by comparing Figs. 28 and 29. In the one experiment the traits shown by the crossovers are the same as those shown by the non-crossovers in the other, and *vice versa*.

These experiments prove that the normal alternatives of the genes for black and for vestigial cross over with the same frequency as do the black and the vestigial genes themselves—a result that agrees with the hypothesis that such alternatives or *alleles*, as they are known, occupy corresponding positions or *loci* on the chromosomes. Expressed otherwise, it is the position of the genes rather than their nature that determines the percentage of crossing-over.

Several hundred genes in *Drosophila* have been tested, one with another, in order to discover their linkage relationships. All have been found linked with other genes, not one being inherited independently of all others. The genes tested fall into four linkage groups, in which every gene shows linkage with all other genes of the same group, but shows independent assortment with all genes of the other three groups. The number of linkage groups

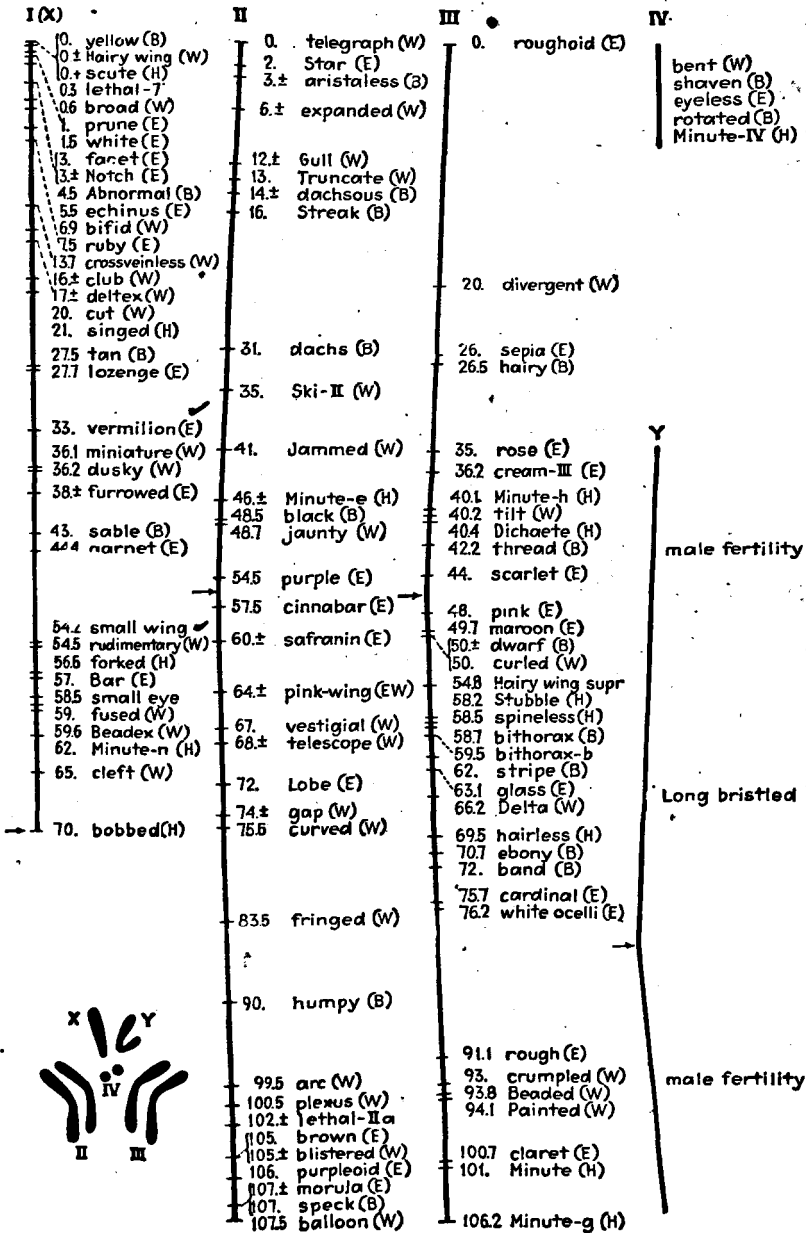


FIG. 30. Linkage map for *Drosophila melanogaster*, showing serial order of the genes of many of the most frequently used mutants. Letters in paren-
(For remainder of legend see p. 112.)

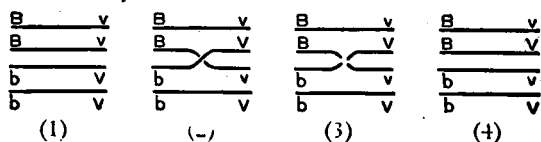
corresponds exactly with the number of pairs of chromosomes. Furthermore, there is a correspondence between the number of genes in each of the four linkage groups and the relative lengths of the four chromosomes, respectively. Thus all but 11 of the known genes belong to the three groups representing the three longest chromosomes; the remaining 11 are located on the tiny fourth chromosome.

Experiments show that the percentage of crossing-over between any two given genes is constant, so that if the experiment is repeated under the same conditions the results may be predicted.

EXPLANATION OF CROSSING-OVER

The theory generally accepted in explanation of crossing-over is, in its broad outlines, extremely simple. Briefly, it states that during the formation of the gametes, while the chromosomes are in the tetrad stage, the members of a pair come into intimate relationships with one another, resulting in an exchange of segments or blocks of genes between chromatids. Several theories have been proposed to explain the method of crossing-over between chromatids, but the details and causes of the process are still uncertain, although a large amount of research has been done on the problem by cytologists. The problem is an extremely difficult one owing to the fact that the chromatids concerned are minute bodies, identical in appearance, interacting in an intimate way within an extremely circumscribed region.

The results of the process of crossing-over may be visualized by reference to the diagram below. The same genes are used as in



the *Drosophila* case described above. It is not assumed that the diagram represents an actual picture of the mode of crossing-over.

theses indicate parts of the fly involved: B, body; E, eye; H, hairs; W, wings. Arrows indicate positions of centromeres. (Courtesy, LESTER W. SHARP: "Fundamentals of Cytology," New York, McGraw-Hill Book Co., 1943; after Morgan, Sturtevant, and Bridges, and C. Stern.)

In (1) the four chromatids are shown lying side by side; in (2) two of them are lying across one another; in (3) these two are broken at one point; and in (4) they are reconstituted to form two new combinations. It is obvious from the diagram that the number of recombinations of one type (*BV*) must equal that of

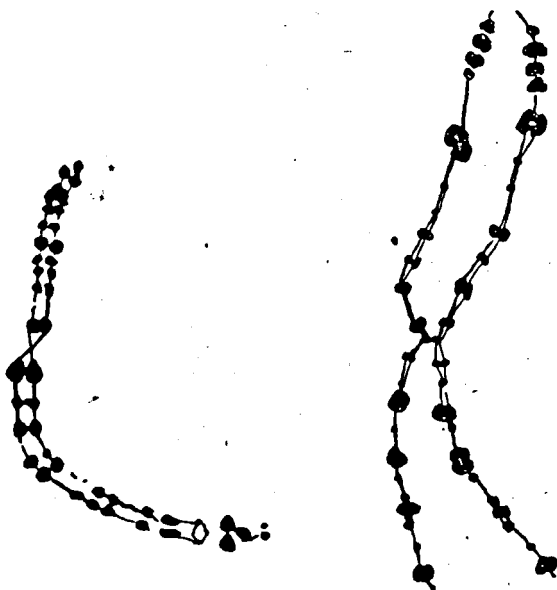


FIG. 31. Drawings of prophase chromosomes in two species of plant. (Left) *Lilium pardalinum*. (Right) *Fritillaria lanceolata*. Note the identity in size and linear order of the particles (chromomeres) of the pairing chromosomes, and on the right the identity of the four strands (chromatids). One chiasma is shown in each figure. (Courtesy, M. B. CRANE and W. J. C. LAWRENCE: "The Genetics of Garden Plants," New York, The Macmillan Co., 1938, after Belling, 1931.)

the other (*bv*). The breeding results, as well as chromosome studies, prove that the end results are as represented in the diagram. Observations of the cells of many species at meiosis disclose the chromatids in the tetrad stage forming characteristic figures with crossed lines known as *chiasmata* (Fig. 31). A chiasma suggests that crossing-over has taken place or is about to take place between chromatids. Frequently several chiasmata are observed

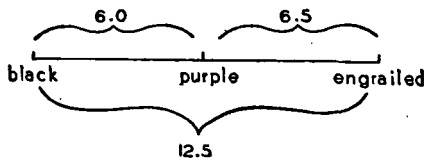
in a single tetrad: two are shown in the longer of the two chromosomes in Fig. 16 (p. 55).

Experiments indicate that crossing-over always involves the exchange of segments of chromatids rather than single genes. Either chromatid of one chromosome may exchange with either chromatid of the homologous chromosome, irrespective, or largely so, of which strands have crossed over at other points. There is evidence that crossing-over does not occur between sister strands resulting from the splitting of one chromosome. As indicated by the chiasmata in Fig. 16, crossing-over takes place between only two of the four chromatids at any particular level. A segmental interchange can be detected only in case the chromatids entering into the trade differ from one another in at least two genes, as shown in the above diagram of *Drosophila* chromosomes, because it is only such crossovers that result in visible recombinations among the offspring.

MAPPING CHROMOSOMES

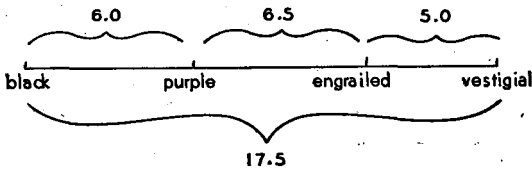
Crossing-over between linked genes may be as little as one tenth of one per cent, on up to 50 per cent, depending on the two genes that are chosen. On the basis of their mutual crossover frequencies the genes in a chromosome may be arranged in a definite order along a single line (Fig. 30). This is, in fact, the only satisfactory way of representing graphically their relationships.

To illustrate the principle by an example let us consider two linked recessive genes in *Drosophila*, black (a body color) and purple (an eye color), both on chromosome II. The crossover frequency of these two genes is 6.0 per cent. A third gene, engrailed (a body character), lies on the same chromosome as the other two. Its crossover frequency with purple is 6.5 per cent. Black and engrailed cross over with a frequency of 12.5 per cent, which is the sum of the other two. These three genes may therefore be arranged on a graph, commonly known as a *chromosome map*, as follows:



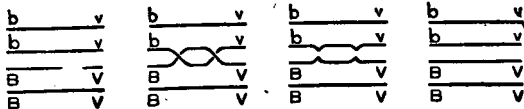
The genes are separated on the line by a distance corresponding to their observed crossover frequencies.

Suppose we now wish to locate the vestigial gene on the map. As already stated, vestigial and black cross over to produce 17 per cent recombinations. Does the vestigial gene lie to the right of black, i.e., beyond engrailed, or does it lie to the left of black? To answer this question vestigial and engrailed flies are mated, and the dihybrid is back-crossed as in the experiment described for vestigial and black. The results show a crossover percentage of 5.0 per cent. Vestigial therefore must be placed to the right of engrailed as follows:



By a continuation of this testing process all of the genes on the chromosome may be arranged in a definite linear order.

DOUBLE CROSSOVERS. We note that the summation of the map distances between black and vestigial gives 17.5; but as shown by the experiments described previously the recombinations equal 17.0 per cent. This slight discrepancy is explained as the result of two simultaneous interchanges between the genes black and vestigial, thus:



Although, as shown in the diagram, two crossovers have occurred, these have resulted in no recombinations with respect to black and vestigial: one crossover has cancelled the effect of the other. When two genes lie far enough apart for double crossovers to take place the frequency of chromatid crossing-over exceeds that of the observed recombinations. Triple and other multiple crossovers also are known to occur. Any even number of crossovers has the same effect as two; only odd numbers result in new combinations. If, as a result of chance, even and odd numbers of

crossovers in a given chromosome pair occur with equal frequency, the number of actual recombinations between two genes should not exceed, on the average, 50 per cent. Experiments demonstrate that this figure is not exceeded.

INTERFERENCE. With certain qualifications one may say that chance determines the exact point on the chromosome at which a crossover takes place. One limitation on the chance localization of crossovers is known as *interference*, a term referring to the observed inhibitory effect of one crossover upon another. The phenomenon of interference was first observed by Sturtevant in 1913. Breeding experiments show that there is always a minimum distance within which two crossovers never occur simultaneously, interference in such cases being complete. In *Drosophila* the minimum is from 10 to 20 map units, depending on the region of the chromosome concerned. As the distance increases, interference gradually decreases. At about 45 map units one crossover no longer inhibits another.

We may illustrate interference by using the same genes in *Drosophila* which have been used in the description of the mapping of chromosomes. As noted previously, crossing-over between black and vestigial occurs with a frequency of 17 per cent, but the actual map distance between these two genes as calculated by adding the distance between black and purple, purple and engrailed, and engrailed and vestigial, is 17.5. The difference of 0.5 per cent was attributed to double crossovers. If we calculate the expected percentage of two simultaneous crossovers (double crossovers) between black and vestigial, we obtain a figure in excess of the observed 0.5 per cent, thus: the chance of a crossover between black and engrailed (12.5 per cent) times the chance of a crossover between engrailed and vestigial (5.0 per cent) gives 0.625 per cent. The difference between 0.625 per cent and 0.5 per cent is the result of interference. We see, therefore, that interference reduces the percentage of actual double crossovers below that expected on the basis of the simultaneous occurrence of independent events.

In agreement with the evidence from breeding experiments proving interference to be a fact, we have the visible evidence of the chiasmata. Assuming that a chiasma marks the point of

crossing over, we should expect to find crossovers separated at a minimum distance since neighboring chiasmata are always a measurable distance apart. Interference is additional proof of the fact that crossing-over is the interchange of sizable pieces of chromosomes.

A second type of limitation on the random location of crossovers is dealt with in the following section.

MAP DISTANCES vs. CHROMOSOME DISTANCES. Do the map distances as ascertained from recombination percentages represent accurately real distances on the chromosome? The evidence indicates that they do not. To quote Morgan on this point:¹

An important reservation must be made here—one that geneticists have always been aware of. We have assumed that the chance of crossing over is the same at every level of the chromosomes. As will be shown presently this may be inexact. The point is illustrated by a railroad timetable. The time a train takes between stations is a fair measure of their distance apart, but it is not exact. There may be grades or variations in speed, or waits at certain points in consequence of which the time between stations is not always an exact measure of their distance from each other. So it may be with the map distances. For, if crossing over should be more frequent in certain regions than in others, the map distances are only approximately true.

From observations of certain types of chromosome changes (Chapter 13) has come the discovery that crossing-over occurs with less frequency near the centromere at the center of the two long chromosomes of *Drosophila* than it does near the ends. The genes near the centromere are therefore actually farther apart on the chromosome than is indicated on the map.

An important peculiarity respecting crossing-over in *Drosophila*—a peculiarity which has made this animal an especially favorable one for the study of chromosome structure—is the failure of crossing-over to take place in the male, under normal conditions. The problem for the investigator is thus simplified in that he can determine directly the percentage of crossing-over merely by observing the new combinations among the offspring, knowing that any new combinations must be the result of crossing-over in the formation of the eggs.

¹ "The Scientific Basis of Evolution," by THOMAS HUNT MORGAN, 1935, W. W. Norton & Co.

LINKAGE IN OTHER SPECIES

Linkage is a general phenomenon in plants and animals. The principles discussed in connection with the experiments with *Drosophila* apply also to other organisms, but in most organisms, unlike *Drosophila*, crossing-over occurs in both sexes. In hermaphroditic plants it takes place in both the male and the female parts of the plant. It is a general rule that the number of linkage groups agrees with the number of chromosome pairs. In corn, the most thoroughly analyzed of the plants, more than 300 genes are known, and these all fall into ten linkage groups corresponding to the ten pairs of chromosomes. All ten chromosomes, incidentally, are visibly distinguishable under the microscope. In peas there are seven pairs of chromosomes and seven linkage groups. In the various species of *Drosophila* (Table 5) there is a similar correspondence.

Let us illustrate the method of calculating F_2 ratios in species which show crossing-over in both sexes. In corn, a dominant mutation known as tassel seed (T) has been located in chromosome 4. Plants with this gene have silks as well as anthers in their tassels. A few seeds usually develop in the tassel.

In chromosome 4 there is a recessive gene s responsible for small pollen. Crossing-over takes place between these two genes in 10 per cent of the cases.

If a plant with small pollen and normal flowers (st)(st) is crossed with one homozygous for tassel seed and large pollen (ST)(ST) the hybrid will be tassel-seeded with large pollen (ST)(st). Self-fertilization of the hybrid will give the result shown in Fig. 32.

Summing up we find that the phenotypic ratio is 70.25 per cent tassel seed, large pollen; 4.75 per cent tassel seed, small pollen; 4.75 per cent normal tassel, small pollen; and 20.25 per cent normal tassel, normal pollen. It is evident that the only difference in the solution of problems in linkage like this and those in independent assortment is that here the gametes are not formed in equal proportions and it is necessary to use the decimal system of multiplication. The resulting ratios are always expressed in per-

centages rather than in common fractions as in independent assortment.

If the above cross had been made before the percentage of crossing-over between these two genes had been determined it would have been possible to have calculated such percentage from the F_2 ratio by the application of formulas developed by the plant geneticists.

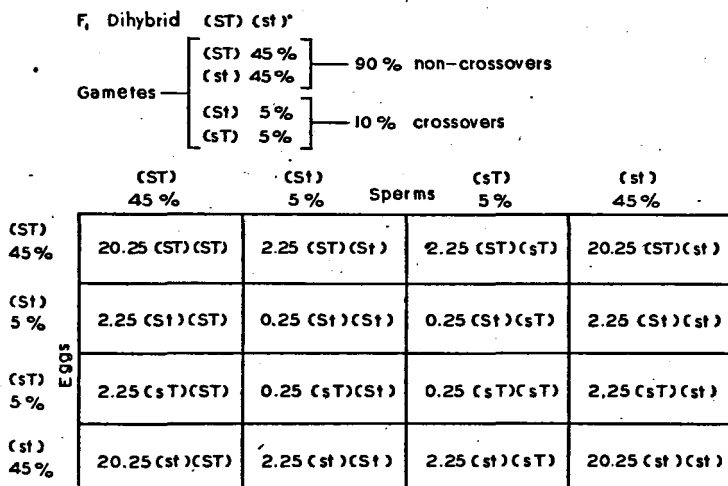


FIG. 32. Diagram showing the checkerboard method of calculating F_2 ratios with two linked genes in an organism having crossovers among both male and female gametes.

Linkage is known in mammals. At least five groups of two or more linked genes have been found in rabbits, in which there are 22 pairs of chromosomes.² Several other pairs of alleles have been shown to be independent of these and of each other. Linkage is known also in mice and rats. In the mouse, 10 of the 20 pairs of chromosomes have been mapped. On these 10 are 29 known loci, five of which have produced more than one mutant gene (multiple alleles). Besides the genes belonging to identified linkage groups there are 28 known mutant genes as yet unlocated.³

² "Mammalian Genetics," by WILLIAM E. CASTLE, 1940, Harvard University Press; CASTLE, W. E., and SAWIN, P. B.: Genetic linkage in the rabbit, *Proc. Nat. Acad. Sci.*, 27: 519-523, 1941.

³ STAFF OF THE ROSCOE B. JACKSON MEMORIAL LABORATORY, A chromosome map of the mouse, *J. Heredity*, pp. 271-273, Sept., 1945.

In man, also, linkage has been demonstrated, principally in the case of the X chromosome (Chapter 11). The observation that in mammals the number of linkage groups so far discovered does not equal the number of chromosomes is due undoubtedly to the fact that mammals have a relatively large number of chromosomes, and that the number of genes so far tested is not sufficiently extensive.

SUMMARY

The number of genes possessed by an organism greatly exceeds the number of chromosomes. Ordinarily each chromosome contains many genes. Those in a single chromosome are said to be *linked*, and this principle of aggregation is known as *linkage*.

As a general rule the genes in a linkage group do not remain permanently linked, but exchange places at meiosis with homologous genes on the opposite chromosome of the pair. This exchange is known as *crossing-over*.

Linked genes cross over with a definite frequency in a uniform stock and under uniform environmental conditions.

Individuals showing characteristics resulting from crossing-over are known as *crossovers* or *recombinations*; those in which no crossing-over is evident are known as *non-crossovers*.

Genes cross over in chains or segments rather than singly. The exchanged chains of genes consist of homologous pieces of chromatids belonging to homologous chromosomes. As a result of crossing-over two types of visible crossovers occur in equal numbers; likewise two types of non-crossovers occur in equal numbers.

The frequency of crossing-over between two genes depends directly, although not wholly, upon the distance apart the genes happen to be upon the chromosome. In general the farther apart two genes lie the higher is the percentage of crossing-over.

The percentage of recombinations does not exceed 50 because:

- (1) Double crossovers, triple crossovers, etc., occur between two genes that are far apart;
- (2) only single and other odd-numbered crossovers between these two genes result in recombination; and
- (3) only two chromatid strands cross over at any one level.

By comparing mutual crossover percentages, linked genes may be graphed on a single straight line. Such a graph is known as a *chromosome map*. The gene loci are separated on the map by dis-

rances corresponding to their crossover percentages. Because of the existence of double and multiple crossovers the map is accurate only for genes relatively close together. Discrepancies between map distances and actual chromosome distances sometimes occur as a result of differentiation of chromosome structure, e.g., it is known that crossing-over is relatively infrequent near the centromere. One crossover also tends to inhibit another nearby, a phenomenon known as *interference*.

A physical basis for crossing-over is found in the behavior of the chromosomes in the tetrad stage of meiosis; where *chiasmata* are formed regularly.

Linkage is an incidental result of the aggregation of genes in chromosomes. Its effect is to limit the variability among individuals. Crossing-over, on the contrary, has the effect of increasing variability. If there were no crossing-over there would be, effectively, only as many series of alleles as chromosomes, since all mutations in the same chromosome would behave as multiple alleles (p. 81). Thus 100 mutations at different loci in a particular chromosome would give only 101 combinations for this chromosome in the absence of crossing-over, but 2^{100} possible combinations with crossing-over.

With respect to the evolutionary significance of linkage and crossing-over probably there are advantages to the species both in the possibility of recombination and in some restraint on the freedom of recombination, and the situation actually found in a species is the result of a process of selection directed toward the most favorable balance.

PROBLEMS

Caution: In working problems in Linkage always keep the symbols for linked genes together, in gametes as well as in zygotes, by enclosing them in parentheses, instead of bringing pairs of alleles together as in independent assortment.

1. In *Drosophila* the percentage of crossing-over between vestigial and lobe (an abnormal eye character) is 5.0 per cent. Vestigial is recessive; lobe is dominant. Make a diagram similar to Fig. 28 showing a mating between a male homozygous for lobe and long-wing, and a normal-eyed vestigial female; follow this by a back-cross of one of the

female offspring to a normal-eyed vestigial male, showing the ratio among the offspring of the back-cross mating.

2. *Drosophila* is exceptional in that crossing-over does not take place in the male, under ordinary conditions. Show the ratio resulting from a mating between a male and a female both obtained in the first cross in Problem 1.

3. Crossing-over in *Drosophila* takes place between lobe and engrailed (an abnormal recessive body character) with a frequency of 10.0 per cent. Determine the ratio from a mating between a female heterozygous for lobed and engrailed and a normal-eyed engrailed male, $(LE)(le) \times (le)(le)$.

4. Show the results of a mating between a male and a female both heterozygous for lobed and engrailed, $(LE)(le) \times (LE)(le)$.

5. As noted above, lobe and vestigial have a cross-over frequency of 5.0 per cent; lobe and engrailed a frequency of 10.0 per cent; while vestigial and engrailed cross over with a frequency of 5.0 per cent. Arrange these three genes on a chromosome map.

Note: In corn, a recessive gene c , known as colorless, eliminates all color from the seed. Seeds with the dominant gene C are colored. A recessive known as shrunken, s , causes the seed to be dented or shrunken; seeds with the allele, S , are full. The genes mentioned cross over with a frequency of 3.0 per cent.

Show the results of the following matings:

6. Colored full, $(CS)(cs) \times$ colorless shrunken, $(cs)(cs)$.

7. Colored full, $(cS)(Cs) \times$ colorless shrunken, $(cs)(cs)$.

8. Colored full, $(CS)(cs) \times$ colored full, $(CS)(cs)$.

9. What is the chance that two genes chosen at random in peas will be linked? What is the chance in man? In both species assume that the genes are equally distributed among the chromosomes.

10. In rabbits the "Dutch" type of white spotting (dd), similar in appearance to the white spotting in guinea pigs, is recessive to self color. Long hair or "Angora" (ll) is recessive to the normal short hair. The genes d and l are linked, with a crossover percentage of about 14 per cent. Show the phenotypic ratios expected from the following crosses:

(a) A hybrid (obtained from a cross between a Dutch, Angora and a homozygous self, short hair) \times a Dutch, Angora.

(b) A hybrid (obtained from a cross between a Dutch, homozygous short hair and a homozygous self, Angora) \times a Dutch, Angora.

HEREDITY IN MAN. I

MENDEL's laws of heredity were discovered in plants, later confirmed in animals, and finally found to apply to man. Mendel's belief in what he called "the unity in the developmental plan of organic life" is therefore proved correct beyond all doubt. A few examples of Mendelian characters in man have been given in previous chapters. In spite of the difficulties involved in studying human heredity, there is available today an extensive and ever growing list of such characters, both normal and abnormal. From the evidence at hand it is clear that every system of the body, and perhaps every organ and structure, is subject to the influence of known genes. Table 9 and Table 10 have been compiled from various sources to illustrate some of the most interesting and best known traits in man, involving all the systems of the body. The tables represent only a fraction of the human traits known to be hereditary.

Most of what we know about human heredity has been learned from a study of family histories or pedigrees, and since such pedigrees are frequently less complete than we would like, uncertainty exists with respect to a number of the characters listed in the tables. Characters which involve the factor principle, i.e., cases resting on a difference in two or more genes, are especially difficult to establish, and very few of these are listed.

The age at which the characters listed make their appearance varies greatly. Some, such as polydactyly, develop long before birth. Others, such as hair and eye color, may not appear until after birth. Again others, such as juvenile amaurotic idiocy, appear in later childhood, while still others, for example, glaucoma, usually develop in advanced age.

Table 9 .

MENDELIAN CHARACTERISTICS IN MAN*

(Arranged in the order in which they are considered in the text)

<i>Dominant</i>	<i>Recessive</i>	<i>Page</i>
SKIN, HAIR, NAILS, TEETH		
Black skin (two genes, incomplete dominance) . . .	"White" skin	74
Piebald (skin and hair spotted with white)	Self color	126
White forelock	Self color	129
Dark hair (several genes)	Light hair	132
Non-red hair	Red hair	132
Dark skin (several genes)	White skin	133
Freckles	No freckles	134
Pigmented skin, hair, eyes	Albino	24
Curly hair (hybrid, wavy)	Straight hair	28
Woolly hair (Negroid type; several genes)	Straight hair	134
Woolly hair (Caucasoid type)	Non-woolly hair	134
Abundant body hair	Little body hair	137
Normal	Hairless (Hypotrichosis)	138
Hairlessness (congenital hypotrichosis)	Normal	139
Early baldness (dominant in male)	Normal	139
Scaly skin (Ichthyosis)	Normal	141
Thickened skin (Tylosis)	Normal	141
Absent teeth (various types)	Normal	142
Defective dentin (opalescent teeth)	Normal	142
Free ear lobes	Adherent ear lobes	143
EYES		
Brown	Blue or grey	147
Hazel or green	Blue or grey	147
Pigmented iris	Albino	146
"Mongolian fold"	No fold	147
Drooping eyelids (Ptosis)	Normal	149
Nearsightedness (Myopia) (curvature of cornea too great)	Normal	149
Normal	Nearsightedness	149
Farsightedness (Hyperopia) (short eyeball)	Normal	150
Astigmatism (cornea not spherical)	Normal	150
Cataract (opaque lens)	Normal	150
Glaucoma (excessive pressure in eyeball)	Normal	151
SKELETON AND MUSCLES		
Short stature (several genes)	Tall stature	152
Dwarfism (Achondroplasia)	Normal	152
Midget (Ateliosis) (two genes?)	Normal	154
Short broad skull (several genes)	Long narrow skull	155
Extra digits (Polydactyly)	Normal	156
Short digits (Brachydactyly)	Normal	157
Split hand ("lobster claw")	Normal	159
Hare lip and cleft palate (also a recessive?)	Normal	160
Rupture, susceptibility to	Normal	161
Absent long palmar muscle	Normal	162

* See Table 10, p. 165, for other characteristics.

The list shows that many characters which are known to be Mendelian are injurious to the possessor. The general rule for organisms is that a change in a character through mutation is much more likely to be injurious than beneficial. This rule probably holds true in man. The explanation of this is not far to seek. According to present theories a gene is at least as complex an entity as a large protein molecule. Mendelian variations apparently result from sudden changes in the structure of the gene. These changes, known as mutations, are induced in some cases at least by forces outside the gene operating in a random manner. A random change in a physiological factor in the development of a complex organism should in theory most often produce an injurious effect, just as a random change in a complex non-living machine is not likely to improve but to reduce the efficiency of the machine. Only rarely should a mutation result in an adaptive change or even in a change that is neutral in effect. Nevertheless, the number of normal human traits proved to be Mendelian is sufficient to indicate strongly that the Mendelian mechanism is the usual one in human beings. The difficulty of establishing typical ratios for many normal human traits is no doubt due to the complexity of such traits rather than to any fundamental peculiarity in their mode of inheritance. There is good reason for thinking that normal characteristics develop under the same system of physiological laws as do abnormal characteristics.

A glance at the list shows us that mutations from the normal may be either dominant or recessive, or that there may be no dominance. In man, recessive mutations probably are more numerous than dominant ones just as in the lower mammals, in spite of the fact that tabulated lists usually suggest the opposite. No doubt most persons carry many recessive genes in the heterozygous condition without knowing it, because the usual mating is between unrelated persons who are not likely to carry the same recessive; the character therefore cannot develop. In pedigrees of dominant traits, the characteristic under investigation shows up in each generation (provided it is due to a single gene) while a recessive frequently skips one or more generations. For this reason it is much easier to find pedigrees showing dominant mutations than recessives.

It is probable that many of the traits listed as dominants would be found to illustrate lack of dominance if we had all the facts. With many of the rare pathological traits there is no evidence that a homozygote has been observed. Defectives do not ordinarily marry defectives. In a few cases where such matings have occurred an extreme defective, probably a homozygote, has been produced.

Let us now consider in some detail the individual traits listed in the tables in connection with sample pedigrees of some of them.

SKIN, HAIR, NAILS, TEETH

The most comprehensive work that has appeared in English on the heredity of the skin, hair, nails, and teeth is a book by an English physician, Cockayne.¹ This valuable work of nearly 400 pages is a mine of information for those who care to delve further in this field. One might gather from reading Cockayne that the skin and its derivatives are peculiarly susceptible to gene mutations, especially injurious ones, since more than 100 separate hereditary defects are listed. But while this may be so, it is also true that skin structures, lying on the outer surface of the body as they do, are more readily noticed and more easily studied than most others. Parenthetically, it may be remarked that the physician is in an unusually fortunate position to observe inherited abnormalities of all kinds. When there arises a generation of physicians, all of whom have had some training in Mendel's laws, we may expect a rapid increase in our knowledge of human heredity.

WHITE SPOTTING (*Piebald*)

In Chapter 5 (p. 74) we discussed the heredity of skin color in crosses between the Negro and white races. The genes there considered affect the development of pigment more or less uniformly over the body. But other genes are known which affect the distribution of pigment in localized areas, resulting in a white and dark spotted (*piebald*) pattern. *Piebalds* have been found in all three major divisions of mankind (Caucasoid, Mongoloid, and Negroid) in various countries of the world since early times. There are several different types of spotting in man, due un-

¹ "Inherited Abnormalities of the Skin and Its Appendages," by E. A. COCKAYNE, 1933, London, Oxford University Press.

doubtedly to distinct mutations. Their counterpart is found in many domesticated mammals in which a variety of types of dark and white spottings occur. In dogs, for example, there is a dominant type of white spotting known as harlequin, in which many small black spots are scattered more or less uniformly over a white ground, as illustrated in the Great Dane and the Dalmatian coach dog. There is also a recessive white spotting in dogs, illustrated in the bull terrier and collie, in which there are a few large spots of white, chiefly on the head and under parts.

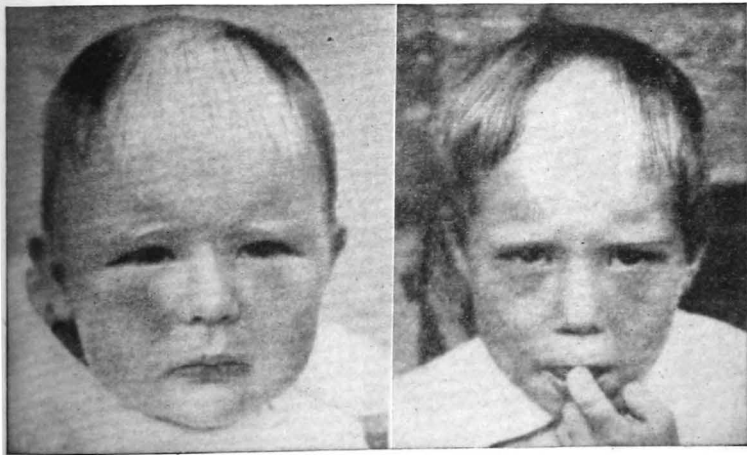


FIG. 33. Children of the fourth generation of white spotting (piebald), inherited as a simple dominant. (Courtesy, SUNDFOR: *J. Heredity*.)

In man the most frequent type of white spotting which regularly involves large areas of the skin is a dominant. Hans Sundfor of Norway has recently published a complete description of a Norwegian family in which this type of white spotting, known as piebald, has been traced through four generations.² His description is accompanied by excellent photographs and drawings. The pattern tends to follow the same general lines in all cases, although the size and area of the white spots are quite variable, as in many other mammals.

There is a "blaze" of white in the frontal region centering at the hair line and frequently extending down the forehead (Fig. 33).

² SUNDFOR, HANS: A pedigree of skin spotting in man, *J. Heredity*, Mar., 1939.

In some individuals the blaze is very small; in others, it extends back to the crown. A large unpigmented area, irregular in outline, occurs on the chest and abdomen, and unpigmented spots are found on the arms, especially on the elbow side (Fig. 34).

The legs show large unpigmented spots centering at the knee and usually extending about half way down the lower leg and the thigh, and sometimes joining the white spot on the abdomen.



FIG. 34. Girl of the fourth generation of white spotting (piebald). Similar unpigmented spots are on the forehead, legs, chest and abdomen of this girl. (COURTESY, SUNDFOR: *J. Heredity.*)

The back, hands, feet, shoulders, back of neck, and hands (excepting the blaze) are usually normally pigmented. The spots are hardly noticeable in fair-skinned persons when the skin is covered, but stand out sharply upon exposure to the sun because of the tanning of the pigmented regions. Unpigmented regions do not tan.

According to Cockayne, who has tabulated the early pedigree studies of families with this type of white spotting, one of

parents of white-spotted children is always white spotted, there being no case on record of two normal parents producing a spotted child. The same thing was reported by Sundfor, who also reports that no marriage between two affected persons has taken place in the family he studied.

The ratio among all the children tabulated by Cockayne is 133 spotted to 118 non-spotted. In the Norwegian pedigree it is 40 spotted to 20 normal, with 5 doubtful. Adding all together, the ratio is 173 spotted to 138 non-spotted (five doubtful). This makes a considerable excess of spotted individuals, since the expected ratio from a back-cross mating is 1 to 1. This deviation from expectancy, however, may be due merely to chance, since by an application of the chi-square test, described in Chapter 3, it can be shown that in accordance with the law of probability one time in 20 we would expect as great a deviation from equality in flipping a coin 311 times. There may of course be some other explanation, such as a failure to record all of the normal individuals.

WHITE FORELOCK

A type of dominant white spotting that is frequently observed and for which several pedigrees have been published, is known as white forelock, since it is said ordinarily to be limited to a white spot on the mid-line at the junction of the scalp and forehead (Fig. 35).

When the hair is combed back, as is the mother's in the picture, there is a false impression of a stripe. In position and appearance the spot is similar to the piebald spotting previously described, but it is usually smaller. Although the relation of white forelock to piebald is somewhat uncertain, the two have always been considered as separate mutations. In a pedigree recently published by Lyle Fitch³ of the University of Nebraska (Fig. 36) the inheritance of white forelock is shown through five generations, the last two of which are represented in the photograph (Fig. 35).

In this family, according to Fitch, the white forelock is often accompanied by a few white spots in the skin on various parts of the body. The boy without the white forelock, in the photo-

³ FITCH, LYLE: Inheritance of a white forelock, *J. Heredity*, Dec., 1937.

graph, has a white spot on one leg; he is the only member of the family known to be so marked. It seems not unlikely that white spots might be found in the skin of most individuals considered as having merely a white forelock, if they were looked for carefully,



FIG. 35. Mother and sons representing the fourth and fifth generations, respectively, of white forelock. The older boy does not have a white forelock, but there is a white spot on one leg. (Courtesy, FITCH: *J. Heredity*.)

and that this condition differs from piebald spotting only in degree. Whether the gene for white forelock is different from the gene for piebald spotting or is the same gene behaving differently in different families must remain uncertain until further studies have been made. In mode of inheritance the two are identical.

HAIR COLOR

The study of hair color in man is complicated by the fact that the hair contains two pigments: (1) a granular melanin, which varies in intensity from black through various shades of sepia to "ash blond," or from dark brown to light golden blond; and (2) a diffuse pigment, which varies from dark red to yellow. Hair color is, therefore, really a resultant of two characteristics: intensity of pigment and quality of pigment. The situation is similar in other mammals. Although the chemistry of these two pigments is imperfectly known, it is certain that there are genes which affect

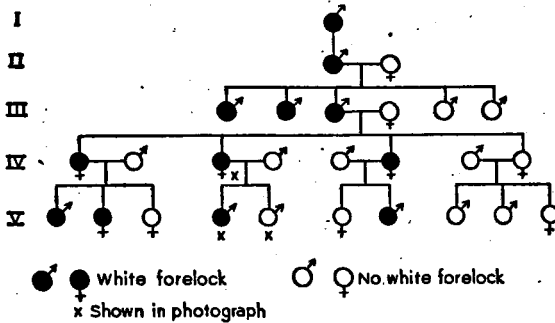


FIG. 36. Pedigree showing inheritance of white forelock through five generations, indicating simple dominance. (Courtesy, FITCH: *J. Heredity*.)

either one pigment or the other alone, and other genes which affect both pigments; some genes primarily affect intensity of pigment, others primarily affect quality of pigment.

In the case of guinea pigs, in which the heredity of hair color has been analyzed more thoroughly perhaps than in any other mammal, we have seen (Chapter 5) something of the complexity of the character. The effects of some of the principal genes involved have been studied exhaustively by Wright.⁴ Many years of laborious experimentation involving many generations of animals, under practically ideal conditions, were necessary for the solution of the problem in guinea pigs. Therefore it is not surprising that in man there are still some uncertainties. Here the situation is probably as complex as in guinea pigs; but in man investigation is

⁴ See pp. 75-85.

limited to chance matings, with only a few generations available for study. Discoveries of biological laws in the lower animals offer valuable clues to the conditions in man, but since details of heredity usually differ from species to species, the rules for each must be worked out separately.

In man, with respect to intensity, dark hair dominates more or less over light hair; and with respect to quality, black or brown dominates over red. In marriages between persons with intense black hair (Eskimos) and light blondes (some Scandinavians), the children, according to the noted anthropologist and explorer Stefansson⁵ and other observers, are essentially black-haired. The results are not so clear in marriages between blondes and brunettes among whites; here the children are often intermediate, with varying shades of hair color. Such results, however, do not necessarily show a lack of dominance, because in a population made up of both blondes and brunettes, the brunette may not be pure-bred. If there is a series of alternative genes (multiple alleles) affecting the intensity of pigmentation, as in the guinea pig, a brunette might be heterozygous with respect to any one of them. The fact that there are so many different shades of sepia and brown hair in man is evidence that there are several genes affecting melanin pigment. Dominance is probably incomplete among some of them. In marriages between two light blondes, on the other hand, it can be safely predicted that the children will be blondes rather than brunettes.

Red hair seems clearly to be due to a single recessive gene. With few reported exceptions, in marriages between red-haired persons the children are all red-haired—as they should be if red is recessive. Moreover, red-haired children are frequently born to parents who do not have red hair, and the ratio of non-red to red is what would be expected if red is a single recessive, namely 3:1. Cockayne quotes studies of a group of families in which only one parent had red hair, and at least one red-haired child was born; the ratio was 46 red to 48 non-red, which is almost a perfect 1:1 ratio, as expected from a back-cross mating between a hybrid and a recessive.

If red hair in man is due to a single recessive, as seems un-

⁵ "The Friendly Arctic," by VILHJALMUR STEFANSSON, 1924, The Macmillan Co.

questionable, it agrees with what is known in guinea pigs, cattle, horses, hogs, and other mammals.

SKIN COLOR

There is considerable correlation with respect to the color of the skin, hair, and eyes in man. Dark-skinned individuals, as well as dark-skinned races, tend to have dark hair and dark eyes; while light-skinned individuals, as well as races, tend to have light hair and light eyes. The correlation between skin color and hair color is not surprising, since the hair is an outgrowth of the layer of the skin which contains the pigment, namely, the epidermis. The iris of the eye which contains the pigment giving the characteristic color to the eye is indirectly related to the epidermis in that they are both derived from the outer embryonic layer known as the ectoderm.

The three major divisions of mankind (Negroids, Mongoloids, and Caucasoids) are distinguished to a certain extent by skin color though by itself this is of little value as a racial distinction because of the great variability in color in all three groups and the overlapping of one group by another. The lighter shades of color among whites of European origin have probably arisen through successive mutations from darker types.

In cases where there is a close correlation in skin color, hair color, and eye color, it is probable that the same genes are at work in these characters. On the other hand, when there is no correlation there must be genes that affect pigment production in skin, hair, and eyes independently. The existence of such genes explains the frequent occurrence of black hair, blue eyes, and fair skin in the same individual in some Irish families; the combination of black hair and fair skin in some Jews; and yellow hair, light skin, and brown eyes among various other Caucasoids.

Many interesting combinations can be observed among mulattoes. Recently the writer noted two young mulatto students, both with skin color of about the same shade of yellow: one had very dark, almost black hair and light hazel eyes; the other had light brown hair and dark brown eyes.

Red-haired persons usually have very little pigment in the skin, and what pigment there is has a tendency to collect in patches

(freckles). Freckles, however, are not limited to red-haired persons. Cockayne reviews a number of studies on the heredity of freckles and concludes that freckles are the result of a single dominant gene.

The true albino in which pigment is almost entirely lacking in skin, hair, and eyes has been considered in Chapter 2. Albinism is a single recessive mutation found in all races. The hereditary basis of the differences in skin color between Negroes and whites was discussed in Chapter 5.

WOOLLY HAIR

The inheritance of the usual types of straight, wavy, and curly hair of Caucasoids has already been discussed in Chapter 2. The typical hair of Negroids, variously known as woolly, kinky, or frizzy, is quite different, both genetically and structurally, from curly hair. Woolly hair is said to grow in the form of a spiral before it leaves the follicle. In cross-section the individual hairs are on the average more flattened than in straight hair, although there is considerable variability in the hairs of the same head, and even in different regions of the same hair.⁶

In crosses between whites and full-blooded American Negroes originating in West Africa, the woolly hair seems to depend upon several genes. In mixed marriages producing children of various percentages of white and Negro blood there is considerable variability in hair form, with an occasional individual having Caucasoid type hair. More extensive studies of pedigrees involving Negro-white crosses are necessary before the method of inheritance can be determined.

Woolly hair in white families has been reported recently in three isolated instances, following several earlier reports. The first of the three is by Professor Otto L. Mohr, The University, Oslo, Norway.⁷ He has written a complete description of the characteristic, illustrated by excellent photographs—one of which is reproduced (Fig. 37)—and a pedigree covering five generations.

⁶ KNEBERG, MADELINE: Improved technique for hair examination, *Am. J. Physical Anthropology*, April-June, 1935.

⁷ MOHR, OTTO L.: Woolly hair a dominant mutant character in man, *J. Heredity*, Sept., 1932.

From his personal investigations he concludes that the hair in its main features parallels the woolly-haired races, but that it must have occurred in a European stock as the result of an independent dominant mutation.

Mohr believes that any intermixture of Negro blood in this family may be safely excluded, since the family is of Norwegian farmer descent known for seven generations showing the clear "Nordic" type. He says,

Even nowadays, with the highly developed means of communication, a negro is practically never seen in Norway. And the occurrence of a negro \times white cross or a hybrid \times white crossing of this order more than seven generations back is for social and other reasons so improbable that it may safely be left out of account.

He thinks the origin of the character from a Negro cross is ruled out also by the fact that in Negroes woolly hair is not due to a single dominant gene.

Mohr describes the hair as being very strikingly curled or frizzled, similar to Negro hair. The curling is of a spiral type. As in the Negroids, the hair never reaches a great length—in the family under discussion not more than about 14 cm. Although it continues to grow, it normally breaks off before this length is reached. In cross section the hair of the woolly-haired individuals is, he writes, "characterized by a flattened shape, giving the cross-sections a flattened oval, or in some cases—presumably near a twist—a kidney-shaped form." The hair is usually very light colored in childhood, and gradually turns darker with age; in some cases, however, a woolly-haired individual had dark hair.

The ratio of woolly hair to normal hair among the children from all 20 matings of woolly hair \times normal hair as shown in the pedigree is 38 woolly-haired to 43 normal-haired; in 3 the hair



FIG. 37. Woolly hair in a Caucasian woman, the result of a dominant mutation. (Courtesy, MOHR: *J. Heredity*.)

type is unknown. This is a very good 1:1 ratio, as expected from a back-cross of hybrid to recessive.

The second recent case of woolly hair in Caucasoids is described by Dr. C. Ph. Schokking of the Royal University of Leiden, Holland.⁸ The author comes to exactly the same conclusion regarding its heredity as Mohr does. In a village near Leiden, Schokking found a number of woolly-haired persons belonging to the same Dutch "peasant" family. The pedigree shows the trait in five generations without the skipping of a generation. There is a total of 13 woolly-haired to 17 normal-haired individuals from marriages of woolly \times normal. The published photographs show most of the individuals, both woolly-haired and normal, with quite dark hair; otherwise, the hair appears much like that in the Norwegian family. Schokking found no correlation whatever between form and color of hair. The description of the structure of the woolly hair, including its brittleness and flattening, agrees perfectly with Mohr's description. The author states, "In no one of the members of the family was the slightest trace of any other character of a colored race to be found."

Schokking summarizes the data from the families reported by himself and Mohr, together with that from three earlier workers. The resulting combined ratio is 138 woolly: 125 normal, which is a very good 1:1 ratio.

The last reported case of woolly hair, which agrees entirely with those already cited, was discovered in the southern United States by Edgar Anderson, Washington University, St. Louis, Missouri.⁹ The published pedigree shows the characteristic appearing in five generations, in a ratio of 1:1. The family came from "Old American stock." The author states,

To one accustomed to the woolly hair of negroes and many mulattoes, the peculiar hair exhibited by these pedigrees seems something quite different. It has an open, unmatted appearance and gives the impression of a peculiar kind of hair rather than of negro hair. As a matter of fact, I first saw the young woman who supplied the information from a passing automobile, but even at that distance recognized the condition as being similar, if not identical, with that illustrated in *The Journal of Heredity*.

⁸ SCHOKKING, C. PH.: Another woolly-hair mutation in man, *J. Heredity*, Sept., 1934.

⁹ ANDERSON, EDGAR: An American pedigree for woolly hair, *J. Heredity*, Nov., 1936.

This raises an interesting question as to whether the woolly hair in the three families mentioned arose from three independent mutations. Mohr states that quite a few members of the Norwegian family migrated to the United States where their descendants now live. Could the American family described by Anderson trace back to these? Norway and Holland are near enough to one another that a common origin of the mutation seems not impossible.

HAIR ON BODY, FACE, AND LIMBS

Man is peculiar among all mammals in the distribution of hair over the body, having normally a heavy growth of hair on the scalp, axillae, pubes, eyebrows, and—in the male of some races—on the face, accompanied by a very scanty growth on other parts of the body. Some other mammals, however, especially some of the Primates, show tendencies in the same direction. The growth of hair in man is more variable than one might realize in view of the habit of covering the body with clothing, and of shaving and cutting the hair.

The growth of hair on the body and face in man varies among the races as well as among individuals within a race, and also between the sexes. The hairiest people are the Ainus (probably of primitive Caucasoid stock) who inhabit the northern part of Japan. Whites come next, then Negroes, with the Mongoloids, including Eskimos and American Indians, least hairy of all. In the Mongoloids, especially the American Indians and the Eskimos, the lack of body hair is pronounced; even the beard is very scanty. These racial differences are of course hereditary, but just how many genes are involved is not known.

In white people, relative hairlessness of the body and limbs seems to be recessive, while excessive hairiness is dominant, although pedigree studies are inadequate. This type of relative hairlessness found normally in man is quite different from those which occur as mutations in the domesticated mammals. In the latter the scalp as well as other parts of the body are devoid of hair, and therefore have more resemblance to the congenital types of baldness in man, a topic to be discussed later.

In man, the male has more body hair than the female, among

genetically similar individuals. This is probably due to the influence of the male sex hormone which is known to be the direct cause of growth of the beard in the male. The occurrence of superfluous hair on the face in women was studied by Trotter and Danforth, who came to the conclusion from the high correlation (about 0.8) between mothers and their daughters that it probably was due to a dominant gene, although this could not be proved by the usual pedigree method, since the gene effect in the male is obscured by the beard.¹⁰ Among about 1700 women examined, slightly over 27 per cent showed superfluous facial hair. The percentage was the same for colored women as for white women, and the same for normal women as for those in mental hospitals. The authors found no evidence of selection against facial hair in women.

HAIRLESSNESS (*Hypotrichosis*)

There are several distinct types of hairlessness in man. Its study is complicated by the fact that infections are a factor in some types. An extensive review of reported cases in which heredity plays a major role is given by Cockayne. In one type of extreme hairlessness, inherited as a recessive, the scalp is either entirely bald or almost entirely so from birth, or soon after birth. There is a strong tendency also for hair to be missing or scanty on other parts of the body. Eyebrows and lashes, for example, are commonly missing or very thin, while in some families the nails, and rarely the teeth, are imperfectly developed. The variations with respect to the expression of the trait makes it likely that several independent mutations have occurred.

This type of hairlessness agrees in general with many cases of recessive hairlessness found in domesticated mammals. Recessive hairlessness, more or less complete, has been found in horses, cattle, sheep, goats, hogs, rabbits, rats, mice, and cats.¹¹ The genetic cause of the normal hairlessness of certain wild animals (walrus, whale, hippopotamus, rhinoceros, and elephant) is not known, but the condition is probably the result of mutations from

¹⁰ TROTTER, M., and DANFORTH, C. H.: The incidence and heredity of facial hypertrichosis in white women, *Am. J. Physical Anthropology*, 5: 391-397, 1922.

¹¹ KISLOVSKY, D.: Inherited hairlessness in the goat, (with literature there cited). *J. Heredity*, Aug., 1937; LETARD, ETIENNE: Hairless Siamese cats, *J. Heredity*, May, 1938.

hairy ancestors. In recent prehistoric times hairy elephants and rhinos lived in Europe, and were hunted by primitive man—as we know from the discovery of their actual remains and drawings of them made by cave man. The lack of hair in the wild species mentioned is, in some cases at least, an adaptation to aquatic or to tropic habitats.

Dominant extreme hairlessness has been reported in many different human families, including a tribe of Australian blacks. As a rule the body is otherwise normal. Dominant hairlessness is found in dogs, of which the Chihuahuan hairless breed of Mexico is the best known example. Also, a dominant type of hairlessness has been found in mice.

BALDNESS

There are numerous types of baldness, some due to infections, others to physical or chemical agents, and still others to hereditary factors. The problem of the cause of the usual variety of partial early baldness in man has not been solved completely. A striking feature of this condition is its much greater frequency and more extreme manifestation among males than females. Most investigators consider it due to a gene which behaves as a dominant in the male and as a recessive in the female. This type of heredity is known as sex-influenced (not to be confused with sex-linked) heredity. The different effect produced by the gene in the two sexes probably depends upon the hormone differences, since the secretions of the ductless glands are known to affect hair development. In line with this is the reported fact that eunuchs do not become bald.

Cockayne believes that many cases of premature baldness are due to seborrhea (dandruff), to which he thinks there is an inherited susceptibility in some individuals, while in others there is a high degree of immunity: Although he has no complete pedigrees showing the inheritance of susceptibility to dandruff, he thinks it is probably a simple dominant. In his view, the gene conditions the development of large and active sebaceous glands, which in turn favor the development of dandruff.

According to Cockayne, it is now accepted that dandruff is due to infection of the skin with a yeast-like fungus (Pityro-

sporum), which is found on most human scalps. That the organism produces the disease is denied, however, by some dermatologists, who maintain that it is merely a saprophyte, that is, that it lives upon dead tissue. Cockayne gives his theory in the following words:

The sebaceous glands normally manufacture a cholesterol fat from the fat circulating in the blood, and this is inimical to the growth of fungi and bacteria, but they can also take the circulating fat from the blood and secrete it unchanged, and these fats derived from the food favor the growth of the pityrosporon. Excess of fats and fat-forming foods such as carbohydrates, coupled with lack of exercise, will lead to some secretion of unaltered fat even when the glands are normal. Thus any one by faulty living can bring about the conditions which conduce to seborrhoea.

If Cockayne's view is correct, there should be some correlation between a dry skin and freedom from baldness, and between an oily skin and baldness.

The type of baldness we have just considered has a definite pattern with which everyone is familiar: the top of the head is first attacked; this is followed by a gradual spreading downward of the denuded area, leaving a fringe of hair on the sides and back of the head. This particular pattern depends perhaps upon differences in the blood supply of the different regions of the scalp, the tightness of the skin, and the amount of subcutaneous fat.

SCALY SKIN (*Ichthyosis*); THICKENED SKIN (*Tylosis*)

The skin in man is a complex organ which develops from two distinct layers of cells, the inner layer or dermis and the outer layer or epidermis. It contains a rich supply of blood vessels and nerve endings, and is closely set with two types of glands (sweat glands and sebaceous glands) and, except in a few regions, with numerous hair follicles. Unlike most organs, the skin does not cease growing in the adult, but continues to produce new cells in the deeper portion of the epidermis while the cells near the surface become flattened, hardened, and dried. An imperceptible shedding of these outer dead cells goes on more or less constantly.

The foregoing facts are mentioned as a necessary background to the appreciation of the many hereditary abnormalities in the structure of the skin. The large number of such abnormalities dependent upon separate genes proves that normal development

of the skin depends upon the cooperation of many genes. This is what we should expect in an organ as complex as the skin.

Most of the defects of development of the epidermal layer are grouped under the heads of ichthyosis, tylosis, and related conditions. Cockayne has assembled the literature, classified the cases, and written an account of them covering sixty pages. Two of the most common types are considered below.

Ichthyosis, in its most common form (*ichthyosis vulgaris*), is described by Cockayne as follows:

The skin is dry and covered with small scales, which are continually being shed in the form of a fine branny desquamation. The face is usually a little glazed in appearance, but otherwise normal, and the skin of the flexures, perinaeum, and genital region is little altered in texture. On the knees and elbows the cornification reaches its maximum, and on the extensor surface of the limbs it is greater than on the flexor surface. The scalp is scaly and the hair thin and dry; the eyebrows are scanty and their outer third may be almost absent, and on the trunk and limbs the hair is sparse and atrophic. The nails are dry and brittle. The palms and soles are dry and smooth with the finer lines obliterated and the deeper ones accentuated. The secretion of sweat and sebum is deficient on the most ichthyotic parts, but on the palms and soles and in the flexures sweating may be normal.

The condition first becomes recognizable in the early months of infancy and gets gradually more noticeable, until at about 10 years of age it is fully developed and thenceforward remains unchanged through life. The physique is fairly good and the general health is unimpaired, but the ichthyotic skin is very liable to mild inflammation.

Histologically the most conspicuous abnormality is a thickening of the horny layer of the epidermis, the cells of which are unduly adherent . . .

Ichthyosis vulgaris is one of the most frequently inherited defects of the skin, but Cockayne finds that few pedigrees have been published. Some of the pedigrees indicate a single dominant; others show the skipping of a generation, and hence require some other explanation. In one group of pedigrees the inheritance is that of a sex-linked recessive (Chapter 11).

Tylosis is an abnormal thickening of the skin, particularly of the epidermis. In one of the common types, restricted to the palms and soles, the epidermis becomes thick, yellowish, and horny. The dead skin is commonly shed in large flakes or scales. There is usually an enlargement of the sweat glands on the affected regions, with excessive sweating. The defect appears in children at varying ages. The ratio of normal to affected individuals in families

with this type of tylosis indicates that it results from a single dominant gene, affecting males and females alike.

Many of the less usual forms of hereditary abnormalities of development of skin structure are discussed by Cockayne.

ABSENT TEETH

Embryologically the teeth have a common origin with the skin, and a number of genes are known which simultaneously modify the development of both. Among genes which seem to affect only the teeth are those for the following: absence of many teeth, including canines (sex-linked recessive, see Chapter 11); absence of upper incisors and molars (dominant); absence of the two central incisors above and below (mode of inheritance uncertain); and absent or reduced upper lateral incisors (dominant—one of the most common abnormalities of the teeth). For additional details the reader is referred to Cockayne, Chapter 8.

DEFECTIVE DENTIN

Recently, Hodge and Finn of the School of Medicine and Dentistry, University of Rochester, New York, have compiled pedigrees of three unrelated families showing a distinct type of gross defect of the teeth known as "opalescent dentin" inherited as a dominant.¹² In cooperation with numerous colleagues they made elaborate clinical studies of the affected persons, together with microscopical, chemical, and physical studies of the teeth. Their report is commendable for its clarity and completeness.

The authors state that the defect is characterized clinically by extreme translucency, discoloration, friability, and wearing away of the teeth. The dentin is extremely soft; the enamel has a grey or bluish color, although appearing normal microscopically. There is little tooth decay, although mass destruction of the crowns and their early excessive wear often simulate rampant caries. The crowns are originally of average size, but the roots are short. Pulp chambers are absent, and pulp canals are completely or partially obliterated.

The clinical studies of affected persons were negative so far

¹² HODGE, HAROLD C., and FINN, SIDNEY B.: Hereditary Opalescent Dentin, *J. Heredity*, Sept., 1938.

as showing any peculiarity of physiological reactions not present in normal members of the families.

One of the families was of recent Italian descent, one was of German-Irish descent, and the third was of American stock living as missionaries in China and India. The pedigree of the American family is shown in Fig. 38; it is quite typical of a single dominant. The other two pedigrees are consistent with the one given. Evi-

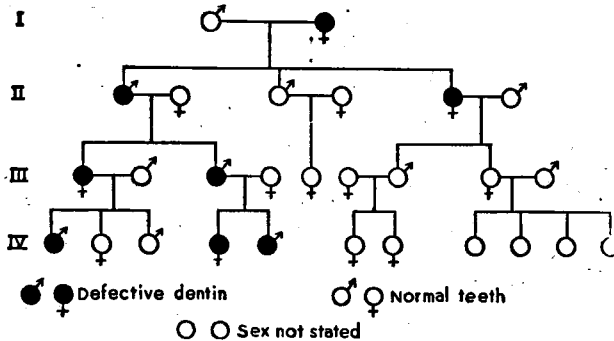


FIG. 38. Pedigree showing the inheritance of defective dentin (opalescent teeth). Defective dentin is dominant. (Courtesy. HODGE and FINN, *J. Heredity*.)

dently the trait is not extremely rare as judged by the numerous reports cited by Hodge and Finn.

EAR LOBES

Whether the ear lobes shall hang free or grow attached seems to depend upon a single gene. The form of the ear lobe (Fig. 39) is a good example of a difference having no adaptive value. It is purely a matter of taste as to which type of ear lobe one may prefer.

A number of pedigrees have been published indicating that free ear lobes are dominant and adherent lobes are recessive. One of the most recent of these (Fig. 40) is reported by Powell and Whitney¹³ of the University of Nebraska.

Although in some families, such as the one reported by Powell

¹³ POWELL, EUGENE F., and WHITNEY, DAVID D.: Ear lobe inheritance, *J. Heredity*, June, 1937.

and Whitney, there seems to be a sharp segregation of free lobes and attached lobes, this apparently is not true in all families. Dr. A. S. Wiener¹⁴ of Brooklyn, New York, reports studies of 124



FIG. 39. Two distinct types of ear lobes in man. (Left) Free lobes; (right) adherent lobes. Free lobes are in general dominant over adherent lobes.

families and 607 children in which all gradations between attached and free ear lobes occur. He states that rarely in the same individual one ear lobe may be free and the other attached. He has classified the individuals studied into four arbitrary groups: completely free ear lobes, completely attached ear lobes, and two intermediate types. The data are presented in tabular form without individual pedigrees.

Wiener concludes that although there is a definite correlation between the types of ear lobes in the parents and children, more

than a single gene probably is involved. Further studies of this trait might yield interesting results.

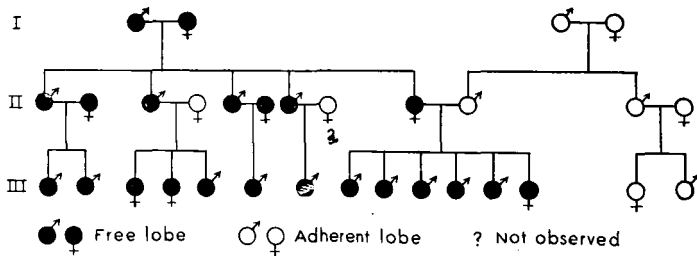


FIG. 40. Pedigree showing inheritance of free and adherent ear lobes. Free lobes probably dominant. (Courtesy, POWELL and WHITNEY, *J. Heredity*.)

than a single gene probably is involved. Further studies of this trait might yield interesting results.

EYES

The most comprehensive work ever assembled on the heredity of eye characters in man is a book by Dr. P. J. Waardenburg, eye

¹⁴ WIENER, A. S.: Complications in ear genetics, *J. Heredity*, Dec., 1937.

specialist of Arnheim, Holland, who for many years has been a contributor in this field.¹⁵ In his excellent volume of more than 600 pages, including 197 figures and eight colored plates, there are descriptions of well over 100 hereditary eye variations (largely defects) in man. The literature list is unusually extensive. The book should be consulted by anyone who has a special problem in this field. Unfortunately it has not been translated into English from the German in which it is written.

The eye is one of the most complex organs in the body. The eyeball itself is made up of several complex layers, while inside the eyeball are the iris, lens, vitreous body, and muscles for changing the curvature of the lens. Attached to the outside of the eyeball are six muscles which move the eye in all directions. Finally, there are the lids, with the associated lachrymal (tear) glands and Meibomian (oil) glands. In order that the eye may develop into a perfect optical instrument there must be co-ordinated development of all of these parts. No wonder that so few persons have really perfect eyes, and that gross developmental defects are not uncommon. The list of eye defects is an imposing one, and it is still growing.

There are a few well-known hereditary eye differences which are recognized as racial differences, and are not to be regarded as abnormalities. These include color of the iris and form of the upper eyelid.

EYE COLOR

Ordinary eye colors are due to the presence of pigment in the cells of the iris. According to Waardenburg, in all shades of eyes from dark brown to blue there is a double layer of cells containing granules of a dark brown pigment covering the back of the iris. There are in addition, in all eye colors except blue and grey, branched pigment cells containing a lighter colored yellow or brown pigment scattered in the body of the iris. The differences in eye color depend largely upon the number, the color, and the arrangement of these branched cells. If the branched pigment cells are absent or very few in number, the dark pigment on the back

¹⁵ "Das Menschliche Auge und seine Erbanlagen," by P. J. WAARDENBURG, 1932, The Hague, Martinus Nijhoff.

of the iris shines through the body of the iris making it appear blue or grey. Increasing numbers of branched pigment cells account for green, hazel, and brown eyes. In complete albinism, pigment is practically absent from both the back and front layers of the iris, and light reflected from the blood in the vessels of the iris gives it a red or pink color.

As we have seen (Chapter 2) albinism is due to a single recessive mutation. If the gene for albinism is present in a double dose, the eye and the skin and hair as well are practically free of pigment, regardless of what other genes are present. This is shown by the reported fact that the children of an albino Negro mated to a blond white are typical mulatto children; the Negro albino has all the genes for pigmentation except the dominant alternative of albino, and this is supplied by the blond white.

Anthropologists have called attention to the fact that the great majority of mankind have dark brown eyes. This includes all the Negroid division except rare mutants, nearly all the Mongoloids except a tribe of Eskimos in Northern Canada and a few Indians in Central America, and a majority of Caucasoids (including the East Indians). Among the Caucasoids, blue eyes are practically limited to some of the Berbers (a mixed group living in Northern Africa) and to the Nordics and East Baltic peoples of Northern Europe, and to their descendants.

Owing to the relatively small numbers of light-complexioned people as well as to their limited geographic range, it is supposed that the original eye color in man was dark brown, and that the lighter colors are relatively recent mutations. This view is supported by the fact that most other mammals in a state of nature have dark eyes.

Several investigators attempted to solve the problem of the inheritance of eye color in man before Mendel's work became known in 1900, and many have worked on it since that time. Although the problem still offers some puzzles, it is now generally recognized that there must be more than one pair of genes involved, for with only one pair of genes, even assuming lack of dominance, there should be only three eye colors instead of the six or more principal types that actually exist.

Waardenburg, after reviewing the work of other investigators

in connection with his own studies, comes to the following definite conclusions regarding the inheritance of eye color in man:

1. Two blue or grey-eyed¹⁶ parents have only blue or grey-eyed children; blue or grey is recessive, and brown is dominant.

2. There are independent genes which are responsible for the various other colors mentioned. Some of these genes affect the amount of pigment; some, its localization (in the form of scattered spots, rings around the pupil, etc.); and others, its quality (light yellow or dark brown).

3. In general, the darker eyes are dominant over the lighter, as green over blue.

4. Much work remains to be done before a complete explanation of the genetics of eye color in man can be given.

Various investigators have reported exceptions to Waardenburg's rule 1 above. In a recent study Hughes¹⁷ found in one family in which no brown pigment could be observed in either of the parent's eyes that two daughters had developed such pigment: one had a trace of brown; the other had eyes showing "one-fourth" brown. In five other such families there were no brown eyes among the 17 children. He concludes from his studies of 107 families of North European ancestry with a total of 212 children that a multiple factor type of inheritance of brown versus non-brown eye color is indicated. This is undoubtedly true; yet the difference between brown eyes and non-brown in a given family may well depend upon a single gene difference.

EYELIDS

Anyone who has observed Mongolians (Chinese, Japanese, etc.) must have noted a peculiarity in the appearance of the eye—the "slant-eye," "slit-eye," etc., of various writers. As a matter of fact, the eyeball itself is not different from that in other races, nor is its position in the skull essentially different. The distinctive appearance is due primarily to an extra fold of skin (the "*Mon-*

¹⁶ Grey eyes and blue eyes have no brown or yellow color visible. Grey eyes or blue eyes having yellow or brown spots are classified as green.

¹⁷ "The Inheritance of Eye Color in Man—Brown and Nonbrown," by BYRON O. HUGHES, Contributions from the Laboratory of Vertebrate Biology, University of Michigan, Ann Arbor, Michigan, No. 27, April, 1944.

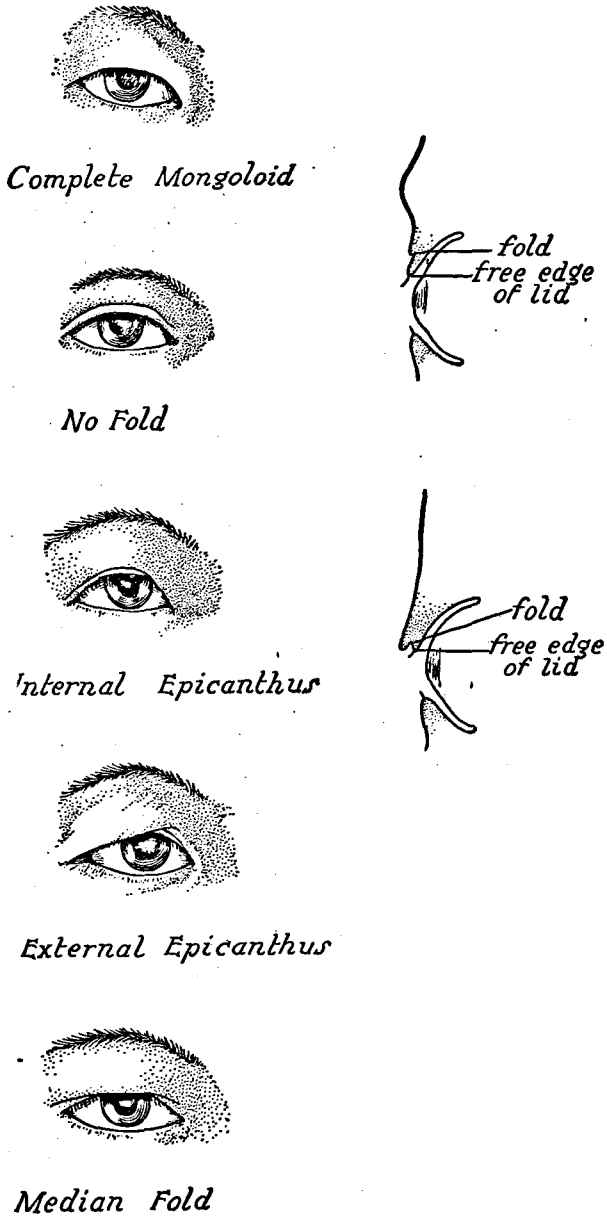


FIG. 41. Human eye folds. (Courtesy, ERNEST HOOTON: "Up From the Ape," New York, The Macmillan Co., 1938.)

golian fold'), which extends from the upper lid down and over the inner corner of the eye toward the nose, making a new angle with the lower lid (Fig. 41). If this fold is lifted up the shape and position of the eye and lids are seen to be essentially the same as in other races. The Mongolian fold is said to occur in a small percentage of persons of European descent, owing probably to early racial mixing. It is found in the great majority of Mongolians, though not in all. There is no doubt that it is an inherited trait, probably differing from "straight" eyes by a single dominant gene.

A defect of the upper lid that is not to be confused with the Mongolian fold is known as *ptosis*, or drooping eyelids. The muscles which raise the upper lids are unable to function, so that only a narrow slit is possible between the two lids. In a pedigree of six generations worked out in this country by Briggs,¹⁸ the defect was shown to be a single dominant. Several types of *ptosis* are described by Waardenburg, in which other defects of the eyes accompany the *ptosis*. In some of the types the whole complex is inherited as a recessive.

NEARSIGHTEDNESS (*Myopia*)

In nearsighted eyes the rays of light coming from a distance are brought to a focus in front of the retina rather than on the retina as they should be. This causes the image of distant objects to be blurred. Without glasses a nearsighted person cannot see clearly unless the object is very near. Anatomically, the most common cause of nearsightedness is an excessively long eyeball. A second less common cause appears to be a too great curvature of the cornea.

Nearsightedness is a very prevalent eye defect and numerous investigators, chiefly European, have collected pedigrees showing that it is hereditary. Although over-use of the eyes without glasses may be a factor in aggravating the condition, authorities are agreed that there must also be a hereditary basis. In the majority of families *myopia* is inherited as a single recessive; long eyeball also is inherited as a recessive. *Myopia* due to excessive curvature of the cornea, which is less common, seems to be a dominant.

¹⁸ BRIGGS, H. H.: Hereditary congenital *ptosis* with report of 64 cases conforming to the Mendelian rule of dominance, *Am. J. Ophthalmology*, Vol. 2, 1919.

FARSIGHTEDNESS (*Hyperopia*)

This defect is the result of an eyeball so short that with the eye muscles relaxed, the parallel rays from distant objects are brought to a focus behind the retina. The retinal image is therefore blurred. To correct for the abnormality the farsighted eye must constantly exert muscular effort—the nearer the object the greater the effort necessary. Consequently there is always more or less eyestrain unless glasses are worn. As an aggravating condition one eye is frequently more seriously affected than its mate. In most cases hyperopia seems to be inherited as a dominant.

ASTIGMATISM

In this defect there is a blurring of vision caused usually by a greater curvature of the cornea in one axis than in others. Special lenses are necessary to correct for this. Astigmatism is often (though not necessarily) associated with farsightedness, and may be more pronounced in one eye than in the other. In most of the pedigrees studied astigmatism seems to be inherited as a dominant.

CATARACT

One of the commonest types of eye defect which leads to blindness is cataract, or opaque lens. Not all cataracts are hereditary, for cataract may result from diabetes, poisons, injuries, high temperatures, and malnutrition. A few years ago a drug, dinitrophenol, was widely used as a fat reducer. For this purpose it was very effective since it is a powerful stimulant of the rate of metabolism, causing the user rapidly to burn up his own fat. Following the use of the drug, however, numerous persons became blind from cataract. Steel workers who are exposed to the high temperatures of molten metals frequently develop cataract. Nevertheless, there are many cases which can be explained only on the hereditary basis.

Different structural types of hereditary cataract are known. The age at which the defect develops varies greatly: in some families it is present at birth, in others it comes on in childhood, at puberty, in middle age, or old age. These facts suggest the presence

of independent mutations. Cataract—or the strong tendency to develop it at a certain age—is inherited as a dominant character.

GLAUCOMA

Glaucoma is an extremely serious eye disease. Eye specialists tell us that in the United States it produces more blindness than any other single cause. Most of the cases develop in persons past 40 years of age. The condition is one in which there is faulty circulation of fluid inside the eyeball resulting in a great increase in the internal pressure. This destroys the optic nerve, thus causing blindness. Glaucoma is a striking example of an undoubted hereditary disease which can be controlled by surgery if it is taken in time. The operation consists in opening up a channel for the circulation of fluid inside the eyeball.

As in cataract, the age at which hereditary glaucoma develops varies considerably. In some families it may develop as early as at 15 to 20 years of age. The character is inherited as a dominant.

SKELETON AND MUSCLES

The skeletal and muscular systems may conveniently be considered together since both are closely related in development and are known to be affected by some of the same genes. Among these, the genes affecting body build and stature are of special interest.

STATURE

Modern man shows great variation in stature, both with respect to individual differences and with respect to racial differences. Fundamentally, racial differences and individual differences depend upon the same causes, since a race is merely a group of related individuals showing certain traits in common, each trait varying about its own mean. Many genes are probably concerned in stature. The environment (especially food) likewise plays an important rôle. The smallest races living today are the pygmies: the Negritos of Africa and Asia. The average stature of these people is between four and five feet. Among the shorter races not classed as pygmies are the Lapps and the Japanese. At the opposite extreme are the Nordics and certain African tribes.

The rate of growth, and perhaps the period over which growth

continues, are affected by the glands of internal secretion, especially the pituitary, the thyroids, and the gonads. Genes may act primarily upon these glands, which in turn modify growth. One type of very tall individual with legs abnormally long in proportion to the trunk is apparently the result of under development of the gonads. Eunuchs are said to have a similar type of body build. The common type of giant—usually seen in the circus—with excessively large hands and feet and a long jaw is the result of oversecretion of the pituitary gland. Another type of growth disturbance leading to a particular kind of dwarf known as the cretin (Fig. 42) is due to a deficiency of thyroxin from the thyroid gland. Cretinism undoubtedly has a hereditary basis, although the exact mechanism has not been established.

There are also genes affecting growth independently of the glands. Professor W. E. Castle of Harvard University has found that rabbits of the breed known as Flemish giants grow more rapidly than small breeds, and that this difference is evident in the very early embryonic stages long before any of the glands of internal secretion are formed.

In some families, tall stature seems to be inherited as a recessive. Two very tall parents ordinarily have only tall children, while short or medium parents frequently have children much taller than themselves. Within the normal range of variation there are probably numerous genes affecting human stature.

It is an interesting fact that the proportions of the parts of the body are often somewhat different in tall and short persons, e.g., the legs of short persons are relatively short as compared with the trunk, while the legs of tall persons are relatively long as compared with the trunk. This holds true among the races, as illustrated by the comparatively short-legged Japanese on the one hand and certain long-legged African Negroes on the other. Exceptions to this rule may, however, be observed. No doubt there are genes that affect independently the growth of the long bones of arms and legs and the trunk.

DWARFISM

Most dwarfs belong to one or the other of two familiar types, the strong man type and the midget (Fig. 42). In the former the

limbs are much shortened and somewhat malformed, while the trunk and head are approximately normal in size. This type of dwarfism is technically known as *achondroplasia*, because of the imperfect development of the skeletal system. Although the growth of the long bones is most severely affected, the shape of the head and facial features are often modified, and the trunk is sometimes deformed. The mentality is apparently normal. The

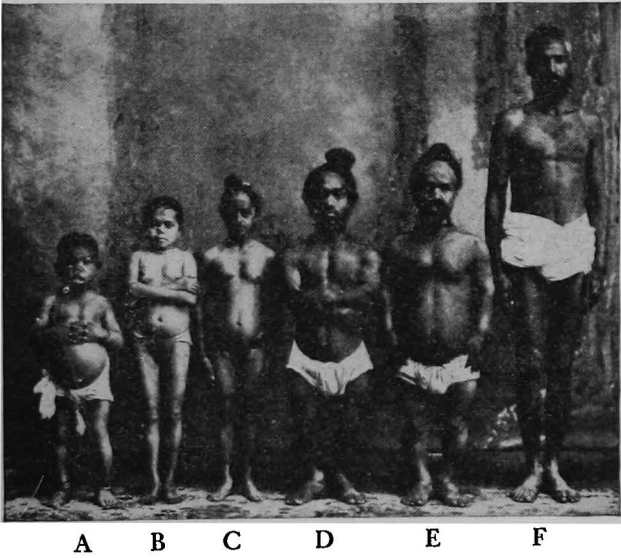


FIG. 42. Three types of East Indian dwarfs, all more than 20 years of age, compared with a native of normal stature: (A) cretin; (B), (C) midgets (ateliosis); (D), (E) achondroplasia; (F) normal. (From Rischbieth and Barrington, courtesy, MAJOR: "Physical Diagnosis," Philadelphia, W. B. Saunders Co.)

writer once had dealings with three dwarfs of this type, a man and his two sisters, who for many years conducted a successful photographic studio. Their intelligence seemed to be above average. The man, who operated the camera, was especially successful in handling children. Such dwarfs may be quite muscular. In circus troops they play the part of strong men.

Many pedigrees of achondroplastic dwarfs have been published. There is no doubt that the condition is inherited, but the exact mechanism has been much debated. Dr. Fritz Lenz thinks

that the pedigrees so far published indicate that in most families it behaves as a recessive.¹⁹ Cockayne is of the opinion that two dominant genes are necessary for its expression, making it a case like that of color in sweet peas (p. 69).

In a recent restudy of the problem, Mörch,²⁰ of the University Institute for Human Genetics, Copenhagen, Denmark, presents pedigrees and other data indicating that achondroplasia is a simple dominant. A critical review of the literature convinces him that there are no reliable observations that contradict this theory. The numerous pedigrees showing a dwarf produced by normal parents he explains as the result of independent mutations.

Achondroplastic dwarfs are fertile, and are sometimes parents of normal children as well as of dwarfs. In such cases the condition could not be due to a single recessive gene. The women usually are unable to give birth to living young except by Cesarean section because of the contracted pelvis.

In several varieties of dogs, including the basset hound, the Pekingese, and the dachshund, achondroplasia has been selected as a breed characteristic: in the dachshund the original purpose in preserving the trait is reported to have been the advantage that short-legged animals have in entering the burrows of badgers and foxes. The short and deformed legs of these breeds seem to be inherited as is achondroplasia in man.

The midget or Tom Thumb type of dwarf (technically known as *atelioidis*) (Fig. 42) has a very different appearance from the strong-man type; hence the midget must be due to entirely different causes. The body may be essentially normal except for the extremely small size. Growth is very slow, and the full stature, rarely exceeding 40 inches, is reached later than in normal persons. In adults, the head is relatively large and round rather than long. The facial features are often noticeably infantile; and the limbs are somewhat shortened. In many respects midgets resemble the African pygmies, although they are smaller than pygmies.

Midgets are frequently fertile, although sexual maturity is

¹⁹ "Human Heredity," by ERWIN BAUR, EUGEN FISCHER, and FRITZ LENZ (translated by Eden and Cedar Paul), 1931, The Macmillan Co.

²⁰ MÖRCH, ERNST TRIER: Achondroplasia is always hereditary and is inherited dominantly, *J. Heredity*, Oct., 1940.

much delayed. Two dwarfs of this type occasionally marry and have normal children, which indicates that the condition is not due to a single recessive gene. Rare cases also are known in which two midgets are the parents of a midget. The small pelvis usually makes Cesarean section necessary in childbirth. Not infrequently midgets are born to two normal parents, in which event the condition cannot be explained as a single dominant, unless we assume that new mutations occur repeatedly, or that the dominant gene shows incomplete penetrance. It could, however, be explained by assuming two or more dominant genes working together. A recent report²¹ indicates that midgets are of several distinct morphological types. There is an extremely rare "fetal-like midget" measuring about 30 to 36 inches in stature. Most so-called midgets are either "true midgets" or "miniatures." The latter seem to be essentially normal persons of unusually small stature. It is probable that the various types have different genetic explanations. Evidently, this problem requires further investigation.

SKULL SHAPE

On the basis of extensive studies of families in Europe by a number of investigators referred to by Professor Gates of the University of London in his interesting book, "Heredity in Man,"²² it seems probable that the shape of the skull is inherited according to Mendel's laws. The short broad skull, known as the brachycephalic skull, tends to be dominant over the long narrow (dolichocephalic) skull, and a number of genes are probably involved.

Skull shape is a well-marked racial character. Among the Caucasoids, for example, the Alpine race is characterized by a short broad skull, and the Nordics by a long narrow one. Most of the Mongoloids have short broad skulls, and most Negroids (except the pygmies) as well as the Australoids have long narrow skulls. In spite of all racial mixings, these contrasting skull shapes

²¹ DUPERTUIS, C. WESLEY: The size and proportions of adult midgets, *Am. J. Phys. Anthropol.*, N.S., 3: 111-127, 1945.

²² "Heredity in Man," by R. RUGGLES GATES, 1929, London, Constable & Company Ltd.

persist. It is not uncommon, for example, to find in a single family children whose heads are of strikingly different shapes. Such differences cannot readily be explained as due to differences in the environment although within limits the environment, especially the food, undoubtedly has some effect upon development of the bones of the skull.

In addition to the shape of the cranium, the facial features, which are so important in distinguishing races and individuals, are certainly hereditary. Among these may be mentioned the size and shape of nose (skeletal framework as well as fleshy parts), breadth of cheek bones, size and shape of jaw, size of mouth, and thickness of lips. Observations of racial hybrids show that these features segregate more or less independently and that some of them, e.g., the nose, are not inherited as a single unit, but as several.

In general, pedigrees for facial features have not been worked out, so that little can be said regarding their exact mode of inheritance. It seems likely, however, from the almost limitless number of minor variations in such features, that many genes are involved.

EXTRA DIGITS (*Polydactyly*)

A fairly common anomaly in man is the presence of extra fingers and toes. The extra digits usually consist of duplicated little fingers, little toes, thumbs, and great toes. These may exhibit almost perfect development, or they may consist of minute imperfectly developed digits hanging by slender connections. The metacarpal and metatarsal bones of hands and feet, respectively, corresponding to the extra digits, are sometimes duplicated, sometimes not, depending upon the size of the extra digits. Since the extra digits, if small, are usually removed by surgical operation during infancy, we are not aware of the actual frequency of this condition.

Polydactyly is usually inherited as a single dominant. Brown S. McClintic of Ft. Sheridan, Illinois, gives an interesting pedigree accompanied by x-ray pictures of a polydactylous mother and her baby (Figs. 43 and 44), showing inheritance of the deformity through five generations.²³ The affected members of this family

²³ McCLINTIC, BROWN S.: Five generations of polydactylism, *J. Heredity*, Apr., 1935, with literature citations.

usually had six fingers on each hand, and seven toes on each foot. From six matings in this pedigree, in which one parent was polydactylous, 13 children had extra fingers and toes and 12 were

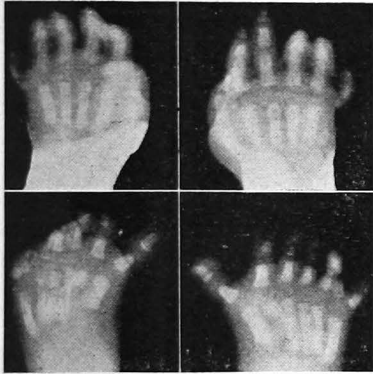


FIG. 43. X-ray photograph of hands and feet of baby, showing six fingers on each hand and seven toes on each foot. No metacarpal bone for the extra little finger is visible and no metatarsal bone for the extra little toe, although there is one for the extra big toe. (Courtesy, McCLINTIC: *J. Heredity*.)

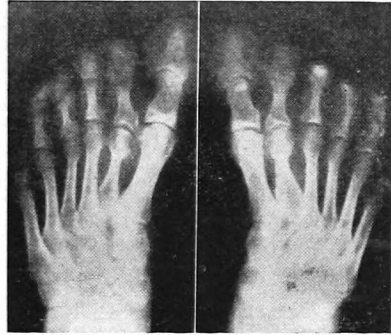


FIG. 44. X-ray photograph of feet of the mother of the baby whose hands and feet are shown in Fig. 43. Note that in both mother and baby the metatarsal bones of the extra (inner) big toes are abnormal in position. (Courtesy, McCLINTIC: *J. Heredity*.)

normal. This is a very good 1:1 ratio, as expected on the theory of a single dominant gene. Other aspects of the pedigree agree perfectly with this explanation.

SHORT FINGERS AND TOES (*Brachydactyly*)

In this condition a single gene acting as a dominant interferes with the normal development of the long bones. In the common form of brachydactyly all the digits of the hands and feet, except the thumbs and great toes, appear to lack one joint. This appearance is in reality due to the marked reduction of the middle joint accompanied frequently by its fusion with the distal one (Fig. 45). The thumbs and great toes have the normal number of joints, but the basal joint is greatly reduced in length. The arms and legs also are shorter than normal. Brachydactylous men are shorter than their normal brothers, and brachydactylous women are shorter than their normal sisters.

Brachydactyly was the first human characteristic shown to follow Mendel's laws. The earliest pedigree was published by W. C. Farabee²⁴ in 1905, for a family in Pennsylvania in which the

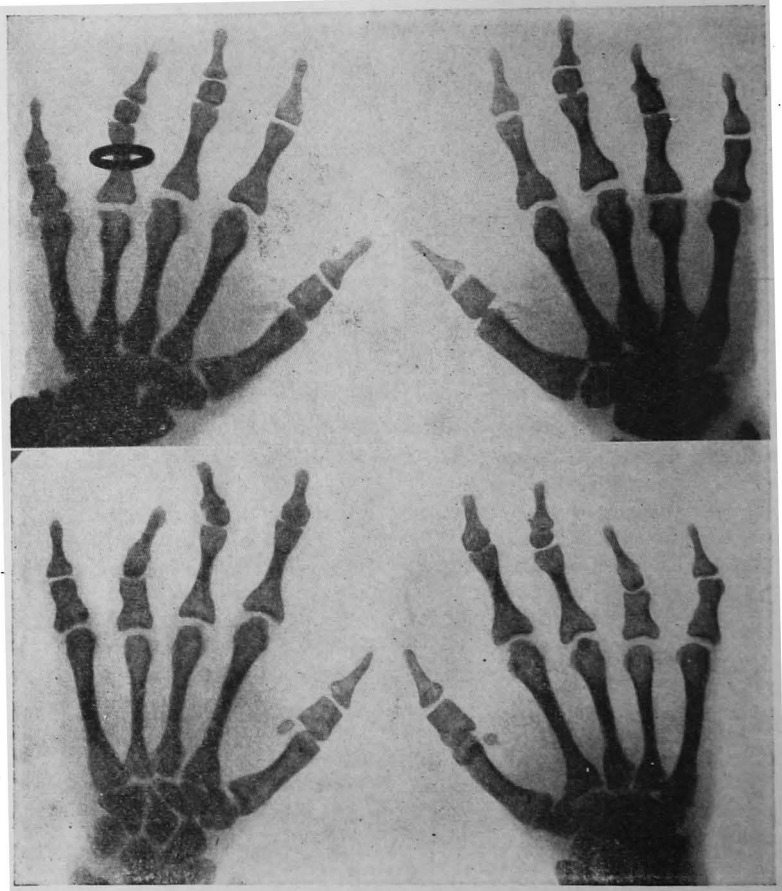


FIG. 45. Brachydactylous hands of mother (*above*) and daughter. Note marked reduction of middle joint of ring finger and middle finger of the mother's left hand. On her right hand all middle joints are fused to distal ones except the middle finger. (Courtesy, *ILTIS: J. Heredity.*)

abnormality was traced through five generations without a break. (Fig. 46.) In matings between persons with brachydactyly and normal persons, he reported 36 brachydactylous offspring to 33

²⁴ "Inheritance of Digital Malformations in Man," by WILLIAM C. FARABEE, *Papers of the Peabody Museum*, Vol. III, No. 3, Harvard University, 1905.

normal offspring. This is almost a perfect 1:1 ratio, as would be expected from a backcross of a hybrid dominant to a recessive. No marriages between two brachydactylous persons were reported by Farabee.

Subsequent studies of other families have confirmed the inheritance of brachydactyly as a single dominant. Several other types of brachydactyly have been discovered, in which one or

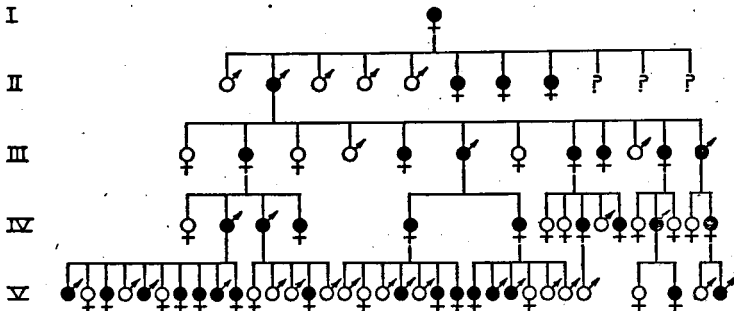


FIG. 46. Pedigree of affected members of Farabee's brachydactylous family.

more definite digits is always involved. These also are dominant. A brief classification of hereditary finger defects is given by Professor Iltis in the paper from which the x-ray photographs shown in Fig. 45 have been taken.²⁵

SPLIT HAND AND FOOT (*Syndactyly*)

A somewhat rare abnormality of hands and feet, sometimes called "lobster claw," has been studied and described in different races from widely separated countries. It has probably arisen independently several times by mutation. In all cases it is inherited as a single dominant. The condition is variable in its expression within a single family. Occasionally it varies on the two sides of the same person, which indicates that its development may be modified by subtle environmental differences during embryonic life. There is sometimes a thumb and only one large finger—the latter indicating the fusion of several digits—with a similar condition of the feet. More often there are four digits, with a deep cleft where the middle finger or toe should be.

²⁵ ILTIS, HUGO: A new case of typical brachydactyly, *J. Heredity*, May, 1944.

In some families the feet alone or the hands alone are affected. John C. Wightman of Brown University has recently published an extensive pedigree of syndactyly in a family in this country, with a review of earlier reports.²⁶

Numerous other types of hereditary abnormality of hands and feet involving shortening, fusing, malformation, etc. are described by Professor Gates in his book already referred to:

HARELIP AND CLEFT PALATE

Harelip is one of the commonest physical abnormalities. It is sometimes accompanied by a longitudinal split in the roof of the mouth known as cleft palate. Developmentally, these defects refer back to early embryonic life at which time the upper lip consists of two lateral and one middle portion, and the upper jaw and the roof of the mouth each consist of two lateral halves. Normally these separated portions gradually grow together. In normal persons the persisting depression and the pair of ridges on the upper lip together with the white line on the roof of the mouth, readily visible with a mirror, indicate the lines of fusion. Professor Bradley M. Patten, of the University of Michigan Medical School, in his excellent book on human embryology,²⁷ says of harelip:

The common designation of a cleft upper lip as a "harelip" is usually a misnomer, for the characteristic cleft in the lip of a hare, or a rabbit, is in the mid-line and, except in exceedingly rare instances, an abnormal cleft in the human lip appears to one side or the other of the mid-line. It is quite obvious that such a defect is located at the line where, during the second month of development, the maxillary process should have fused with the nasomedial process. As to the possible causes underlying such a failure of fusion, our knowledge is less satisfactory. Such defects have been attributed rather generally to some disturbance in intra-uterine living conditions which was supposed to be operative at the time the growth processes leading toward the fusion were in a critical phase. Of late an increasing amount of evidence points toward a more remote cause involving a gene defect. The accumulating data—still admittedly inadequate—seem to indicate that the condition is inherited, behaving as a Mendelian recessive.

The foregoing explanation is accompanied by drawings contrasting normal development with the abnormal development which produces harelip.

²⁶ WIGHTMAN, JOHN C.: A pedigree of syndactyly, *J. Heredity*, Dec., 1937.

²⁷ "Human Embryology," by BRADLEY M. PATTEN, 1946, The Blakiston Company.

A number of pedigrees showing the recurrence of harelip in several consecutive generations have been published. From these the character might be interpreted as a single dominant. In other families both parents of a child with harelip are apparently normal. This fact precludes the single dominant explanation unless there is great irregularity in the expression of the gene, or unless new mutations occur. For a final answer to the question of its heredity we shall have to await further studies of pedigrees.

In mice, harelip is hereditary and, as in man, is found more often in males than in females and more frequently on the left side than the right. The number of genes and their effects are still undetermined. Differences in intra-uterine conditions seem to play a part in its development in mice.²⁸

MISCELLANEOUS SKELETAL DEFECTS

Many other skeletal abnormalities which seem to have some hereditary basis have been described. In some, the Mendelian mechanism is clearly indicated. The problem may be complicated by the important influence of the environment. Dr. Lenz mentions as either Mendelian or probably Mendelian the following abnormalities: clubfoot, flat-foot, knock-knees, bow-legs, double-jointedness, congenital dislocation of the hip, arthritis deformans, absence of the knee cap, cartilaginous and bony outgrowths (exostoses), prominent lower jaw (prognathism), pin-head (microcephaly), absence of collar bones with skull abnormality, brittle bones, funnel breast, lateral curvature of the spine, and "round back."

RUPTURE (*Hernia*)

Comparatively few abnormalities of the muscular system are known to exist, and in only a few cases have they been shown to be Mendelian in character. Rupture is a defect in which heredity undoubtedly plays a part. According to Dr. Lenz, about one in every 20 or 30 men is ruptured, as compared with only about one in 150 women.

The striking difference in the frequency of rupture in men

²⁸ "The Genetics of the Mouse," by HANS GRÜNEBERG, 1943, Cambridge University Press.

and women depends partly upon the nature of the work of the two sexes, since the strain of lifting heavy objects is a factor. But the anatomical differences in the sexes probably is more important. In the male the testes develop within the abdominal cavity, and are forced downward gradually between the muscles of the lower abdomen, finally coming to lie outside the abdominal cavity in a sack called the scrotum. This migration usually occurs before birth. The passage-way through the body-wall is known as the inguinal canal. The muscles normally close around the canal leaving only sufficient room for the passage of the sperm duct, nerves, and blood vessels of the testes. In case the muscular wall around the canal is weak or imperfectly formed, a loop of the intestine may be forced into the canal and through the body wall, forming a bulge under the skin in the region of the groin. This condition is known as an inguinal hernia. The descent of the testes, therefore, plays a part in the high frequency of this type of hernia in males.

Dr. Lenz concludes that hernia unmistakably runs in families, and suggests that it is dominant, although he gives no pedigrees. Luther S. West²⁹ of Battle Creek College has published two instructive pedigrees showing the frequent recurrence of hernia through three and five generations, respectively. In these pedigrees a number of the individuals were born with hernia, but in most cases it was brought on as a result of some physical exertion. In these families it seems clear that a weakness of the abdominal wall was inherited, probably as a dominant, and that occasionally a person with the inherited tendency escaped developing a hernia.

The frequency with which both members of a pair of identical twins—necessarily of the same heredity—have ruptures is evidence for its hereditary basis.

LONG PALMAR MUSCLE ABSENT

The *long palmar* is an important muscle of the forearm. It is inserted on the palm of the hand and serves to flex the wrist. Its presence or absence can be studied on living persons by observing the tendons on the palm side of the wrist. Thompson, McBatts,

²⁹ WEST, LUTHER S.: Two pedigrees showing inherited predisposition to hernia, *J. Heredity*, Nov., 1936, with literature citations.

and Danforth³⁰ found from a study of a large number of white families that this muscle was missing in about 16 per cent of males and about 24 per cent of females. In Negroes its absence was much less frequent. They concluded that absence of the muscle was inherited as a dominant, with some irregularity in the expression of the gene.

Another muscle which shows a racial difference and is probably in the same category as the long palmar is the *sternalis*, a long slender muscle visible under the skin of the chest, lying superficially over the pectoral muscles. It is reported to be several times as frequent in Japanese as in Europeans.

Various types of paralysis and atrophy of the muscles are known to be hereditary, but since many of these are primarily defects of the nervous system they are considered in a later section.

³⁰ THOMPSON, J. W., McBATTIS, J., and DANFORTH, C. H.: Heredity and racial variation in the musculus palmaris longus, *Am. J. Physical Anthropology*, 4: 205-218, 1921.

HEREDITY IN MAN. II

IN THIS CHAPTER we conclude the systematic treatment of human hereditary characteristics which was begun in the preceding chapter. Traits chosen as examples for discussion in the present chapter are listed in Table 10.

CIRCULATORY AND RESPIRATORY SYSTEMS

The circulatory system is the seat of a number of hereditary defects and diseases, the best known being the sex-linked disease hemophilia, discussed in Chapter 11. Heredity is clearly an important factor in susceptibility to allergic and parasitic diseases; and these commonly involve the circulatory and respiratory systems. Normal hereditary differences in the circulatory system also are well established; the most important of these are the chemical differences which account for the large number of blood groups and blood types found among individuals.

THE BLOOD GROUPS O, A, B, AB

In recent years the widespread use of blood transfusions following severe hemorrhages and as a treatment in certain diseases, and the knowledge that the blood of donor and recipient must be tested for compatibility before a transfusion can safely be made, has made us all conscious of the existence of individual differences in human blood. Not everyone, however, realizes that these differences are hereditary. There are four major blood groups designated as O, A, B, and AB, respectively.

Classification of the individual with respect to his group is carried out by means of a simple laboratory test using a drop of blood. The basis of the test is the ability of the serum of an indi-

Table 10

MENDELIAN CHARACTERISTICS IN MAN*

(Arranged in the order in which they are considered in the text)

Dominant	Recessive	Page
CIRCULATORY AND RESPIRATORY SYSTEMS		
Blood groups A ₁ , A ₂ , B, A ₁ B, A ₂ B (4 alleles) . . .	Blood group O	164
Blood types M, MN, N (2 alleles)	(No dominance)	171
Rh blood factor (6 alleles)	Rh negative	172
Hemolytic jaundice	Normal	174
Nose bleed and blood cysts (Telangiectases)	Normal	174
Varicose veins and hemorrhoids	Normal	175
Hereditary dropsy (Edema)	Normal	175
High blood pressure (Hypertension)	Normal	176
Allergy	Normal	176
Resistance to tuberculosis	Susceptibility to T.B.	176
EXCRETORY SYSTEM		
Polycystic kidney	Normal	179
Diabetes insipidus	Normal	179
ENDOCRINE GLANDS		
Diabetes mellitus	Normal	180
DIGESTIVE SYSTEM		
Normal	Pyloric stenosis	180
Ulcers (mode of inheritance uncertain)		181
Enlarged colon (Hirschsprung's disease)	Normal	181
REPRODUCTIVE SYSTEM		
Hypospadias	Normal	182
CANCERS AND OTHER MALIGNANT TUMORS		
Normal	Xeroderma pigmentosum	184
von Recklinghausen's disease	Normal	185
Cancer of the stomach (?)	Normal	186
Normal	Retinal glioma	186
NERVOUS SYSTEM		
Tasters	Non-tasters	187
Normal	Congenital deafness	189
Auditory nerve atrophy	Normal	189
Otosclerosis	Normal	189
Normal (Mild type dominant)	Muscular atrophy	189
Normal	Spinal ataxia	190
Paralysis agitans	Normal	190
Huntington's chorea	Normal	191
Normal (Mild type dominant)	Feeble mindedness	191
Normal	Amniotic idiocy	193
Normal	Schizophrenia	194
Manic-depressive psychoses	Normal	197
SPECIAL TALENTS (Dominance uncertain)		
Musical ability		199
Ability in drawing, painting, sculpture		201
Mathematical ability		201

* See also Table 9, p. 124.

vidual of one group to cause a clumping (agglutination) of the corpuscles of an individual of another group, according to a definite system, to be described later.

The fact that such differences exist was not discovered until 1900, when Dr. Karl Landsteiner, an Austrian physician, curious to see whether any reaction occurred when bloods of human individuals were mixed, such as were known to take place in the mixing of bloods of different species, tried the experiment of mixing the serum of one person with the blood of another. He found that in certain cases a marked agglutination reaction followed, while in other cases there was no reaction. On the basis of his studies Landsteiner recognized three distinct human blood groups. The fourth group was discovered in 1902 by one of his students.

Subsequently Landsteiner came to this country where he continued his researches on blood at the Rockefeller Institute for Medical Research. For his many original contributions he was awarded the Nobel prize in medicine for 1930.

Beginning sometime in the early nineteenth century blood transfusions had been made from person to person, frequently with fatal results. The fatalities, it now seems probable, followed the mixing of incompatible bloods, resulting in the clumping of the donor's corpuscles in the veins of the recipient. In blood transfusions the serum of the donor is not likely to produce a severe reaction, even though, it is antagonistic to the corpuscles of the recipient, because of the dilution with the recipient's own serum. The chief danger comes from introducing corpuscles which are agglutinated by the recipient's serum. Surprising as it may seem, there is a possibility that a mother's blood may be of a type that will kill her own child if a transfusion is made from mother to child, while the blood of a member of a different race may be perfectly safe. Since 1900 a vast amount of research on the blood groups of man has been done, including numerous studies of the mode of inheritance and racial significance of the groups.

As to mode of inheritance, the existence of a series of three alternative genes (triple alleles) is now well established. Every person has a pair—and only one pair—of these genes, which may consist of any one of the six possible combinations (using the

symbols i , I^A , and I^B to represent the three alternative genes) as follows:

<i>Blood Groups</i>	<i>Genotypes</i>
O.....	ii
A.....	$I^A I^A$ or $I^A i$
B.....	$I^B I^B$ or $I^B i$
AB.....	$I^A I^B$

In this scheme, note that both I^A and I^B are dominant over the gene i , but that neither I^A nor I^B is dominant over the other. Group O, being a recessive, must always breed true; group AB always breeds as a hybrid; and groups A and B may be either true-breeding or hybrid.

Since the blood group of babies is fixed by their own genes before birth, and since one's blood group remains fixed throughout life, it is apparent that a knowledge of the blood groups may in certain matings solve the problem of disputed parentage. Such knowledge is, in fact, being used in an increasing number of cases in many States in this country. To illustrate how this might be applied, let us consider a case where both parents are of group O. Obviously their baby could belong only to group O. If, however, the parents are O and AB, respectively, their children must all belong to group A or B as follows:

Parents	(O) ii	\times	(AB) $I^A I^B$
Gametes	i		I^A I^B
Children	(A) $I^A i$		(B) $I^B i$

The other possible matings may readily be worked out in the same way and the offspring accurately predicted.

In applying the blood group test, sera of groups A and B are required. A drop of each is placed on a slide and to this is added a drop of a normal saline suspension of the blood of the person to be tested. A cover glass is added, as shown in Fig. 47. Note that the corpuscles of group O are not agglutinated by the serum from group A or group B; that the corpuscles of group A are agglutinated by the serum of group B; that the corpuscles of group B are agglutinated by the serum of group A; and the corpuscles of group AB are agglutinated by sera of both groups A and B.

These reactions are the result of the presence of specific sub-

Blood Group	Serum A (Anti-B)	Serum B (Anti-A)
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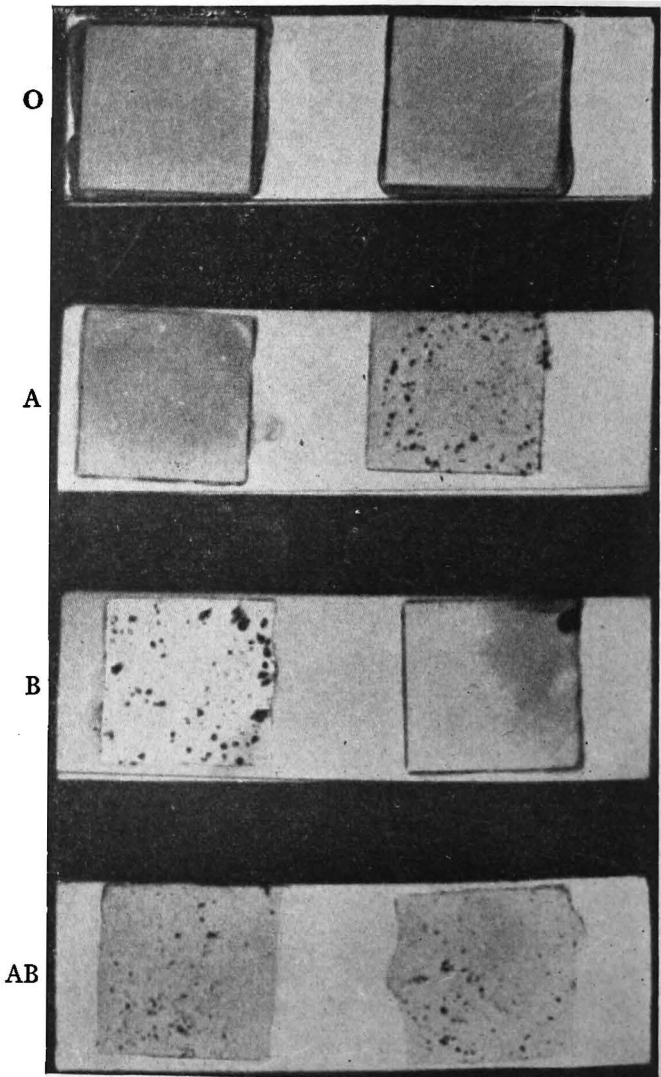


FIG. 47. Blood grouping on glass slides (actual size). Numerous dark specks of various sizes indicate agglutinated red blood corpuscles. On slides that remain clear there is no agglutination. (Courtesy, ALEXANDER S. WIENER: "Blood Groups and Transfusion," 3d ed., Springfield, Ill., Charles C Thomas.)

stances known as agglutinogens in the corpuscles and the presence in the plasma (or serum obtained from the plasma) of substances known as agglutinins, which bring about an agglutination or clumping of the corpuscles of incompatible groups.

Gene I^A is responsible for the production of agglutinin A and gene I^B for agglutinin B. Persons of group AB ($I^A I^B$) produce both agglutinins. The homozygous recessive individual (ii) produces neither agglutinin. The general rule is that the plasma of an individual causes an agglutination of corpuscles containing agglutinogens not found in his own blood; in other words each person produces agglutinins against agglutinogens which he does not possess.

For a number of years the foregoing account was accepted as an adequate serological and genetic explanation of the observed facts. Further studies, however, have demonstrated that agglutinin A is not a single substance, but that there are really two substances. These have been designated as A_1 and A_2 . This discovery means that there are two kinds of group A blood, depending on whether the agglutinin is A_1 or A_2 . Likewise there are two sorts of group AB individuals, $A_1 B$ and $A_2 B$. According to Wiener,¹ approximately $\frac{1}{4}$ to $\frac{1}{5}$ of all group A individuals belong to subgroup A_2 .

The mode of inheritance of the subgroups of groups A and AB now seems well established. Beginning with the first studies, reported in 1927, numerous investigators in this country and abroad have, according to a tabulation by Wiener, examined a total of 1068 families, with 3134 children. These families include 16 different matings—all possible ones, in fact, except the rare combinations $A_1 B \times A_2 B$ and $A_2 B \times A_2 B$. The conclusion reached is that instead of a series of only three blood group alleles I^A , I^B , and i there exist four allelic genes, I^{A_1} , I^{A_2} , I^B , and i . The first three in the series are dominant over i , and I^{A_1} is dominant over I^{A_2} . The existing six phenotypes and their ten genotypes are therefore as follows:

¹ "Blood Groups and Transfusion," by ALEXANDER S. WIENER, Charles C Thomas, Publisher, 3d ed., 1943. This is an excellently written and illustrated book dealing with all aspects of the blood groups, including historical, clinical, genetic, anthropological, and medicolegal aspects.

<i>Phenotype</i>	<i>Genotype</i>
O	ii
A ₁	I ^A ₁ I ^A ₁ , I ^A ₁ i, I ^A ₁ I ^A ₂
A ₂	I ^A ₂ I ^A ₂ , I ^A ₂ i
B	I ^B I ^B , I ^B i
A ₁ B	I ^A ₁ I ^B
A ₂ B	I ^A ₂ I ^B

The frequency of the four groups (combining the subgroups of A and of AB) has been studied in practically every racial and national group in the world through the efforts of many investigators. A recent summary of the data is given by Wiener. From the anthropological point of view the results are most interesting. All four groups are found to be present and widely distributed in all three major divisions of mankind—Caucasoids, Mongoloids, and Negroids—as well as in most of the racial subdivisions. In the United States tests of many thousands of persons indicate the frequency of the groups to be roughly as follows: O 45 per cent, A 38 per cent, B 12 per cent, AB 5 per cent. These proportions are fairly typical of the peoples of Western Europe. As one travels eastward through Europe and Asia and southward into Africa and India there appears a more or less gradual rise in the percentage of group B. In Europe and Japan this rise is largely at the expense of group O; among African Negroes it is at the expense of group A; and on the continent of Asia it is at the expense of both O and A. There are high spots in the frequency of B in the centers of Asia and Africa, with a falling off in all directions.

Among North American Negroes the group frequencies resemble closely those of the natives of the Congo region of Africa, as might have been expected from the known origin of the Negroes in this country. The figures for Negroes are approximately as follows: O 47 per cent, A 28 per cent, B 20 per cent, AB 5 per cent.

The most striking variations from the distributions in the larger populations are found among certain small and isolated populations, as illustrated in the following:

	<i>Number</i>	<i>% O</i>	<i>% A</i>	<i>% B</i>	<i>% AB</i>
Australian Aborigines	398	33.9	66.1	0	0
Tuamotus (Polynesians)	176	48.3	51.7	0	0
Indians, pure (Peru)	200	100	0	0	0
Bush Negroes (Dutch Guiana)	336	83	0	17	0

Knowing the frequencies of the blood groups in a population it is possible, assuming random matings with respect to blood groups, to calculate the frequencies of the three genes I^A , I^B , and i . The extensive list of gene frequencies given by Wiener shows that in all but a few populations the recessive gene i is more frequent than the other two combined.

Several attempts have been made to find some correlation between the blood groups and various other characters, including susceptibility to specific infections and other diseases, but without success. There is no critical evidence that any of the groups has any selective importance. They seem merely illustrations of non-adaptive differences that have arisen through mutation and chance preservation.

BLOOD TYPES M, N, AND MN

In 1927 two additional hereditary agglutinogens, designated M and N, were discovered by Landsteiner and Levine in human blood. All persons so far tested have either one or the other or both of these, and are therefore classified as Type M, N, or MN. The frequencies of the three types are the same in persons of all four blood groups; hence the agglutinogens M and N have no relation to agglutinogens A and B. Human beings do not produce agglutinins against the agglutinogens M and N. The test sera are obtained from rabbits that have been injected with human blood of types M and N, respectively, and have developed agglutinins against the agglutinogens. Since human blood does not contain the agglutinins it is unnecessary to take into consideration these blood types in making transfusions. A knowledge of the heredity of the types is made use of at present largely as an additional means of deciding disputed parentage, since the M and N agglutinogens are fully developed at birth and are inherited in accordance with Mendel's laws.

The mode of inheritance of the blood types was correctly deduced from a study of families by Landsteiner and Levine. Wiener summarizes the results of investigations by the original discoverers and by numerous later workers; 2165 families with 6718 children are included in his table. The results demonstrate the presence of two alleles, I^M and I^N , with no dominance: type

M is always of genotype $I^M I^M$, type N is $I^N I^N$, and type MN is $I^M I^N$. It is evident that the M-N series would be like the A-B series genetically provided the recessive gene i in the latter series did not exist.

As with the major blood groups, there is considerable variation in the proportions of the three types M, N, and MN among the peoples of the world. For example, many Western Europeans, American Whites, American Negroes, and Japanese agree closely in the proportions of the three types: roughly these are 29 per cent M, 21 per cent N, and 50 per cent MN. Among Finns, Swedes, and Hindus there is a greater excess of M over N; and in American Indians a still greater excess. Eskimos of East Greenland are reported to show the greatest excess of all, with type M present in about 84 per cent and type N in less than 1 per cent. The Ainus of Northern Japan, a small group of primitive Caucasoids, and the Australian Aborigines are exceptional in showing a higher percentage of N than of M.

The blood types, so far as known, have no adaptive significance. Their distributions among the races suggests that we are dealing with non-adaptive or neutral differences and that chance and isolation have played leading rôles in the present distribution.

THE RH BLOOD FACTOR

In 1940 Landsteiner and Wiener reported the discovery of a new and, as subsequent events have demonstrated, important difference in human bloods. Using a serum obtained from rabbits immunized with the blood of a rhesus monkey they found that about 85 per cent of white persons showed a positive reaction, while the other 15 per cent were negative. They accordingly designated the former as Rh positive and the latter as Rh negative.

From tests of 60 families with 237 children the discoverers concluded that the Rh factor was due to the presence of a dominant gene. Later studies by Wiener and Sonn of 40 additional families confirmed this theory. Two Rh negative parents produce only Rh negative children, as theory demands of a recessive. The other possible matings, between positive and positive and positive and negative, also agree in the expected ratios of Rh positive and Rh negative offspring produced.

Further investigation has brought out the fact that there is more than one form of the Rh factor. To date five variants of the Rh agglutinin have been identified. To account for these Wiener proposed the theory, which has now been confirmed by other workers, that the five kinds of Rh factor are due to a series of five alleles; these, with the allele associated with the Rh negative genotype, make a series of six alleles in all.²

At present, the chief importance of the Rh factor is its rôle in the causation of a disease known as erythroblastosis in the fetus and newborn infant. If the mother is Rh negative and the fetus Rh positive, having received an Rh gene from a positive father, the Rh agglutinin produced by the fetus may pass through the placenta into the mother's blood and stimulate in her body the production of antibodies against the Rh positive corpuscles of the fetus. These antibodies in turn pass through the placenta from mother to the fetus and cause the destruction of fetal red corpuscles, which may be so extensive as to cause the death of the fetus and so a stillbirth. Sometimes the destructive effect appears only after birth. Affected babies show severe anemia, jaundice, and edema, with enlargement of the spleen and liver. Most affected infants die, although in some cases they have been saved by transfusions of Rh negative blood, repeated until the antibodies have been eliminated from the infant's body. Rarely is there a spontaneous recovery. Fortunately, the disease is much less common than one would expect on the basis of the frequency of marriages between Rh negative women and Rh positive men. It has been estimated that erythroblastosis develops in only about $\frac{1}{40}$ of the infants in which it would be expected.

As with the other human blood differences previously described, we find an interesting racial difference in the frequency of the Rh factor. In Negroes the percentage of Rh positive individuals is from 92 per cent to 95.5 per cent; among Japanese 98 per cent and in Chinese 99 per cent.³ As one should expect, erythroblastosis is of less frequent occurrence among these races than among whites.

² WIENER, ALEXANDER S.: The Rh series of allelic genes, *Science*, Dec. 29, 1944.

³ WALLER, R. K., and LEVINE, P.: On the Rh and other blood factors in Japanese, *Science*, Nov. 17, 1944.

Research on the serological differences in human blood is still in a very active phase. There is evidence of numerous specific differences other than those described above. Apparently only a beginning has been made in discovering the real number.

HEMOLYTIC JAUNDICE

Jaundice is an abnormal condition in which there is a visible accumulation of the yellowish bile pigment in the skin and whites of the eyes. It is sometimes caused by an obstruction of the bile duct (the tube leading from the liver to the intestine) through infections or gall stones, so that the dammed up bile is forced into the blood. In hemolytic jaundice there is, as the name implies, an excessive destruction of the red corpuscles. The hemoglobin thus released is converted, in part, into bile pigment by the liver and finds its way into the blood by which it is carried over the body. In many such cases the spleen is the site of corpuscle destruction. The removal of the spleen by operation has frequently produced good results. Gates gives several references to studies of this disease, including one to a large monograph on the subject. In its degree of severity there is much variation. Pedigrees show that hemolytic jaundice is inherited as a dominant, with considerable irregularity in its expression.

NOSE BLEED WITH BLOOD CYSTS (*Telangiectases*)

According to Cockayne, the first indication of this vascular defect is repeated and serious nose bleed, which may begin in childhood, at puberty, or not till early adult life; and which often becomes more frequent and more severe as time passes, attaining the greatest frequency and severity at 30 to 35. In some individuals nose bleed is the only symptom, but in most cases this is followed by the development of red spots in the skin, especially about the face and hands and on the lips, tongue, and nasal mucous membrane. These red spots consist of swollen blood vessels caused by the lack of muscular and elastic tissue in the walls of small arteries. Hemorrhages often result from the rupture of the swollen vessels, sometimes with fatal results. Many pedigrees have been published which have been tabulated by Cockayne. The ratios indicate a clear-cut case of single dominant inheritance.

VARICOSE VEINS AND HEMORRHOIDS

Veins sometimes become greatly swollen, elongated, and tortuous in their course. When they persist in this condition more or less permanently because of the failure of the blood to flow normally back to the heart they are known as varicose veins. The superficial veins of the legs are most commonly affected. Varicose veins in the lower end of the intestine are known as hemorrhoids. Varicose veins in the legs seem to result from defective valves: valves normally function in preventing the backward flow of blood in the veins. The veins in the rectum have no valves; consequently, hemorrhoids result merely from dilation.

The activities of the individual are undoubtedly factors in the onset and severity of the symptoms. Any occupation requiring heavy lifting, long hours of standing on the feet, or activity otherwise retarding the circulation in the legs, throws an added strain upon the veins of the legs, thus favoring development of varicose veins. Child-bearing is an important factor. Sedentary occupations predispose to hemorrhoids. A hereditary factor is indicated, however, by the tendency to hemorrhoids and to varicose veins to run strongly in families. Many persons subjected to all of the predisposing conditions never develop the defects; hence they probably lack the hereditary factor. The tendency to varicose veins and to hemorrhoids is probably inherited independently, in each case as a dominant.

HEREDITARY DROPSY (*Edema*)

Dropsy or edema is the name given to the excessive accumulation of watery fluid in the tissues. It is evidenced by a swollen appearance. Certain types of heart disease and kidney disease cause dropsy. One type of edema, confined to the legs, and causing conspicuous swelling of these members is known to be hereditary. According to Cockayne, it may affect both legs alike or it may be confined to one. The swelling ends abruptly at the ankle, knee, hip or groin, and after reaching the upper limit persists throughout life. Although it is an annoying defect, there are no painful symptoms and the general health and longevity may be good.

In some families the edema is present at birth. Cockayne thinks

that this type is distinct from a somewhat similar form which appears in later childhood or in early adult life. In the type present at birth he suggests that there is an abnormal development of the lymphatics, whereas the other gives indications of an involvement of the nerve supply to the swollen parts. Both types follow the usual lines of dominant heredity with some irregularities.

HIGH BLOOD PRESSURE (*Hypertension*)

Abnormally high blood pressure, accompanied by hardening of the arteries, and often resulting in heart failure, apoplectic stroke, or kidney disease, has been found to run in families. External conditions of course play a part in the development of the symptoms, but a study of pedigrees gives one the impression that the inherited tendency is very strong. Dr. Lenz refers to a number of studies made in Germany which indicate that the tendency to high blood pressure is inherited as a dominant.

ALLERGY

Allergy is the term used to denote the peculiar sensitivity exhibited by certain persons to specific foods and foreign substances, usually proteins. This sensitivity expresses itself in a variety of symptoms and conditions, such as eczema, hives, gout, asthma, hay fever, and migraine. Cockayne and Lenz both give extended discussions of allergy as it relates to heredity, illustrated by a number of pedigrees. In agreement with most other authors they regard allergy as hereditary, and both consider it as dominant. Cockayne concludes that one main dominant gene produces a special liability to become sensitized, and that the particular manifestation of this general sensitivity depends upon other genes. This would explain the fact that in some pedigrees the affected individuals are all allergic to the same substances and develop the same symptoms, while in other pedigrees there is considerable variation in these respects. The age at which allergy appears is variable. In some cases there is a tendency to outgrow the susceptibility.

RESISTANCE TO TUBERCULOSIS

There are many lines of evidence which prove beyond reasonable doubt that people differ in their natural or inherited resistance

to various infectious diseases. Some of these differences are racial. Thus the Negro is more resistant to scarlet fever, measles, erysipelas, malaria, yellow fever, and diphtheria than the white man, but less resistant to tuberculosis and pneumonia.⁴ In making such comparisons one must always be on guard to recognize the other factor of resistance, namely, the environment and general living conditions, but when people living under practically identical conditions show marked differences in their resistance to specific infections, as is often the case, we can only conclude that heredity probably is a factor. An excellent recent exhaustive study of racial differences in susceptibility to diseases is found in a book by Dr. Julian Lewis, pathologist at the University of Chicago.⁵

It is not possible at present to say how important such environmental conditions as food, shelter, dust, and extent of exposure to the bacillus of tuberculosis may be as compared with the natural resistance of the individual. Nor can we give the exact mode of inheritance. What evidence exists seems to indicate that high resistance is dominant, and susceptibility is recessive.

Instructive on this point is a series of controlled experiments on guinea pigs performed by Wright and Lewis⁶ in which 412 animals were inoculated with tuberculosis germs in order to discover how long they could survive the infection. Nearly half the animals were from five distinct and homogeneous inbred lines; the rest were cross-bred animals. There was much variability in resistance within each inbred line; nevertheless a striking difference was found among the inbred lines themselves. In various crosses between individuals of two inbred lines, resistance proved to be dominant over susceptibility, and in some cases the hybrids were even more resistant than either parental line. No attempt was made to estimate the number of genes concerned in resistance and susceptibility to tuberculosis.

⁴ "The Negro's Struggle for Survival: a Study in Human Ecology," by SAMUEL J. HOLMES, 1937, University of California Press.

⁵ "The Biology of the Negro," by JULIAN HERMAN LEWIS, 1942, University of Chicago Press.

⁶ WRIGHT, SEWALL, and LEWIS, PAUL A.: Factors in the resistance of guinea pigs to tuberculosis, with especial regard to inbreeding and heredity, *Am. Naturalist*. Jan.-Feb., 1921.

In man, Professor Raymond Pearl⁷ reports studies on the frequency of tuberculosis in a total of 564 matings producing 2,480 offspring. He finds that when both parents have tuberculosis the child is about 4.3 times as likely to have tuberculosis as when neither parent is affected. With one parent affected the child is about 1.7 times as likely to have it as when neither parent is tuberculous. One might naturally conclude that these differences are the result of greater opportunities for infection in families with one parent or both infected, but Pearl concludes from his analysis that in the cases studied the differences in heredity are the only factors which play a significant rôle in the result. Quoting from Pearl:

The regular increase in the offspring percentage incidence as the amount of parental tuberculosis increases seems impossible of rational explanation on any other basis than that of hereditary influence. Increasing chance of massive contact infection in the home cannot reasonably explain it, in the opinion of clinicians whom we have consulted about these results. For plainly the chance of clinical tuberculosis resulting from such contact infection when both parents are tuberculous is nothing like quantitatively double what it is when only one parent is tuberculous. Yet the offspring incidence in this case is more than double. Nor does it seem probable that a child with one parent in the home actively tuberculous is only 1.7 times as likely to develop clinical tuberculosis as a child with no tuberculous parent. The risk seems probably greater than this.

Studies of the frequency of tuberculosis in twins—identical twins versus fraternal twins—also lead to the conclusion that heredity plays an important rôle in the development of tuberculosis.^{8,9}

EXCRETORY SYSTEM

A number of diseases and structural abnormalities of the kidneys have been found to run in families. Among these are various infections of the kidneys known as nephritis, in which a susceptibility to the infection appears to be dominant.

⁷ PEARL, R.: On the incidence of tuberculosis in the offspring of tuberculous parents, *Zeitschrift für Rassenkunde*, 3: 3, 1936.

⁸ "Zwillingstuberkulose I," by KARL DIEHL and O. F. v. VERSCHUER, 1933, Jena, Gustav Fisher—reviewed in *J. Heredity*, Jan., 1934.

"Zwillingstuberkulose II," (same authors) 1936—reviewed in *J. Heredity*, Mar., 1937.

⁹ "Familial Susceptibility to Tuberculosis," by RUTH PRICE PUFFER, 1944, Harvard University Press.

POLYCYSTIC KIDNEY

A structural abnormality known as polycystic kidney, so called because of the presence of cavities in the kidney tissue, is frequently met with. The condition causes insufficient functioning of the kidneys. According to Gordon and Trasoff¹⁰ it is found in one case in 500 at postmortem examination. The authors state that the hereditary aspect of polycystic kidney has often been noted, and a familial history is of the greatest diagnostic importance. In a family studied by them a father who died of chronic nephritis had seven children, five with proven polycystic kidney disease. A brother of this father and one of the brother's daughters also had polycystic kidney disease. This pedigree suggests a dominant gene.

DIABETES INSIPIDUS

Unlike sugar diabetes, this condition usually has no serious aftermath. Affected individuals often live to a very old age. The principal symptom is an excessive activity of the kidneys accompanied by inordinate thirst. In some cases the pituitary gland is said to function abnormally. There is no sugar or albumin in the urine. The trouble usually appears in childhood and persists throughout life. Under living conditions where water is scarce, as in the desert, it might well become a condition dangerous to its possessor.

Investigators of family pedigrees of diabetes insipidus have usually come to the conclusion that it is inherited as a single dominant. In some pedigrees, however, there are instances of generations skipped. The irregularity in the expression of the gene has recently been emphasized, with the need for further investigation of the genetics of the disease.¹¹

ENDOCRINE GLANDS

Reference has already been made to the part played by the endocrine glands in such conditions as gigantism, dwarfism, hair

¹⁰ GORDON, GEORGE R., and TRASOFF, ABRAHAM: Congenital polycystic kidney, with report of its occurrence in several members of one family, *Am. J. Med. Sc.*, 194: 112-117, 1937.

¹¹ LEVIT, S. G., and PESSIKOVA, L. N.: The genetics of diabetes insipidus, *J. Heredity*, Nov., 1936.

growth, etc. It is probable that these glands are concerned as links in the chain of development of many other hereditary differences, although in only a few cases do we have the evidence to establish the connection. In the case mentioned below a gene is known to control the functioning of an endocrine gland.

DIABETES MELLITUS (*Sugar Diabetes*)

This serious form of diabetes is caused by a failure of the endocrine cells in the pancreas to secrete an adequate amount of the hormone insulin, which is necessary for the metabolism of sugar in the body. Excess sugar therefore accumulates in the blood and is excreted by the kidneys. There are severe symptoms, including loss of weight and strength, excessive thirst, and over-activity of the kidneys, leading eventually to coma and death unless insulin is supplied from an external source.

Environmental factors such as syphilis, poisons, and over-eating are important in favoring the development of diabetes, but the hereditary factor plays a part. It is said that diabetes in children is almost always hereditary. Recent studies indicate that it is due to a dominant gene but that in some families only about 10 per cent of persons with the gene actually develop the disease.

DIGESTIVE SYSTEM

Comparatively few hereditary differences have been reported for the digestive system, and in some of these the exact mechanism is still in doubt.

CONSTRICTED STOMACH (*Pyloric Stenosis*)

This condition, which appears in infancy, is characterized by violent vomiting. There is an abnormal contraction of the lower or pyloric end of the stomach, which prevents the normal exit of food from the stomach. Most affected persons die as infants. One pedigree has been reported in which a father and his son and daughter were afflicted.¹² There seems to be good evidence that it is inherited as a recessive.

¹² CAULFIELD, E. J.: Familial incidence of pyloric stenosis, *Am. J. Dis. Children*, 32: 706-708, 1926.

ULCERS

One factor in the development of ulcers of the stomach and duodenum seems to be an excessive secretion of hydrochloric acid. This causes the self-digestion of an area of the stomach (usually in the pyloric region) or in the intestinal wall, resulting in the production of raw ulcers. The ulcers are often difficult to heal and may become dangerous either by reason of the loss of blood they occasion or because of infections following the perforation of the wall of the affected organ. The activity of the nervous system seems to be a factor in the excessive secretion of hydrochloric acid by the stomach.

A number of studies of family histories referred to by Lenz indicate that ulcers have some hereditary basis since there is a strong tendency for the defect to run in families.

In a recent clinical study in the United States, evidence is adduced to show that predisposition to peptic ulcer is hereditary, probably as a simple recessive.¹³ The author compared the families of 255 ulcer patients with the families of 400 patients having other diseases, finding that stomach ulcers were almost five times as frequent in the former group as in the latter. In this study the *family* was taken to indicate parents, brothers, and sisters of the patient. From the frequency of ulcers in the 255 families it was concluded that only about one-half of the persons genetically susceptible actually developed the disease. Apparently, environmental factors necessary for the production of the symptoms were lacking in about 50 per cent of the cases.

ENLARGED COLON (*Hirschsprung's Disease*)

In this condition the child is born with a large intestine of excessive caliber, resulting in a tendency to abnormal accumulation of feces in the lower end of the colon. Gates refers to a family in which several members in three generations were afflicted. In a pedigree referred to by Lenz it appeared to be dominant.

¹³ BAUER, JULIUS: The relation between peptic ulcer and cancer of the stomach from the genetic point of view, *Rev. Gastroenterology*, 7: 21-24, 1940.

REPRODUCTIVE SYSTEM

The reproductive system in man is subject to numerous individual variations as well as abnormalities, some of which have been shown to be hereditary. The tracing of family histories involving the reproductive system is difficult because the system is different in the two sexes, and the natural tendency is toward concealment of any peculiarity. The case of female intersexuality or pseudo-hermaphroditism appears to rest in part upon a hereditary basis. This will be referred to again in the next chapter. The tendency to produce twins likewise runs in families. The hereditary basis of twinning is considered in Chapter 10.

HYPOSPADIAS

Hypospadias is a developmental abnormality of the penis in which the opening of the urethra is on the under surface rather than at the end of the penis. The defect results from a failure of the groove, which represents the urethra at one stage in embryonic development, to close over normally and form a tube. According to Dr. Lenz, about one male in three hundred shows this malformation to a greater or less extent. In certain families it has been traced through the male line for several generations, behaving as a dominant.

CANCERS AND OTHER MALIGNANT TUMORS

The word cancer is derived from the Latin word for crab and refers to any persisting and destructive (malignant) growth originating in the epithelial tissues. The epithelial tissues include the outer skin, the mucous membranes, which line cavities, and glands which develop as ingrowths of the skin or mucous membranes. In medical literature a cancer is known as a carcinoma. Most malignant tumors are of this type; less often such tumors develop from cells of other tissues such as bone, cartilage, connective tissue, muscle, and nerve cells. When a malignant tumor develops from connective tissue cells it is known as a sarcoma. In popular usage the term cancer is usually applied to all malignant tumors, including carcinomata and sarcomata.

Malignant tumors are distinguished from non-malignant

growths such as moles, warts, etc.; by the fact that the latter grow for a time and then spontaneously cease growth, while malignant tumors keep on growing until eventually they invade the surrounding areas, causing the destruction of normal tissues and organs and finally death. A cancer expert is able to diagnose a cancer prior to the invasive and destructive phases by microscopical examination of the cells. In cancer the cells show abnormal nuclei and atypical mitotic figures.

The factors contributing to the origin of malignant tumors are not yet fully known, but it is certain that in many cases there are two sets of factors: (1) the natural susceptibility of the individual; and (2) some inciting environmental agent. It is well established that persons differ in their natural susceptibility to cancer and that these differences are hereditary. It is probable, however, that cancer of some kind would develop in almost everyone under the appropriate stimulus. Repeated exposure of the skin to x-rays and radium frequently causes skin cancer, and in the early days before this danger was recognized and guarded against, many doctors and x-ray workers fell victims to it. In some industries such as clock and watch factories numerous workers in radium developed sarcoma of the bones as a result of chronic radium poisoning. Tar, soot, lubricating oils, and various products of coal tar in contact with the skin have a similar effect. It is reported that in certain chemical industries a majority of the workers who are repeatedly exposed to poisons such as aniline develop cancer of the bladder.

The precise manner in which such irritating agents convert a normal healthy cell into a malignant cell is not known. It was suggested as early as 1914 by the famous biologist Theodor Boveri that malignancy results from a change in the chromosome constitution of the cell, of such a nature as to lead to uncontrolled multiplication of its descendants. The behavior of cancer cells makes the mutation theory an attractive one but the proof of it is still lacking, and some students of cancer regard malignancy as due to some chemical change of the cytoplasm and not to chromosomal or gene alteration.¹⁴

¹⁴ *The Cultivation and Cytology of Cancer Cells*, by WARREN H. LEWIS, in "Some Fundamental Aspects of the Cancer Problem," Symposium of the A.A.A.S., 1937, Science Press.

Malignant tumors are known to affect all the systems and organs of the body, although some parts are much more frequently affected than others. A study of family histories indicates a strong tendency for malignant tumors of specific types to run in families. In such cases there can hardly be any doubt that heredity is an important factor. Among these types are the examples discussed below.

CANCER OF THE BREAST

In a recent study of human cancer of the breast in 201 family histories, R. P. Martynova¹⁵ comes to the conclusion that hereditary factors play a definite rôle in predisposition to cancer of the breast. He rejects, however, the hypothesis that cancer is due to a single recessive gene, and leaves open the question of the number of genes involved, the question of dominance, and the relative influence of the environment in conditioning the expression of the genes.

XERODERMA PIGMENTOSUM

This hereditary abnormality is often discussed in works on diseases of the skin, the name meaning pigmented dry skin. At birth, the skin is apparently normal. According to Cockayne, the first symptom, an abnormal avoidance of light, may be noticed during the first few weeks of life. Reddening of the exposed skin of the face and hands, and of the whites of the eyes, follows in succeeding months, usually before the third year. Freckles, which may even appear on the lips and whites of the eyes, accompany or closely follow the reddening. The freckles grow larger, more numerous, and darker. Between the freckles are white areas which undergo degenerative changes, leading in most cases to the development of cancerous growths.

There is no known cure, and death ordinarily results between five and 15 years, although in rare cases where the disease appears later and progresses more slowly, life may be prolonged to the age of 40. Fortunately the disease is rare, only a few hundred cases having been reported.

¹⁵ MARTYNOVA, R. P.: Studies in the genetics of human neoplasms, cancer of the breast, based upon 201 family histories, *Am. J. Cancer*, 29: 530, 1937.

Xeroderma pigmentosum is a striking example of an inherited condition which requires for its expression the cooperation of a gene with an environmental factor—in this case light. Cockayne states:

The distribution of the pigmentation and other lesions corresponds closely with the parts exposed to sunlight; the face and backs of the hands suffer most, the neck, the upper part of the chest, the forearms and dorsal surfaces of the feet are less severely affected, and only if the children have been allowed to go out with bare legs does the skin of the legs become greatly altered. Lesions on the covered parts are relatively uncommon and usually trifling.

In some families brothers and sisters of children who have the disease are heavily freckled, but are otherwise normal. It has been suggested that this type of freckling (which, unlike ordinary freckles, shows no correlation with red hair) indicates a person who is heterozygous for the gene of xeroderma pigmentosum. If this is true, the marriage of two such persons will stand a chance of one in four of producing afflicted children, since the numerous pedigrees clearly show that the disease is due to a single recessive gene.

VON RECKLINGHAUSEN'S DISEASE (*Neurofibromatosis*)

This particular type of tumor is usually inherited as a single dominant, although in a few families some other explanation seems necessary. Cockayne gives a lengthy discussion of the disease with numerous pedigrees.

The most common lesions are large pigment spots in the skin, with multiple tumors of the skin and peripheral nerves. Less often the brain, spinal cord, and sympathetic nervous system become tumorous. The pigment spots may be present at birth, but the tumors usually do not appear until puberty or later. The tumors frequently develop into cancers and cause death.

Other abnormalities such as mental deficiency and defects of the reproductive system often accompany the tumors. In general, the disease is so serious that relatively few who suffer from it marry and have children. It is, therefore, constantly tending to eliminate itself from the population. The fact that it is not so rare as some less serious diseases indicates that independent mutations continue to occur.

CANCER OF THE STOMACH

Cancer of the stomach is the most common type of malignant tumor. Its tendency to afflict certain families has long been noted. The most famous example is that of the Bonaparte family. Napoleon I, three of his brothers and sisters, and his father all supposedly died of cancer of the stomach. A number of pedigrees are reproduced by Baur, Fischer and Lenz. One of these, originally published by Paulsen, is shown in Fig. 48.

It is noted that both parents and six of the seven children died of cancer of the stomach, and all at about the same age, as indicated by the numbers in the pedigree. The one son who escaped died from an accident at 28.

The frequency with which similar pedigrees have been discovered makes it highly improbable that they are merely chance occurrences. The importance of the role of environmental factors in cancer of the stomach is not clear. It is of course conceivable that some external agent might account for the attack of an entire family by cancer as illustrated in Fig. 48, but the advanced age at which the cancer develops makes this seem very unlikely. Lenz thinks that stomach cancer "develops by preference upon the soil of an old gastric ulcer," and that in part, therefore, the hereditary predisposition is identical with that of gastric ulcer. Julius Bauer, in a study previously cited, found that cancer of the stomach was almost four times as frequent in families of ulcer patients as in families of controls. Lenz concludes that cancer of the stomach in man is probably dominant in character.

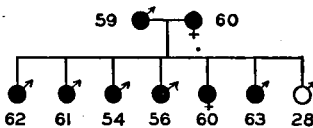


FIG. 48. Pedigree showing cancer of the stomach. The numbers indicate the age at death. The male who died at 28 was killed by accident. (Courtesy, BAUR, FISCHER, and LENZ after Paulsen.)

TUMOR OF THE EYE (*Retinal Glioma*)

This is a rare type of malignant tumor which develops in infancy, leading as a rule to a rapidly fatal end. According to Lenz, about 30 families have been studied in which retinal glioma occurred in several brothers and sisters. The pedigrees lead him to think that it is inherited as a recessive.

NERVOUS SYSTEM

In man the nervous system reaches a superlative degree of complexity. Its functions are intricate and diverse, ranging from the detection of all manner of stimuli and the regulation of muscular and glandular activities to the highest mental processes of the brain. The great development of that part of the brain concerned with conscious and voluntary activities (cerebrum) constitutes man's chief claim to superiority over all other forms of life.

Among individuals who are regarded as normal the nervous system shows great variability, and the normal grades downward by imperceptible stages into the abnormal. Included in the latter category we find a long list of variations consisting of defects and diseases of many sorts. Some of these exhibit marked physical signs and symptoms. Others are detectable at present only from the abnormal behavior of affected individuals, although undoubtedly they rest on physical changes in the nervous system, in the glands of internal secretion, or in other parts of the body.

Let us first consider an example of a normal hereditary difference which apparently has no adaptive significance. This will be followed by a description of a few of the best known hereditary defects and diseases of the nervous system. Afterwards will come a brief discussion of the inheritance of special talents. For further details and additional examples the reader is referred to the extensive discussion and literature citations by Lenz and to the comprehensive work of Rosanoff of Los Angeles.¹⁶

TASTERS AND NON-TASTERS

In 1931 Arthur L. Fox,¹⁷ an American chemist, discovered that persons differ in a striking way in their ability to taste a chemical substance known as phenyl-thio-carbamide ($C_7H_7N_2S$). This fact was soon confirmed by other investigators. To most persons (about 70 per cent of Caucasoids) this substance is very bitter. Nearly all the others detect no taste, although occasional individuals report a sour, sweet or salty taste.

¹⁶ "Manual of Psychiatry and Mental Hygiene," by AARON J. ROSANOFF, 7th ed., 1938, John Wiley and Sons, Inc.

¹⁷ Fox, A. L.: *Science (Suppl.)*, 73:14, 1931.

In the same year of Fox's discovery, Professor L. H. Snyder¹⁸ of Ohio State University concluded from his studies of parents and children in 100 families that the taste deficiency was inherited as a single recessive. A. F. Blakeslee and M. R. Salmon¹⁹ of the Carnegie Institution independently reached the same conclusion. The latter investigators found no connection between the ability to taste this substance and the ability to taste ordinary bitter substances such as quinine. They also reported extreme variability in the acuity of taste for phenyl-thio-carbamide in different persons. Differences in taste discrimination and taste acuity for other substances also were found.

A number of other investigators subsequently have shown that there is a racial difference as to frequency of tasters and non-tasters for phenyl-thio-carbamide. The percentage of tasters among Negroes seems to be slightly higher than among Whites: tests of Negroes from Alabama gave 76.5 per cent tasters. Mongoloids have much the highest proportion of tasters. American Indians, Chinese, and Japanese are all very similar, ranging from about 90 per cent to 95 per cent tasters.

The physiological basis for this hereditary taste difference is still unknown, but its existence is highly interesting and important because it demonstrates the possibility of human beings living in different sensory worlds. We know of many other respects in which individuals differ in their sensory perceptions, including those of color, sound, and odors. It is highly probable that differences in taste—where taste is used in the figurative sense to denote a decided preference for one thing over another—may often depend upon physical differences in the nervous system. The old saying that “regarding tastes there can be no argument” thus appears to rest upon a sound biological basis.

DEAFNESS

Deafness may result either from environmental or hereditary causes. Babies are sometimes born deaf as a result of infection with syphilis from the mother. Children are frequently rendered

¹⁸ SNYDER, L. H.: *Science*, 74: 151, 1931.

¹⁹ BLAKESLEE, A. F., and SALMON, M. R.: Odor and taste blindness, *Eugenical News*, 16: 105, 1931.

deaf by infections such as meningitis, influenza, and scarlet fever. Injuries sometimes cause deafness. Where deafness results from infection or injury it is not transmitted to the offspring.

Many cases of congenital deafness and of deafness appearing in later life are hereditary, the gene in some way causing an imperfect development of the internal ear or the middle ear, or causing the later degeneration of these structures. *Hereditary congenital deafness* (due to imperfect development of the internal ear) has been studied extensively, and the conclusion has been reached that two distinct recessive mutations have occurred on different chromosomes. Deafness develops when either recessive gene is present in the homozygous state. In most cases the deaf person has only one pair of these genes. If he should marry a deaf partner who has the other pair of recessives the children should all have normal hearing. They will, however, be heterozygous in both pairs and thus likely to produce deaf children if they marry persons who are heterozygous for either gene. Genetically, it is apparent that this case in man is identical with the sweet pea case described in Chapter 5.

Certain other types of hereditary deafness have their onset in middle age. Among these are *auditory nerve atrophy*, and *otosclerosis*. Atrophy of the auditory nerve begins at about 40, and may progress for several years until complete deafness results. It is apparently due to a dominant gene. Otosclerosis is a type of progressive deafness having its onset at about 30; the hearing gradually diminishes, but is not entirely lost. It is usually accompanied by subjective buzzing or ringing in the ears. The immediate cause is an abnormal growth of bone about the ear bones of the middle ear. In some families otosclerosis is inherited as a dominant.

HEREDITARY MUSCULAR ATROPHY

Under the above designation ten or more distinct diseases have been described. In some, the muscles themselves seem to be primarily affected. In others, the seat of the trouble is in the nervous system. Destruction of a cell body of a motor neuron in the brain or spinal cord, whether the result of a virus infection like infantile paralysis, of a wound, or of a gene, leads to a degeneration of its nerve fiber and the muscle cells supplied by the fiber.

The different forms of muscular atrophy are distinguished in part by the various muscle groups affected.

Hereditary muscular atrophy usually involves a progressive wasting of the muscles, so that the afflicted person becomes steadily weaker until finally he is helpless. During this process the muscles may appear to increase in size owing to the accumulation of fatty tissue. The symptoms become evident at different ages, varying from early childhood to middle age according to the type of the disease. Death commonly ensues in some forms within a few years of the onset of the symptoms.

In the severer forms, muscular atrophy is inherited as a recessive, but pedigrees of milder forms have frequently been published indicating dominance. Sex-linked recessive types also have been described.

HEREDITARY SPINAL ATAXIA (*Friedreich's Disease*)

The first symptoms of this disease, which usually appear before the age of 20, point to defective muscular control. In the standing position the body sways, and with the eyes closed the victim is not able to stand at all. The gait in walking resembles that of a drunken person. In the advanced stages the patient loses completely the power of independent movement, becoming a helpless invalid. The cause of these symptoms seems to be a degeneration of the sensory neurons in the spinal cord with the consequent loss of sensations from the muscles.

A recessive type of the disease with onset at an early age is said to be comparatively common in certain valleys in Switzerland where much inbreeding has taken place.

A milder form of ataxia in which the degeneration is centered in the brain rather than the cord, and which is inherited as a dominant, has been reported a number of times.

PARALYSIS AGITANS (*Parkinson's Disease*)

This disease, known also as shaking palsy, is characterized by the involuntary movements of the fingers, the rhythmic nodding of the head, and a peculiar stiffness of the muscles. The symptoms fluctuate with the emotional state of the affected individual: they are exaggerated under stimuli tending to cause excitement. The

face has an immobile expression owing to rigidity of the facial muscles, and the head and trunk are carried bent slightly forward. It is often found in persons of superior physique and mental ability and in the milder forms does not seem to interfere seriously with the capacity for mental work.

The symptoms seldom make their appearance before 40 and usually not later than 60. The late onset of the disease makes the securing of pedigrees difficult. Some authors accordingly consider that heredity has little to do with it. Lenz takes the view that heredity is the principal cause and that environmental factors have little if any effect in the development of the disease. Maloy states that he has seen several persons with paralysis agitans whose fathers or mothers were similarly affected.²⁰ Such families suggest a dominant heredity.

HUNTINGTON'S CHOREA

This is one form of St. Vitus's dance, a classical description of which was given by Huntington of Ohio in 1872. It develops usually during the thirties or forties, although not infrequently at earlier or later ages. The early symptom is persistent twitching of the head, limbs, and trunk, which tends to grow worse as time passes; mental deterioration commonly ensues. The physical changes in the nervous system are brain atrophy with disappearance of nerve cells in the cerebrum.

Many pedigrees have been collected in this country and Europe which clearly show that it is inherited as a single dominant. There is no known preventive or cure. Owing to the wide variability in age of onset of Huntington's chorea, Rosanoff recommends that not only patients afflicted with the disease but also their seemingly healthy brothers and sisters should forego having children.

FEEBLEMINDEDNESS (*Mental Deficiency*)

Feeble-mindedness is a condition of abnormally low intellectual capacity existing from birth or an early age, caused by abnormal development of the brain, or destruction or degeneration of brain cells. It is not a single biological entity. There are many degrees

²⁰ "Nervous and Mental Diseases," by BERNARD S. MALOY, 1935, Bobbs-Merrill Co.

of feeble-mindedness ranging from idiocy, in which the mental capacity is so low that the afflicted individual may not even be able to dress or feed himself, through stages of increasing capacity finally shading imperceptibly into low grade normal mentality.

The range of variability in mental capacity is much greater than the range for physical differences such as height, head form, and weight. Based upon the scores made in standardized "intelligence" tests, it is found that the population in general varies in accordance with the normal probability curve. By definition, an intelligence quotient (I.Q.)²¹ of 100 is the mean. About 50 per cent of the population have I.Q.'s between 90 and 110, with about 25 per cent below 90, and 25 per cent above 110. According to Rosanoff, those with an I.Q. below 70 are more or less arbitrarily classed as subnormal; those between 70 and 80 are "borderline" cases; and those between 80 and 90 are "dull normal." Individuals with an I.Q. between 50 and 70 are classed as morons; those between 20 and 50 as imbeciles; and those below 20 as idiots. A few superior individuals have an I.Q. as high as 180 or higher.

As pointed out by Rosanoff, the intelligence score is based upon an average of several abilities in which the individual may show uneven development, while certain special abilities such as musical, artistic, and mechanical are not tested at all. A low I.Q. sometimes accompanies high proficiency along one of these special lines.

There is no general agreement as to what is meant by intelligence. The so-called intelligence tests have usually aimed to test innate mental capacity rather than the knowledge acquired by experience, but it is recognized that no test yet devised eliminates the latter factor. Moreover, it is an obvious fact that intelligence is not a single unit, but that many separate abilities exist. The present task of psychologists, in which a good beginning has been made, is to analyze intelligence into these special abilities, and to devise means of measuring each by itself. After this is done it may be possible to show how these separate abilities are inherited. If we may judge from what we know of the inheritance of physical

²¹ The I.Q. is found by dividing the mental age, as indicated by standard tests, by the chronological age and multiplying by 100. For example, if a child has a mental age of ten and a chronological age of eight, his I.Q. is $1\frac{2}{8} \times 100 = 125$.

characteristics, we may anticipate a certain amount of independence among the mental abilities in their mode of inheritance.

The lowest grades of the feeble-minded are usually abnormal physically. The microcephalic idiots ("pin-heads") constitute a conspicuous type in which the skull, and necessarily the brain, are extremely small. According to Lenz, feeble-mindedness shows itself above all in abnormal smallness of the skull, and although occasionally an idiot has an unusually large head, persons with distinct microcephaly are invariably feeble-minded. This, of course, does not mean that a large brain always goes with high mentality, nor *vice versa*. The quality of the brain, as well as its quantity, is important. Some very superior persons have brains smaller than the average. Furthermore, the size of the brain is correlated positively with the size of the individual as a whole.

The majority of feeble-minded individuals probably owe their misfortune to defective heredity, but congenital syphilis is said to be responsible for a considerable number. Other environmental factors, such as injuries at birth and various infections, are at times to blame. In the discussion which follows, hereditary types of mental deficiency alone are considered.

In most pedigrees feeble-mindedness seems to be inherited as a recessive, probably due to several genes; in some pedigrees it appears to be dominant. In this, as in other defects, Lenz points out that the milder forms tend to be dominant, and the severe forms recessive. A large percentage of idiots have normal parents, whereas the high grade feeble-minded often have feeble-minded parents. The most severe type, idiocy, could not result from a single dominant gene since idiots are usually incapable of reproduction. The high grade feeble-minded, on the other hand, are often unduly prolific.

The question of the part played by heredity in determining the intelligence of normal individuals is dealt with in connection with the study of twins (Chapter 12).

AMAUROTIC IDIOCY

Amaurotic idiocy (*amaurosis*, blindness), of which several types have been described, is characterized by a progressive degeneration of the central nervous system. It differs markedly

from other types of idiocy. The disease is hereditary, and there is no known preventive or cure. The two most common types are designated as infantile and juvenile, respectively, in accordance with the age of the patients.

In *infantile amaurotic idiocy*, according to Dr. Rosanoff, the following symptoms are characteristic. The subjects seem normal and healthy at birth, but between four and eight months the disease becomes manifest. The course is steadily progressive, and death usually ensues before the end of the second year of life. There is early impairment of vision, soon leading to blindness; a rapidly growing general muscular weakness; frequently, epileptiform convulsions; and gradual emaciation. Post-mortem findings consist in very widespread and highly characteristic changes in the nerve cell bodies throughout the central nervous system, including the spinal root ganglia.

The disease is inherited as a single recessive. A large percentage of the cases arise from the intermarriage of relatives.

In *juvenile amaurotic idiocy* the child is normal until five to eight years of age. The early symptoms are a steady and rapid loss of vision. At the end of a year or two the patient is able merely to distinguish intensities of light or to count objects at close range. A fairly rapid mental deterioration, accompanied by marked speech disturbances, sets in, along with loss of vision. Later, progressive motor disturbances of posture and gait appear. There is finally extreme emaciation with almost complete obliteration of mentality. Death usually occurs between 14 and 22 years.

The pathological changes in the nerve cells parallel those in the infantile type; nevertheless the two diseases are considered as genetically distinct. The juvenile type is also inherited as a recessive. Cousin marriages are frequent among the parents of patients.

SCHIZOPHRENIA (*Dementia Praecox*)

Schizophrenia (*schizo*, divided; *phrenia*, mind) is a term originated by a German, E. Bleuler, to replace the older name, dementia praecox, used to designate a certain type of mental disease which is said to affect from 0.5 per cent to 1 per cent of the population, and to account for more than one-half of all patients in mental hospitals. Bleuler's reason for suggesting the change in name is

set forth in the following quotation from an English translation of a book by Bleuler, as reported by Rosanoff:

As the disease needs not progress as far as dementia and does not always appear praecociter, i.e., during puberty or soon after, I prefer the name *schizophrenia*.—This disease may come to a standstill at every stage and many of its symptoms may clear up very much or altogether; but if it progresses, it leads to a dementia of a definite character.—It is characterized by a specific kind of alteration of thinking and feeling, and of the relations with the outer world that occur nowhere else.

Lenz describes the disease and its symptoms in the following quoted paragraphs.

The trouble usually begins in the second or third decade of life, but sometimes later. There are various forms of the disorder; common to them all, however, is an extensive failure of the affective or of the voluntary life. In most cases, too, there is a more or less marked failure of the intellectual powers.

The patients are subject to purposeless impulses and purposeless inhibitions. Irregular impulses to movement may prove fatal; but in other cases there is an irremediable hebetude [dullness] and a failure of will power, as we see in the severest form of the disease, which is known as catatonia . . .

Persons suffering from a schizophrenic taint usually show slight mental anomalies before the actual outbreak of the disease. We note in them a certain blunting of the affective and voluntary life. On the other hand, in the families to which persons suffering from schizophrenia belong, we can usually detect the presence of "schizoid" psychopaths, who may never become affected, and indeed usually do not become affected, with well-marked schizophrenia. Most of the persons who are commonly spoken of as "eccentric," persons who are shy, unsociable, self-centered, reserved, cold, and devoid of a sense of humor, belong to this category. The Bavarians have a way of saying that some one "is spinning," and the term applies aptly to these minor degrees of schizophrenia. A schizophrenic condition may well be compared with spinning after the old style, the spinner being one who spends hour after hour twisting a thread, repeating the same movements over and over again and having no contact with the outer world. For the schizoid psychopaths who wrap themselves up in their own qualities, a comparison to a caterpillar which invests itself in a cocoon of its own spinning may be regarded as apter still.

According to Rosanoff, no anatomical change has been found in the brain of persons suffering with schizophrenia. Physiologically, it is probable that schizophrenia develops as a metabolic disturbance, since, as has been discovered recently, the administration of repeated overdoses of insulin large enough to reduce the blood sugar to the point of shock and unconsciousness may remove the symptoms, especially if the treatment is begun in the early

stages of the disease. Repeated electric shocks and administration of the drug metrazol have similar beneficial effects.

As to the relationship between schizophrenia and heredity, Lenz concludes from his review of the extensive studies of family histories of the disease in Germany that in all cases there is a basic hereditary predisposition. He does not regard schizophrenia as a single biological unit, and thinks that different types may be inherited differently.

Some investigators have attributed it to two pairs of recessive genes; others have considered it a single gene case. The final answer to this question is one for future investigation.

There is some evidence that a person who is heterozygous for the gene or genes of schizophrenia shows abnormal symptoms, that is, that he is of the "schizoid type." But it is not certain that carriers can always be diagnosed. Owing to the high frequency of schizophrenia in the population at large, the percentage of carriers must be high.

In a recent book Kallmann²² has described extensive studies of pedigrees of schizophrenia. He agrees that it is inherited as a recessive, but does not decide whether it is due to a single gene or not. This difficulty of analysis is due in part to the fact that external conditions are important in calling forth the expression of the genes; about 30 per cent of all persons who are thought to have the genes making them susceptible to schizophrenia do not actually develop it. Just what these external factors are is not known. Obviously it would be highly important to find out.

Rosanoff points out that the term schizophrenia, as heretofore applied in diagnosis in no sense implies a definite pathological entity, since under this particular name has been included mental disease of adolescence and early adult ages resulting from injuries to the brain during childbirth or later, or injuries due to acute infections involving the brain. A large percentage of the cases of schizophrenia, he is convinced, are due to internal conflicts resulting from repressed homosexuality. From his study of family histories and the frequency with which both members of a pair of identical twins develop schizophrenia, if either one develops it,

²² "The Genetics of Schizophrenia," by FRANZ J. KALLMANN, 1938, New York, J. J. Augustin.

he would judge that hereditary factors are the essential if not the sole causes of such "chaotic sexuality." Quoting Rosanoff:

Up to the present time experience has not been encouraging as to the possibility of modifying to a material extent a person's abnormal psychosexual make-up; but in most cases the prospect is good for attaining a more or less satisfactory life adjustment, either spontaneously or with medical assistance.

MANIC-DEPRESSIVE PSYCHOSES

Dr. Rosanoff defines the above term as follows:

. . . a group of constitutional mental disorders in which the disturbances are primarily and mainly in the sphere of the emotions. They are characterized by attacks of excitement, or depression, or of mixtures of the elements of both; each attack generally terminates in recovery, but leaves behind a tendency toward recurrence.

During the depressive or melancholic phase the sufferer often seriously considers ending his own life as a means of escape from his mental suffering, and not infrequently does so. William Cowper, the famous English poet of the eighteenth century, who suffered several attacks of the disorder, attempted to take his own life, and was saved only by an accident. Robert Mayer, the great German physicist of the nineteenth century, discoverer of the law of the conservation of energy, who was a periodic victim of the disease, made a similar unsuccessful attempt. As is proved by the cases mentioned, and by others that could be cited, the disease does not spare those of superior mental ability. Contrary to what many persons suppose, however, there is no proof of a positive correlation between genius and insanity.²³

As with schizophrenia, no evidence of pathological changes in the tissues of the brain has been discovered. Some authors think that the root of the trouble may be a disturbance in the endocrine glands of a susceptible individual brought on by some great loss or disappointment.

Many persons are subject to alternate moods of depression and elation of a mild degree, some much more than others. The point at which this tendency ceases to be considered normal cannot be sharply defined.

Manic-depressive psychoses are from one and one-half to two times as frequent in females as in males. The first attack

²³ EAST, E. M.: Insanity and genius, *J. Heredity*, Aug. 1938.

usually occurs between 20 and 50; in persons past 50 the chance of an attack steadily decreases.

As to the rôle of heredity in manic-depressive psychoses, Rosanoff has this to say:

In the etiology of manic-depressive psychoses *hereditary factors* seem to play a very important part. Among students of the subject there is almost a complete consensus that manic-depressive psychoses are "the most hereditary" of all the commoner psychoses. This is based on many genealogic studies and is borne out by observations in monozygotic twins. In such twins with manic-depressive psychoses there is concordance of findings (i.e., both twins affected) in 69.6% of the cases; the corresponding figure for so-called schizophrenic psychoses is 61.0%; and for epilepsy it is but 52.2%.

However, the high percentage of discordant findings (i.e., only 1 twin of the pair affected) proves that the hereditary factors, in themselves, are often inadequate, i.e., they do not suffice to produce a manic-depressive psychosis: the *etiologic mechanism* is evidently *not simple*, as it is in Huntington's chorea, amaurotic family idiocy, or hereditary mental deficiency, *but complex*; for, as all know, the environmental factors, including those of psychogenic nature, that are so often mentioned in the case histories, are also in themselves inadequate.

The mode of inheritance of manic-depressive psychoses is not fully demonstrated. Pedigree studies indicate dominance, but the number of affected persons is smaller than would be expected in a single gene case. This deficiency is readily explainable if an environmental factor—which may not make its appearance—is also necessary. The lateness of appearance of the disease makes difficult the study of pedigrees. Rosanoff suggests that two dominant genes (one of which is located on the X chromosome) are necessary for the development of the disease. This he thinks best fits the facts, including the excess of cases among women as compared to men. Lenz, however, explains the higher prevalence of the disease in women as the result of the general physiological differences in the two sexes, pointing out that the endocrine glands probably play an important rôle in the chain of events leading to the development of the disease.

SPECIAL TALENTS

There are many special abilities including mechanical ability, musical ability, and ability in other artistic lines that are not measured by the ordinary "intelligence tests." Rosanoff says:

Not a few subjects, who have a mediocre or even a subnormal intelligence, possess at the same time a high degree of mechanical ability. . . . Some children

display a strong interest in music and seem to be specially gifted with musical talent. There does not appear to be a high degree of correlation between musical ability and general intelligence; and quite outstanding musical ability has been noted in subjects of mediocre and even subnormal intelligence; on the other hand, subjects of very superior intelligence have been known to be totally lacking in musical appreciation or ability.

Conversely, persons of high intelligence and lively imaginations may have well developed powers of appreciation of music with little or no inclination toward or ability in musical expression.

All that has been said of music probably could be said of other artistic lines—drawing, painting, and sculpture. Such statements apply primarily, however, to the imitative and performing phases of the arts, for there is no good evidence that a person of subnormal intelligence can become a great inventor, a great composer, or a great painter. The statement attributed to Turner who, in answer to the question as to what he used in mixing his paints, replied “brains,” is probably true for all great creative artists.

MUSICAL ABILITY

Musical ability is far from being a single unit, but depends at least upon the following factors: (1) sense of pitch, (2) sense of loudness, (3) sense of time or rhythm, (4) sense of harmony, (5) sense of sequence of tone or melody, and (6) memory. These all exist as independently measurable capacities.^{24,25} A successful composer must have, in addition to these, strong powers of imagination and the ability to put his mental creations on paper.

In view of the complex nature of musical talent, we should not expect it to be inherited in any simple way. That heredity is an important factor, however, is beyond dispute. The early age at which special musical ability often makes its appearance, and the persistence of the urge to musical expression, frequently in the face of severe discouragements, is strong evidence of the hereditary factor. The particular line of expression of the talent and the degree of its development depend, of course, to a large extent upon the immediate cultural surroundings and opportunities for expression.

²⁴ SEASHORE, CARL E.: New vantage grounds in the psychology of music, *Science*, Dec. 11, 1936.

²⁵ SEASHORE, CARL E.: Science in music, *Science*, Apr. 24, p. 417, 1942.

Many pedigrees of musical families have been published, but since musical talent probably depends upon the cooperation of several genes, it is not surprising that such pedigrees offer difficulties of interpretation in Mendelian terms. One of the most noted of such pedigrees is that of the Bach family (Fig. 49), published by Mj oen.²⁶

Apparently, little is known about the females in the early generations of the Bach pedigree, since they are not even indicated on the chart. A strong tendency for musicians to marry musicians,

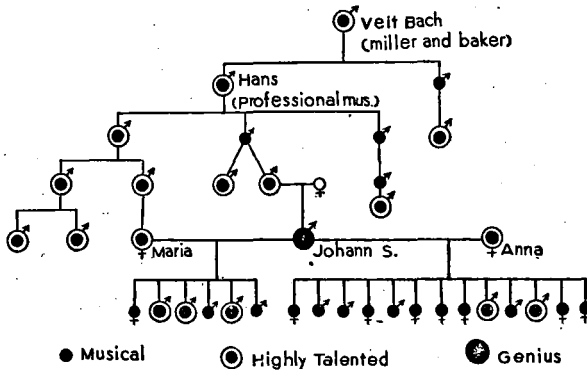


FIG. 49. Pedigree of the Bach family through six generations, showing unusual musical talent. (After Mj oen.)

however, has long been known to exist, and this may have played a part in the piling up of musical ability in the Bach family. Both of the wives of Johann Sebastian Bach were musical. Bach and his first wife, Maria, were second cousins, both having a great-grandfather in common in the male line. From this marriage, 50 per cent of the children showed eminent musical ability. All 19 of Bach's children are indicated as more or less musical.

It is interesting to note that Johann Sebastian Bach was the son of a member of a pair of identical twins, of whom Bach's son wrote, "They resembled one another so closely that even their wives could not tell them apart . . . In speech, in mood, in everything, they were alike. In music, too, you could not distinguish them, so like was their execution, so like their interpretation"

²⁶ Mj oen, Jon A.: Genius as a biological problem, *Eugenics Rev.*, V. 17, No. 4, 1926.

(Lenz). This in itself is evidence of the part played by heredity in musical ability.

Mjöen also gives a pedigree of the Mozart-von Weber family and one of the Backer-Lunde-Gröndahl family, showing musical ability running through several generations, although on a less grand scale than in the case of the Bachs. From his studies of these and many other families, Mjöen concludes in the following words:

The higher the average talent of the parents, the higher the average talent of the children. In our material "very talented" parents have no "untalented" children, and "untalented" parents no "very talented" children.

Regarding the manner of inheritance of musical talent, Mjöen states that his studies give little information.

DRAWING, PAINTING, AND SCULPTURE

Relatively little can be said about the inheritance of talent in the graphic and plastic arts. Although inherited differences undoubtedly exist, they have received much less attention than in the case of music. This is due in part to the much greater number of musicians than of artists in other lines. It is well known that the powers of discrimination with reference to color, line, and form, and their graphic representation depend to a certain extent upon innate capacity, although of course these powers are highly influenced by training. The existence of inborn differences is borne out by observation of very young children in their attempts to draw and paint. Children who receive the same training in drawing, painting, and sculpture continue to differ markedly in their ability in these arts.

Pedigree studies for the graphic and plastic arts seem to be very few. An early investigation by Francis Galton,²⁷ founder of the scientific study of human heredity, disclosed that the famous Italian painter Titian (1477-1576), had eight relatives who were good painters.

MATHEMATICAL ABILITY

Special aptitude in mathematics seems to be inherited, often independently of ability in some other directions, such as ability in literary and philosophical expression. Occasionally, remarkable

²⁷ "Hereditary Genius," by FRANCIS GALTON, 1869, New York, Macmillan Co.

ability in rapid mental calculating—explainable largely as an innate capacity—makes itself evident at an early age.

The Bernoulli family of Swiss mathematicians of the seventeenth and eighteenth centuries is noteworthy for the number of its members who made original contributions to mathematics. According to Galton, there were eight men in this family in three generations, as shown in Fig. 50, who possessed special mathematical ability. Five became members of the French Academy. One was early destined for the church and two for business, but they left these occupations to become mathematicians.

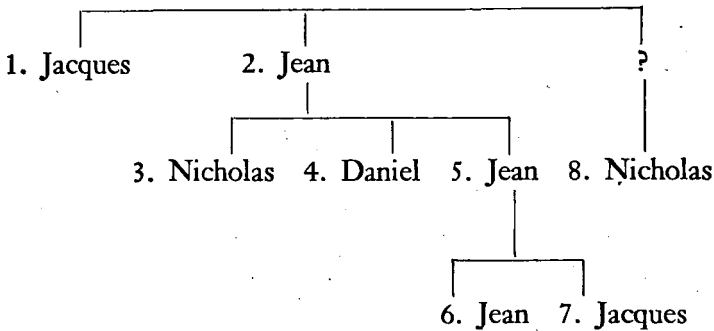


FIG. 50. Pedigree of the Bernoulli family of mathematicians. (After Francis Galton.) (For explanation see text.)

Following Galton's account, the characteristics of the individuals in the pedigree are summarized briefly as follows:

1. **JACQUES.** Early destined for the church. Accidentally became acquainted with mathematics. Slow but sure. A mathematician of the highest order in originality and power. Member French Academy.

2. **JEAN.** Destined for commerce, but left it for science and chemistry. French Academy.

3. **NICHOLAS.** A great mathematical genius.

4. **DANIEL.** Physician, botanist, anatomist, writer on hydrodynamics; very precocious. Obtained ten prizes. French Academy.

5. **JEAN.** Jurisconsult, mathematician, and physicist. Obtained three prizes of the Academy. Member French Academy. Destined for commerce but hated it. Loved oratory.

6. **JEAN.** Astronomer, mathematician, and philosopher. Wrote many works.

7. JACQUES. Physician and mathematician. Drowned at 30.
8. NICHOLAS. Mathematician. French Academy.

PROBLEMS

1. How may one explain the fact that the list of known dominant traits in man is longer than the list of known recessive traits, while the opposite is true for most experimental plants and animals?

2. Calculate the expected ratios among the children from matings of persons of the following blood groups: (Show phenotypes as well as genotypes.)

(a) $O \times A (I^A i)$

(b) $O \times AB$

(c) $A (I^A i) \times A (I^A i)$

(d) $A (I^A i) \times B (I^B I^B)$

(e) $A (I^A i) \times B (I^B i)$

(f) $A (I^A I^A) \times AB$

(g) $B (I^B i) \times AB$

3. Are there any cases in which it is possible, knowing the blood group of a child, to state positively the blood group of its parents?

4. If matings are at random with respect to the blood types what percentage of marriages among Caucasoids in the United States should be $M \times M$; $M \times MN$?

5. In a case of disputed parentage the baby was of blood type N, and the mother was of type MN. State all that you can about the type of the father.

6. In a case of disputed parentage two babies were of types MN and N, respectively. Their mothers also were of types MN and N, but it was uncertain to which mother either baby belonged. The husband of woman MN was of type N; the husband of woman N was of type M. To which mother did the type N baby belong?

7. If marriages are at random with respect to the Rh factor, what is the chance that a marriage of Caucasoids in the United States will be such that the child may suffer from erythroblastosis?

8. What is the chance that a marriage of Negroes in the United States will be such that a child may suffer from erythroblastosis? Assume random matings with respect to the Rh factor.

9. If matings are at random with respect to the Rh factor the frequency of gene r among Caucasoids should equal $\sqrt{15}$ per cent or approximately 39 per cent, since an Rh negative person results from the chance union of an egg carrying gene r with a sperm carrying gene r . The frequency of gene R should then be equal to the difference between

100 per cent and 39 per cent or 61 per cent. What percentage of Rh positive Caucasoid men in this country should be homozygous for gene *R*?

10. Make a list of normal human traits for which there is good evidence of Mendelian heredity. (By normal differences we mean those which are not pathological, that is, those that do not handicap the individual in his usual environment.)

11. Suggest a reason for the fact that the most extreme types of hereditary defect in man which are either congenital or that develop in the first few years of life, e.g., amaurotic idiocy, are recessive, whereas equally serious defects, e.g., Huntington's chorea, that usually develop in middle life, are often dominant.

12. Make a list of non-adaptive differences distinguishing the races of mankind, i.e., differences that have no survival value.

13. Make a list of adaptive differences between the races of mankind, i.e., differences that fit their possessors to their respective environments.

14. List the special difficulties involved in identifying hereditary traits in man and in analyzing the mechanism of their inheritance.

SEX DETERMINATION AND SEX DIFFERENTIATION

AS A RESULT of investigations made since the resurrection of Mendel's paper, we now know that sex is a characteristic which follows the law of segregation. Mendel himself, in a letter to the botanist Nägeli, had suggested this as a possibility. The final solution of the problem of sex determination was, in fact, a logical outgrowth of the discovery of Mendel's first law.

The importance of sex in the biological world, including the world of human affairs, can hardly be overestimated. Since ancient times men have speculated on the causes of sex differences, and the great number of earlier theories revolving around sex goes to show how inadequate these theories proved to be.

Before the mechanism of heredity became known, the theories of sex determination usually emphasized the *external* environment rather than the *inherent* nature of the reproductive cells. Thus, at various times, it had been maintained that the sex of the child was determined by the relative vigor of the parents, by their relative ages, by the nutrition of the mother, by the season of mating, by the ripeness of the egg (time elapsed between the release of the egg from the ovary and its fertilization by the sperm), by the particular ovary or testis (right or left as the case may be) which produced the egg or sperm, etc. None of these environmental factors, however, had stood the test of critical examination. Therefore, investigators finally turned their attention to the internal mechanism of the cell, where eventually they found the true explanation.

CHROMOSOMES AND SEX DETERMINATION

The first definite suggestion of a chromosome mechanism for the determination of sex came from Professor C. E. McClung, an

American zoologist, who observed in 1902, while studying the cells of grasshoppers, that one of the chromosomes of the male always lacked a mate. The male thus possessed an odd number of chromosomes, in contrast to the even number in the female, in which sex all of the chromosomes occurred in pairs. Such odd chromosomes had been observed previously in males of several insects by various investigators, but without anyone connecting them to the determination of sex.

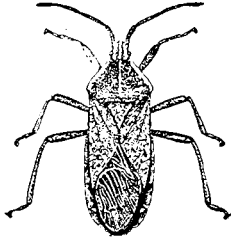


FIG. 51. A squash bug, *Anasa tristis*, one of the species which furnished the material for proof of the chromosome theory of sex determination. (Courtesy, ROBERT W. HEGNER: "College Zoology," 4th ed., New York, The Macmillan Co.)

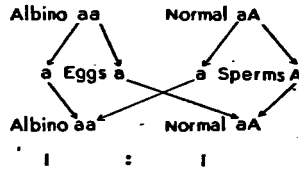
McClung suggested that as a result of the odd number of chromosomes in the male the reduction division must lead to the production of two kinds of sperms—those with the odd chromosome and those without it—and that the two kinds of sperms should occur in equal numbers. All the eggs would be alike in chromosome number, and eggs fertilized by one kind of sperm should develop into one sex, while those fertilized by the other kind of sperm should develop into the other sex, thus accounting for a

sex ratio of 1:1. McClung therefore called the odd chromosome the "sex-determiner."

It was not until 1905, however, that two other American biologists, Professor E. B. Wilson of Columbia University and Miss N. M. Stevens of Bryn Mawr College, added the final visible proof of the chromosome theory of sex determination by demonstrating that chromosome distribution follows a course exactly parallel to that of sex distribution.¹ A chromosome homologous to the unmated chromosome of the male (later dubbed by Wilson the "X" chromosome) was identified in the female also, but always present in pairs. One of the species used in these classic investigations was the ordinary squash bug (*Anasa tristis*) shown in Fig. 51. The chromosomes in the two sexes of

¹ "The Cell in Development and Heredity," by EDMUND B. WILSON, 3d ed., 1925. New York, Macmillan Co. This book is the greatest classic in the English language on the topic indicated by its title.

This mechanism—which could hardly be simpler—is perfectly adapted to account for the production of equal numbers of each sex, since the eggs are all alike, and since the two kinds of sperms (X and O) are formed in equal numbers. If the preceding diagram is compared to that of a back-cross mating in an ordinary Mendelian case such as the one below, the essential likeness of the two with the resulting 1:1 ratio is obvious.



Upon examination of the cells of many animals, the foregoing type of chromosome arrangement was found to be a very common one, especially in certain insects and nematode worms.

In 1905 Wilson described a slightly different type of chromosome arrangement in a number of other insects; namely, a condition in which both sexes had the same *even number* of chromosomes, the female having two X's and the male one X paired up with a much smaller "Y." The sexes in such cases are therefore designated: XX = female; XY = male. Wilson regarded this as the more primitive condition, from which the XO condition had evolved. Obviously, a gradual reduction in the size of the Y chromosome in a species and its final complete elimination would result in the XO condition.

Recently Professor J. T. Patterson and coworkers of the University of Texas have made a thorough study of the *Drosophilidae* of Southwestern United States.² They report that in 42 of the 88 forms studied the Y chromosome is morphologically distinguishable from the X in the metaphase configuration (Fig. 53). Two XO types were found (see *orbospiracula* in Fig. 53). In *Drosophila* they are able to detect almost a continuous range of variation, ranging from species in which the Y is larger than the X to species which have no Y chromosome. For us, the chief interest in the discovery of the XY arrangement is that we ourselves, in

² "Studies in the Genetics of *Drosophila* III. The *Drosophilidae* of the Southwest," directed by J. T. PATTERSON, University of Texas Publication No. 4313, Apr. 1, 1943.

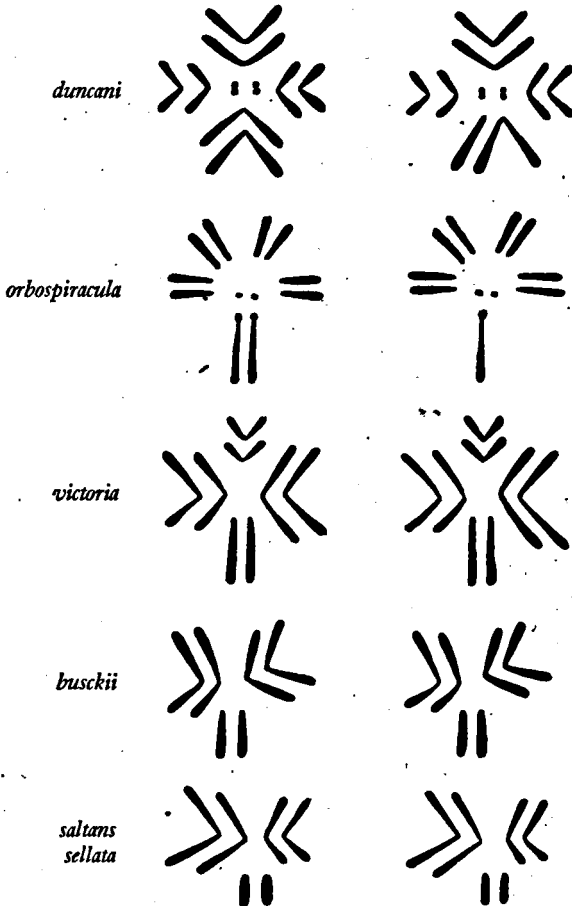
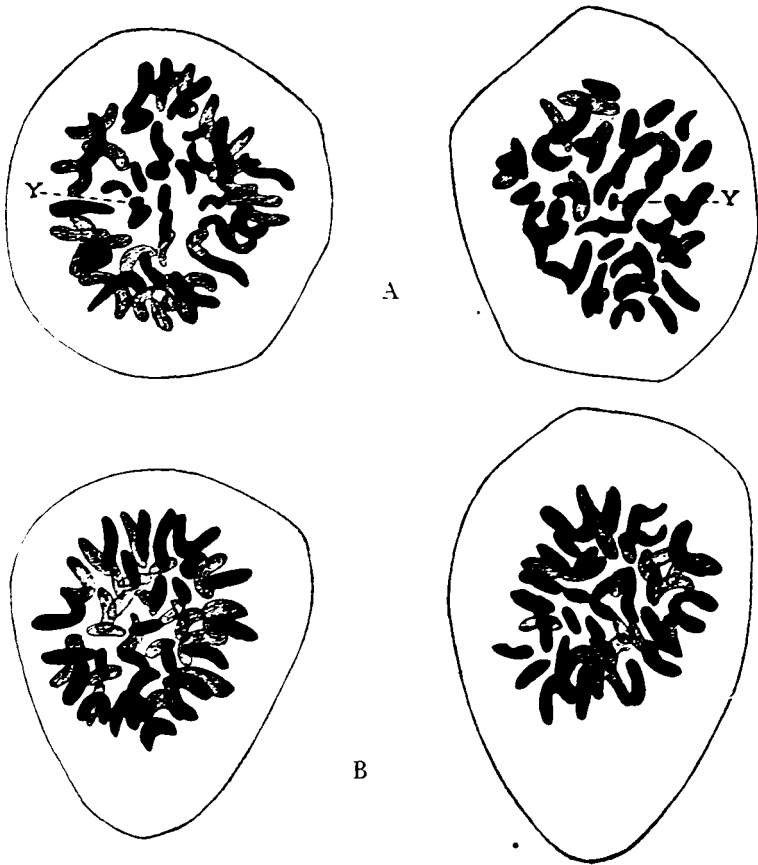


FIG. 53. Semi-diagrammatic drawings of the chromosomes in the metaphase plate stage in six species of the genus *Drosophila*. Chromosomes of females are shown on the left and males on the right. X and Y chromosomes are placed at the bottom of the diagram in each case. The lower figure serves for two species. In *D. duncani* the Y chromosome is a straight rod and the X chromosome is V-shaped; in *D. orbospiracula* the male has no Y chromosome; and in the other four species the X and Y chromosomes are visibly alike. (Courtesy, J. T. PATTERSON: "Studies in the Genetics of *Drosophila*, III. The *Drosophilidae* of the Southwest," University of Texas Publication, No 4313.)

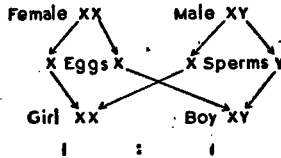


(A) (B) (C) (D)

FIG. 54. Human Chromosomes. (A) Male: metaphase plate stage of spermatogonia from two different men, each cell showing 48 chromosomes. The smaller chromosomes typically are arranged in the center of the cell. Magnification, 3600 diameters. (B) Female: metaphase plate stage in two cells from the uterus, each cell showing 48 chromosomes. Magnification, 3600 diameters. (C) Male. (D) Female. Chromosomes from somatic prophase nuclei, arranged in pairs according to size. The X and Y chromosomes of the male and the two X chromosomes of the female are shown at the extreme right. (Courtesy, HERBERT M. EVANS and OLIVE SWEZY: "The Chromosomes in Man, Sex and Somatic," Memoirs Univ. of California, Vol. 9, No. 1, Univ. of California Press, 1929.)

common with the majority of animals, ranging from worms to vertebrates, and like many plants, ranging from liverworts to seed plants, possess the XY arrangement (Fig. 54).

The mechanism of sex determination in man, therefore, is represented as follows:



A striking conclusion that emerges from these discoveries is that the primary difference in the sexes—in the XO type at least—is a mere quantitative one. It is apparent that in each generation sons always receive their one X chromosome from their mother, and daughters always receive one of their X chromosomes from their father. The X chromosome itself is the same in the male as in the female; but when present in a single dose it determines the development of a male, while in a double dose it causes the development of a female. In some way these original quantitative differences subsequently give rise to the qualitative differences between the sexes.

In most animals and plants with separate sexes, so far investigated, sex has been found to depend upon a difference in the chromosomes of the male, as already described. An interesting exception exists in the case of birds and some species of moths and fishes. In these animals the female rather than the male is heterozygous for sex. In some of these the female has but one X chromosome and no Y and in others the female has an X and a Y and the male has two X chromosomes. The end result is identical, however, so far as the sex ratio is concerned, since with two kinds of eggs produced in equal numbers and only one kind of sperm, males and females will appear in equal numbers just as in the more numerous species whose males are heterozygous for sex.

SEX-RATIO IN MAN AND ANIMALS

How is the chromosome theory of sex determination actually borne out by birth records in man and other species? According

to Professor F. A. E. Crew of the University of Edinburgh,³ the sex-ratio at birth (expressed in number of males per 100 females) for man and some of the common domesticated mammals is as shown in Table 11.

Table 11
SEX-RATIO AT BIRTH

	<i>Males</i>	<i>Females</i>
Man.....	103-107	100
Dog.....	118.5	100
Mice.....	100-118	100
Pig.....	111.8	100
Cattle.....	107.3	100
Rabbit.....	104.6	100
Horse.....	98.3	100
Sheep.....	97.7	100

Table 12
HUMAN SEX-RATIO AT BIRTH, 1921-1925*

	<i>Males</i>	<i>Females</i>
Germany.....	106.8	100
Finland.....	106.3	100
Sweden.....	105.9	100
United States†.....	105.8	100
Netherlands.....	105.6	100
Norway.....	105.5	100
Italy.....	105.3	100
Scotland.....	105.1	100
Belgium.....	104.9	100
France.....	104.9	100
Switzerland.....	104.8	100
England & Wales.....	104.7	100
Japan‡.....	104.1	100

* "Encyclopaedia Britannica," 14th ed., article on Sex-ratio at Birth and Death, by S. DE JASTRZEBSKI.

† Report U. S. Bureau of the Census. (In 1921 there were 24 states, chiefly in the South and West, which were not included in the birth-registration area. Ten of these were added in the period 1921-1925; and in 1933 the last one, Texas, was added.)

‡ 1921-1924.

³ "Encyclopaedia Britannica," 14th edition, article on Sex.

The deviation from the expected ratio of 1:1 in man, although not great, is highly significant and not due to errors of sampling, since it is based upon millions of births, and is true for the human species in general all over the world. This is illustrated in Table 12 showing some of the countries in which relatively accurate birth statistics have been kept.

What is the cause of the excess of male births over female births in man? One of the most natural explanations that might occur to the reader would be a differential mortality of the two sexes operating against the females prior to birth. All the evidence available, however, leads to the opposite conclusion. It is the male sex which suffers the higher prenatal mortality. This has been proved by a number of studies of the sex of premature births including embryos as young as four months and less. The greatest excess of still-born males is found in the youngest group.⁴ In 51,810 still-born young tabulated by Greulich the ratio was 135.8 males to 100 females.

If the same rule holds in the still younger aborted embryos which are not ordinarily observed, and so on, all the way back to fertilization, we are left with the necessity of concluding that a higher percentage of fertilizations must be effected by sperms carrying a Y chromosome than by sperms carrying an X chromosome. The existence of such a differential fertilization has not been proved, but it is not unreasonable to suppose, as suggested by T. H. Morgan,⁵ that since the Y chromosome in man is only about one-half the size of the X chromosome, the sperm carrying the Y chromosome may be slightly smaller, and has, therefore, a little the advantage in the long race up the uterus and oviduct of the female to the upper end of the oviduct where fertilization is effected.

In conformity with this theory is the reported fact that two sizes of sperms actually exist. In a number of animals, including the pig, the dog, the horse, and the worm *Ascaris*, measurements of the sperm heads (largely chromatin) have been made by a number of observers, and the dimensions plotted in curves of

⁴ GREULICH, W. W.: The sex ratio among human stillbirths, *Science*, July 10, 1931.

⁵ "The Physical Basis of Heredity," by T. H. MORGAN, 1919, J. B. Lippincott Co.

variability. According to Wilson,⁶ "in nearly all cases the curves have been bimodal, indicating the existence of two size-groups." In man also, two classes of sperms, based on size differences, have been reported.⁷

No one has yet been able to separate experimentally the X and Y sperms, although the attempt has been made using several methods such as centrifuging and electrolysis. Nor have there been any dependable successes in controlling the sex in mammals by the use of chemicals introduced into the female genital tract prior to mating, although this has been tried with substances such as acids and alkalis. A reliable means of controlling the sex of offspring would be of great practical importance in breeding domesticated mammals, dairy cattle, for example, to say nothing of the effect it might have upon the human population.

From another point of view, it is possible that race is a factor tending to modify the sex-ratio in man. The statistics available indicate that the Negro race has the lowest proportion of males to females. According to the Bureau of the Census, in the United States in 1937 there were 1,928,437 living white births reported, with a sex-ratio of 105.8 males to 100 females. In the same year 262,462 living Negro births were reported with a sex-ratio of 102.7 males to 100 females. Whether this difference in the races—which is not very great, although unquestionably significant—is due to hereditary differences or to environmental differences is not clear.

It seems well established, however, that differences in heredity may modify the expected 1:1 sex-ratio in mammals. The most extensive experiments on this point are those of Helen D. King,⁸ an American biologist, who, starting with two pairs of albino rats, all brothers and sisters, developed by inbreeding and selection two families of rats which differed strikingly in their sex-ratio. The offspring from one pair (family A) were bred brother to sister for six generations in order to develop a uniform strain.

⁶ "The Cell in Development and Heredity," by EDMUND B. WILSON, 3d ed., 1925, New York, Macmillan Co., pp. 300, 783.

⁷ PARKES, A. S.: Head length dimorphism of mammalian spermatozoa, *Quart. J. Micr. Sci.*, 67: 617-625, 1923.

⁸ "Studies on Inbreeding," by HELEN DEAN KING (reprinted from *J. Exp. Zool.*, Vols. 26, 27, and 29), Wistar Institute, 1919.

Selection was then applied by choosing brothers and sisters for mating from litters showing an excess of males. In the other family (family B) after six generations of inbreeding, as in Family A, selection was carried on by mating animals from litters with an excess of females. After 15 generations, family A was producing offspring showing a ratio of 125 males to 100 females, while in family B the ratio was 83 males to 100 females.

Although the difference between the two families of rats is obviously hereditary, the environment having been the same for both, the way in which the genes affect the ratio is not known.

TWINS: CAUSE AND SEX-RATIO

The discovery that sex is inherited in a manner analogous to ordinary Mendelian traits has opened the way to the solution of the problem of human twins. Everyone is interested in twins—especially identical twins—but until the mechanism of sex determination was known no one could explain them. Twins are of two types—identical and fraternal—and each type results from a quite different cause.

Fraternal twins may be of the same or of opposite sex. They have no more in common than brothers and sisters born to the same parents at different times excepting the slight effects which may come from sharing the same uterine home during the nine months of their embryonic life. The explanation of fraternal twins is that two eggs happen to be released from the ovary or ovaries at the same time, instead of the usual single egg; each egg is then fertilized by a separate sperm. Such twins are therefore designated two-egg twins. Plural births of this type, whether twins, triplets, quadruplets, quintuplets, or sextuplets, are in exactly the same category as plural births in most of the other mammals, in some of which, especially the smaller mammals, plural births are the rule. There seem to be no reliable records of more than six children being born to human parents at one time.

Twins of the other type, known as identical twins, are always of the same sex, and in other respects are so much alike that they are often distinguished with difficulty by friends, relatives, and even parents. The twin girls, college students, whose photographs are shown in Fig. 55 are examples of a pair of extremely similar

identical twins. Identical twins are sometimes more alike than the opposite sides of a single individual; and significantly, this is true of such highly individual characteristics as fingerprint patterns.



FIG. 55. A pair of attractive and strikingly similar identical twins. Facial features and other physical traits—coloring, body build, etc., are practically indistinguishable. They are alike also in aptitudes, interests, and personality. (Photographed by the author during their second year in college.)

From what we know of heredity, we conclude that identical twins are identical because they have identical sets of genes. On the basis of the large number of chromosomes and genes in man

we have already seen how improbable it is that any two fertilized eggs, even from the same parents, would ever possess identical sets of genes. As a practical matter, the only way two identical sets of genes ever arise in nature (in biparental organisms at least) is through mitotic cell division such as occurs in embryonic development and growth. If in early embryonic development, before differentiation has taken place or organs have been laid down, the

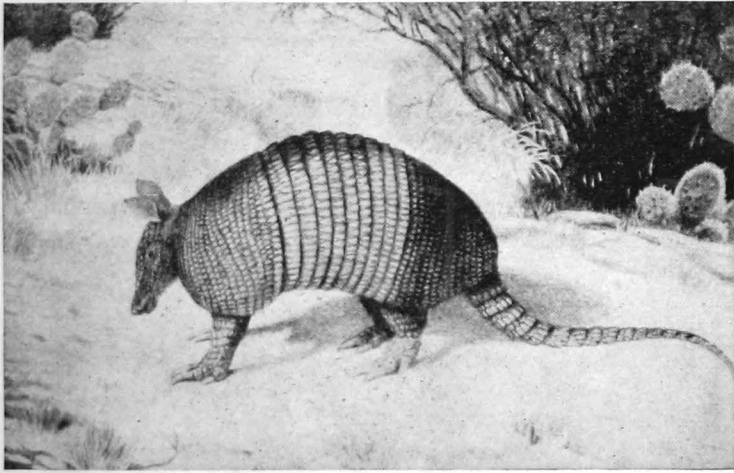


FIG. 56. The nine-banded armadillo of Texas (*Dasypus novemcinctus*), showing the animal in its native habitat. (Courtesy, NEWMAN: "The Biology of Twins," University of Chicago Press.)

embryo could be separated into two halves, these might develop into two identical individuals. This appears to be exactly what happens in the production of identical twins.

Identical twins have been produced experimentally in lower animals by various methods including the tying of a fine hair around a newt embryo in the two cell stage in such a way as to separate the two cells; by lowering the temperature; or by reducing the oxygen supply in the case of developing fish eggs, thus causing twin embryos to develop from one egg.

Because of the difficulties in observing early development in human beings, the complete visual proof of the origin of identical twins in man from a single egg has not been obtained. In one

mammal, however, the proof is available. The mammal referred to is the nine-banded armadillo of Texas (Fig. 56). In 1909 two American zoologists, H. H. Newman and J. T. Patterson, discovered that the armadillo habitually produces a litter of four (quadruplets); that the members of any given litter are always

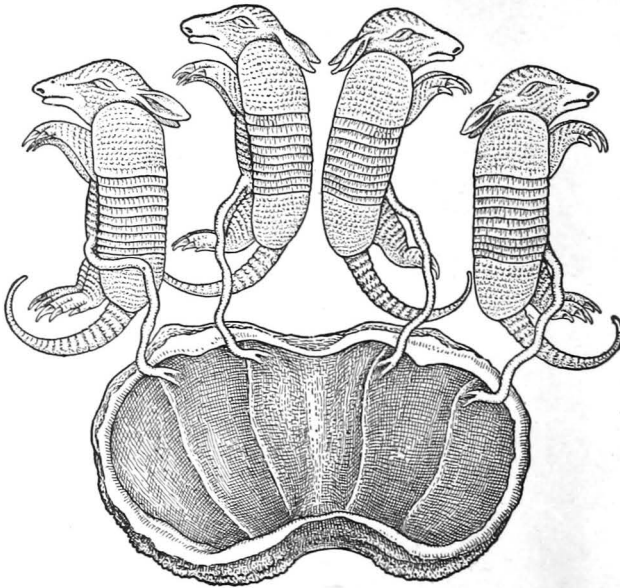


FIG. 57. Identical armadillo quadruplets in the embryonic stage, shown removed from their common membranes. The nine-banded armadillo produces quadruplets at each birth; all four are of the same sex and come from a single fertilized egg. (Courtesy, NEWMAN: "Outlines of General Zoology," New York, The Macmillan Co.)

of the same sex; and that the members of any one litter are usually strikingly alike (Fig. 57). This discovery was followed by a series of papers in one of which⁹ Professor Newman showed that in armadillos only one egg—a typical mammalian egg—is released from the ovary at each breeding. On the basis of these studies Newman formulated a theory as to the cause of the division of the early embryo into four independent embryos. He suggested that a lowering of the rate of metabolism resulted in the "physiological

⁹ "The Physiology of Twinning," by H. H. NEWMAN, 1923, University of Chicago Press, contains a summary of the armadillo studies.

isolation of parts at certain distances from the dominant (apical) region. When such isolation occurs new centers of control arise, which produce buds capable of establishing whole new systems like the original."

In 1913 Patterson added the final visible proof of the origin of the quadruplets by observing a number of embryos in pre-twinning stages, as well as in many stages of twinning which showed the four embryos arising from a single egg. It was dis-

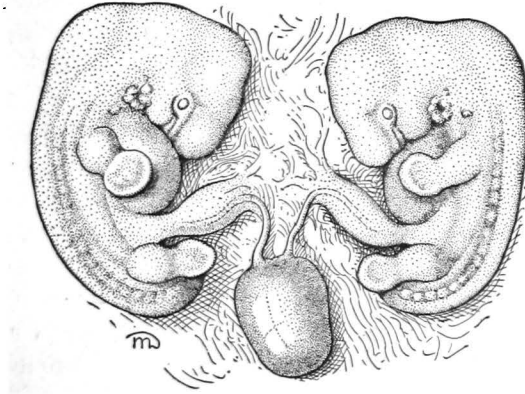


FIG. 58. Twin human embryos (12 mm. in length and about 6 weeks of age), each with its own umbilical cord and yolk stalk, but with common yolk sac and placenta. Both embryos probably developed from a single egg. (Courtesy, AREY: "Developmental Anatomy," Philadelphia, W. B. Saunders Co.)

covered also that in the early pre-twinning stages the embryos were very slow in establishing connections with the uterine wall. As pointed out by Newman, this delay would result in an arrest of development, with the subsequent twinning.

Whether a similar situation exists in man in the case of identical twins, triplets, and other multiple births, has not been discovered, but it is probable that the conditions are essentially the same as in the armadillo. This probability is supported by the discovery of a few early human twin embryos showing certain characteristics comparable to those observed in armadillo quadruplets (Fig. 58). In human beings the early embryo requires several days to become implanted in the uterine wall after it has

reached the uterus. It is not unlikely that in the case of some human embryos, for one reason or another, there is an undue delay in implantation, with a result similar to that in the armadillo, except that in man there are usually only two embryos instead of four.

Identical triplets, quadruplets, quintuplets, and even sextuplets occasionally occur in man. According to Professor John W. MacArthur¹⁰ of the University of Toronto, and others who have studied the Dionne quintuplets, after application of all the known tests for identical and fraternal twins, there is no doubt that all five girls are identical, having come from a single fertilized egg. There is good evidence, according to Dr. Dafoe,¹¹ that there were originally six embryos, the sixth having aborted very early.

In man, besides the evidence from the study of twins themselves, and argument from analogy with other animals, we have convincing supplementary evidence for the existence of one-egg twins; this evidence has to do with the sex-ratio of twin births. For example, in 1937, in the United States there were born 25,908 pairs of twins, including stillbirths.¹² This is about one twin birth in each 85 births. The twins were distributed by sex as follows:

2 males.....	8,776
1 male, 1 female.....	8,681
2 females.....	8,436
Sex unknown.....	15
Total.....	25,908

Note that this is nearly a perfect 1:1:1 ratio of the three possible combinations of the sexes. Let us suppose that each of these pairs of twins came from two separate fertilized eggs, i.e., that they are all fraternal twins. What then would be the expected ratio of the three combinations? Obviously it would be quite different from the numbers above. With separate eggs, each fertilization is an independent event, and the ratio of the three possible combinations

¹⁰ MACARTHUR, JOHN W.: Genetics of quintuplets: I. diagnosis of the Dionne quintuplets as a monozygotic set," *J. Heredity*, Sept., 1938.

¹¹ DAFOE, A. R.: The Dionne quintuplets, *J.A.M.A.*, 103: 673-677, 1934.

¹² "Vital Statistics of the United States, 1937, Part I," United States Bureau of the Census.

of sexes in the twins will be 1 (2 males) : 2 (1 male and 1 female) : 1 (2 females). This ratio is an illustration of the rule (Chapter 2) which states that the chance of the simultaneous occurrence of two independent events is equal to the product of the chances of the separate occurrence of the events. Since approximately one-half of all births are male births, two males should occur in $\frac{1}{2} \times \frac{1}{2}$ or $\frac{1}{4}$ of twin births. For the same reason two females should occur in $\frac{1}{4}$ of the twin births, leaving $\frac{1}{2}$ of all twin births as one male and one female.¹³

But the birth statistics cited above show a ratio very close to 1:1:1 instead of 1:2:1. The same-sexed twins are obviously much too numerous, if we assume that each individual is derived from a single fertilized egg; and with numbers as large as these, the discrepancy cannot be due to a mere chance deviation. If all twins were fraternal twins the expected numbers in each combination (assuming a sex-ratio of 1:1) would be as indicated in the second line of Table 13.

Table 13
TWIN BIRTHS IN THE UNITED STATES FOR 1937

	<i>Two Males</i>	<i>Male and Female</i>	<i>Two Females</i>
Pairs of twins born, including stillbirths.....	8,776	8,681	8,436
Expected if all twins were fraternal.....	4,341	8,681	4,340
Correction for excess of male births.....	+85		-85
Expected fraternal twins (corrected).....	4,426	8,681	4,255
Excess of same-sexed twins (probably identical)...	4,350		4,181

From the preceding figures we see that there were almost exactly twice as many same-sexed twins as there should have been had each individual originated from a single fertilized egg—in other words, about half of all same-sexed twins must have been identical (one-egg) twins. This conclusion seems to agree perfectly with the actual diagnosis of twin types; for, according to

¹³ The truth of the law here illustrated may be verified readily by tossing simultaneously two coins. In 100 throws there will on the average be 25 (2 heads):50 (1 head, 1 tail):25 (2 tails).

Professor H. H. Newman, leading student of twins in this country, the numbers of identical twins and same-sexed fraternal twins in the population are about equal.

According to the above calculations, 32.9 per cent of all twin births in the United States for 1937 are classed as identical. A comparison of the statistics for whites and "other races" (almost entirely Negroes) discloses an interesting racial difference in the proportion of fraternal and identical twins: in twins classed as "white" 34.1 per cent are identical, while in "other races" only 27.0 per cent are identical. A similar difference is found to exist for the year 1939, although in that year the percentage of identical twins in whites as well as Negroes exceeds that for 1937. The calculated percentages of identical twins for 1939 are: all races combined, 34.3 per cent; whites, 35.3 per cent; Negroes, 28.1 per cent. Whether this racial difference is due to environmental factors or to heredity or to a combination of the two we do not know.

"SIAMESE" TWINS AND "DOUBLE MONSTERS"

Twins are occasionally born physically joined one to the other. The extent of the union varies from a superficial one permitting their ready separation, to a union so deep-seated that life is not possible. Surviving conjoined twins usually find their way eventually into the circus or vaudeville shows, as did the famous original Siamese twins of the nineteenth century, who toured the country on exhibition for many years.

Conjoined twins are probably always of the one-egg variety in which separation, for some unknown reason, stopped short of completion. They are always of the same sex, and otherwise give evidence of having come from a single egg; although, for reasons given in Chapter 12 they are usually less alike than separate identical twins. Corresponding parts are united, with the result that the twins are joined symmetrically with respect to one another. If the union results in a highly abnormal condition, for example, a single head and a double body, or two heads and a single body, they are popularly known as "double monsters." These extremely abnormal specimens usually do not live. In ancient times various superstitious beliefs grew up around double monsters; some people even maintained that they were the hybrid

offspring of man with some other mammal. As a matter of fact, there is no evidence of the origin of a hybrid between man and any other mammal.

HEREDITY OF TWINNING IN MAN

Is the tendency to twinning hereditary in man, and if so how? The answer seems to be that twins run in families, but that the exact mode of inheritance is not known. According to R. A. Fisher,¹⁴ famous English biometrician, the frequency of twinning differs in different family lines. In data which he collected he found that the influence of the father was apparently confined to one-egg twinning; the production of two-egg twins was influenced only by the mother. This is what we might expect, since it is highly improbable that the father could affect the number of eggs released at one time, but quite possible that the nature of the sperm might be a factor in producing an arrest of embryonic development with resulting one-egg twins.

Fisher found that the production of two-egg twins depends greatly upon the age of the mother; that the frequency increases at least three-fold from the age of 18 to that of 38; and that it probably is influenced also by inherited qualities.

He concludes that the frequency of one-egg twins depends upon the heredity of the father as well as on that of the mother, but is not known to be influenced by age or other environmental factors. No attempt is made by Fisher to analyze the tendency to twinning in Mendelian terms.

A number of recent students of twins have doubted that there are hereditary differences in man in the tendency to produce one-egg twins. The question calls for further research.

SEX DIFFERENTIATION

The differentiation of the sexes in man is a gradual process involving a long chain of cause and effect. As we have already seen, the primary factor is a difference in the chromosomes, two X chromosomes producing a female and an X and a Y a male. The first indication of sexual differentiation is in the gonads. Up to about six weeks of embryonic development when the embryo is

¹⁴ "Encyclopaedia Britannica," article on Twins and Twinning.

about 12 mm. in length (Fig. 58) the sexes cannot be distinguished; the gonads of both sexes look alike. At about 13 mm. the male shows the first signs of differentiation, and at this time the gonads are recognizable under the microscope as developing testes. The gonads of the female embryo remain indifferent in appearance for about one week longer than those of the male, and then begin a process of differentiation into ovaries.

One of the characteristic differences between the sexes of adults is in the ducts used for carrying sperms and eggs to the exterior. Before the gonads differentiate, each sex develops both male and female ducts; with the differentiation of the gonads into testes or ovaries, the ducts of the opposite sex degenerate. The stimulating factor in this process seems to be the hormones secreted by the testes and ovaries.

The external genitalia begin their development during the sixth week of embryonic life, but for a week or more are alike in both sexes. By the end of the seventh week sex may be distinguished—though with some uncertainty—by external differences. Differentiation proceeds, and by the twelfth week the external genitalia in each sex have become clearly distinguishable and fairly characteristic.

After birth other sexual differences not directly a part of the reproductive system and hence known as secondary sexual characters gradually appear. These differences are not particularly marked until sexual maturity approaches. The arrival of sexual maturity, known as puberty or the beginning of the period of adolescence, is associated with the sudden increase in secretion of hormones by the gonads and some of the other glands of internal secretion. One effect of the hormones is a difference in the rate of metabolism in the two sexes. At five years of age the rate in males is about 3 per cent above that of females; this difference rises to about 12 per cent at 16 years and falls gradually thereafter. Associated with the difference in metabolic rate is the tendency of the female to store up a larger amount of energy in the form of fat.

Since the gonad hormones are a necessary link in the differentiation of sexual characters, it is natural that anything which causes a destruction or removal of the gonads should result in a profound modification of sexual development. Removal of the testes before

sexual maturity, as formerly practiced in the production of eunuchs, results in striking effects. Masculine characters fail to develop normally, and the eunuch retains some of the neutral characters found in preadolescent children. The voice remains high-pitched, resembling that of the female; the beard fails to develop; and fat is deposited in unusual amounts.

If normal development is interfered with either by genes or by some environmental factor, prior to birth, there may result what is known as a hermaphrodite. True hermaphroditism (from the Greek God Hermes and the Goddess Aphrodite) refers to that condition—normally present in many lower animals, including some vertebrates—in which sperms and eggs are produced by the same individual. This is extremely rare in man, although actual cases have been reported. According to Professor Arey, there is no proof that such an individual can function both as a father and as a mother. The internal genitalia are imperfectly developed, while the external genitalia show mixed male and female characteristics. The secondary sexual characters such as beard, mammary glands, and voice are intermediate.

Most so-called hermaphrodites display false hermaphroditism, i.e., the gonads are of one sex only, while the external genitalia tend in the direction of the other sex. Technically they are known as intersexes. The internal genital tract also is intermediate or mixed in type. In male false hermaphroditism the testes are often undescended, while the external genitalia resemble somewhat those of the female. This is due to an arrest of development, including hypospadias (Chapter 9). Such an individual, as a child, may for a time be considered a female, but with the onset of adolescence the increase in male hormones suddenly causes the child to develop male secondary sex characters. This is the type of case that is sometimes wrongly described in the popular press as an example of sex-reversal.

In female false hermaphroditism ovaries are present and sometimes descended; in position they resemble the testes in the male, while the external genitalia tend in the male direction. This type of individual may be taken for a male during early childhood; at puberty suddenly it may seem to be transformed into a female. Obviously, cases of male and female false hermaphroditism are

not to be regarded as sex-reversals. There is no proof that true sex-reversal ever occurs in man or in any other mammal. Sex-reversal seems to be incompatible with the peculiarities of uterine development possessed by mammals, including the highly standardized temperature and nutritional conditions. Furthermore, the fact that a complex genital apparatus differentiates early in embryonic life in mammals makes sex-reversal during late embryonic stages impossible, because once differentiation of sex has proceeded very far in either direction, there can be no retracing of the steps.

It is possible, however, to have an interference with the normal hormone conditions during embryonic life in mammals of such a nature as to produce false hermaphroditism or intersexuality. A well-known case of this type occurs naturally in cattle twins. Practically all cattle twins arise from two separate eggs. They may consist of two males, two females, or a male and a female. When both twins are of the same sex, development proceeds normally; but when one is a male and the other a female, it is found in a large percentage of cases that the female is an intersex. The external genitalia are of female type while the internal organs resemble the male. The male, on the contrary is always normal. Such abnormal females are known as freemartins; they are always sterile.

In 1916, Professor F. R. Lillie of the University of Chicago, taking advantage of the abundant material available at the Chicago stockyards, examined many pairs of cattle twin embryos in an attempt to discover the cause of freemartins in cattle. On examining the twin embryos he found that there was usually a fusion of the embryonic membranes and embryonic blood vessels of such a nature as to permit the blood from one embryo to pass directly to the other (Fig. 59). Whenever such fusions took place the female of the pair of twins of unlike sex was always damaged in that its sex organs were modified in the male direction. In those rare instances involving no fusion of the blood vessels, the female developed normally. Since the sex hormones constitute the only known difference between the blood of the male and that of the female, and since the testes develop ahead of the ovaries, it was

assumed that the male hormone was responsible for the partial sex-reversal of the female.

This theory has recently been called into question by Professor Carl R. Moore of the University of Chicago,¹⁵ who doubts that the embryonic testis is secreting hormones at this early stage. In his opinion the responses of the duct system in the freemartin are

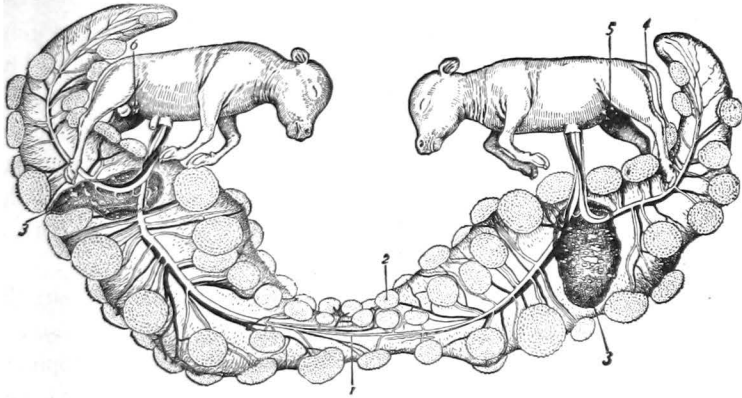


FIG. 59. A typical opposite-sexed pair of cattle twins, male on the left and freemartin on the right, showing: (1) the connecting artery between the two twins; (2) a single placental cotyledon entered by veins from both embryos; (3) opening into the chorion through which the embryos have been removed; (4) clitoris of the freemartin; (5) the well-separated anterior and posterior teats characteristic of the female; (6) the much closer teats characteristic of the male. (Courtesy, H. H. NEWMAN: "Outlines of General Zoology," 3d ed., New York, The Macmillan Co., 1936, after F. R. Lillie.)

not yet duplicated by any experimental treatment in mammals. He agrees that a chemical substance transported through the blood stream is the effective agent but doubts that the substance is of the true sex hormone type. He offers the suggestion that a difference in chemical substances produced by the body cells in general of males and females, rather than the testis specifically, may be the explanation of the freemartin.

There is no evidence that intersexes in man are ever caused by a mingling of blood in twins as in freemartins in cattle. Accord-

¹⁵ MOORE, CARL R.: Gonad hormones and sex differentiation, *Am. Naturalist*, 78: 97-110, 1944.

ing to Professor Newman, there are no known cases of two-egg twins in man involving fusion of fetal blood vessels.

The problem of the cause of intersexes and of true hermaphroditism in man has not been solved. No environmental factor is known that can be held accountable, and by analogy with certain insects (the moth *Lymantria* and the fruit fly *Drosophila*) it is quite possible that genes are responsible. A. H. Sturtevant¹⁶ of the California Institute of Technology has recently discovered a gene in *Drosophila melanogaster* that transforms females into males. The gene is a recessive, lying between 44 and 45.3 in chromosome III (see Fig. 30, p. 111). The transformed females are indistinguishable from normal males except for their sterility, a reduction in testis size, and apparently an approach to the body size and the development rate of females. The gene has no effect on normal males:

Of special significance in mammals is the fact that in goats the intersexual condition seems to be inherited as a simple recessive.¹⁷ It is probable that the gene produces its effect on development through the hormones as intermediaries.

PARTHENOGENESIS

Parthenogenesis (Gr. *parthenos*, virgin + *genesis*, to be born) refers to the development of an individual from an unfertilized egg. The scientific literature contains no record of parthenogenesis in man, but among many groups of invertebrate animals, as well as in some plants, parthenogenetic development is the rule. In a number of vertebrate animals, as we shall see below, parthenogenesis has been experimentally induced.

In some animals having natural parthenogenesis, e.g., in the group of insects known as plant lice or aphids, the reduction division is omitted; consequently the unfertilized eggs have the double number of chromosomes, and develop into females. In others, such as the honeybee, all the eggs, including those that develop parthenogenetically, have undergone a reduction division,

¹⁶ STURTEVANT, A. H.: A gene in *Drosophila melanogaster* that transforms females into males, *Genetics*, 30: 297-299, 1945.

¹⁷ EATON, O. N., and SIMMONS, V. L.: Hermaphroditism in milk goats, *J. Heredity*, June, 1939.

and the parthenogenetic eggs develop into males exclusively. These males have but a single set of chromosomes in each cell of the body, including the testes. The sperms produced by these haploid males are formed without a reduction division and therefore contain the complete set of chromosomes. It is an interesting fact, as Professor E. B. Wilson points out, that in the bee and many other hymenopterous insects

a kind of vestigial reduction division takes place, the primary spermatocyte making an abortive attempt to divide, in the course of which an incomplete spindle is formed, and the chromosomes appear, but no nuclear division occurs. The result is the extrusion of a non-nucleated mass of protoplasm or "polar body," and this is followed by one complete mitosis in which both nucleus and protoplasm divide normally.

Wilson suggests that animals which now reproduce parthenogenetically undoubtedly are descended from ancient ancestors in which ordinary biparental reproduction was followed. The ultimate step in this direction has been taken by a few species, such as the gall-fly *Cynips kollari*, among which males seem to have become entirely unnecessary since they have never been found. All the individuals are females, and develop in each generation from unfertilized eggs.

Obviously, no species are known in which males only and no females exist, for although the sperm is the equivalent of the egg so far as the genes are concerned, sperms are almost totally lacking in the cytoplasm and stored food which are necessary for embryonic development.

The determination of sex in species that reproduce parthenogenetically presents interesting variations from the chromosome mechanism previously discussed. The honeybee is a classic example. In a colony of bees there is one queen (a fully mature female whose function it is to lay the eggs), thousands of sterile females, aptly known as workers, and a few males, known as drones (Fig. 60). Queens and workers are genetically alike; both develop from fertilized eggs. Drones develop from unfertilized eggs.

Before settling down to found a colony, the queen goes on a nuptial flight with a single male. For the realization of this function the male pays dearly since a moment after mating, and as a

result thereof, he dies. The one supply of sperms received from the male is sufficient, however, to last the queen the rest of her life—which may be as long as four or five years, or in exceptional cases, longer.

Most of the eggs laid by the queen are fertilized by these retained sperms; such eggs develop into females. A small number of eggs are not fertilized and these develop into males. Males thus possess no father, although they have had a grandfather. Sex chromosomes have not been identified in the honeybee.

The development of workers and queens is of unusual interest. Since both come from fertilized eggs, which so far as known are

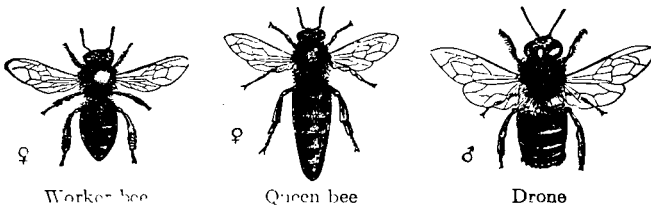


FIG. 60. The honeybee, *Apis mellifica*, showing the three castes. (Courtesy, H. H. NEWMAN: "Outlines of General Zoology," 3d ed., New York, The Macmillan Co., 1936, from Shiple and MacBride.)

exactly alike, the differentiation of worker and queen is due entirely to the environment. Their differences involve not only numerous structural details adapting each caste to its special work, but include instincts as well. The queen is merely a queen-mother: she apparently has nothing to do with governing the colony, but devotes her whole energies to the laying of eggs, and pays no attention to her own offspring after they hatch. The instincts of caring for the young, gathering food, and defending and maintaining the hive reside solely in the workers. Only rarely are workers able to produce eggs.

The workers alone control the development of a new queen in the following interesting manner. An ordinary cell containing an egg or a larva under three days of age is first enlarged by the workers to allow room for the extra size of the queen-to-be. During the first two days of life all larvae are fed "royal jelly," a white fluid secreted by glands in the mouth of worker bees. The larval queen continues to receive royal jelly during the remaining

two and one-half days of her larval existence. The larval workers are denied further royal jelly and are fed on pollen and nectar only. They develop slowly and undergo pupation at about eight and one-half days, requiring about 18 days from egg to adult. The queen requires a total of only 12 or 13 days for her development, and upon emergence is nearly twice the size of workers (Fig. 60).

ARTIFICIAL PARTHENOGENESIS

Beginning with the brilliant discovery by Jacques Loeb in 1899 that eggs of sea urchins could be stimulated by chemicals to undergo parthenogenetic development, with the production of normal larvae, there has been a long list of similar successful experiments with various animals, including the vertebrates. A great variety of chemical and physical agents have proved effective.

In later experiments Loeb successfully raised frogs to sexual maturity from unfertilized eggs which had been treated merely by puncturing with a fine needle. According to Wilson, in no other animals has it been possible thus far to rear larvae from artificially parthenogenetic eggs up to sexual maturity.

Of the twenty parthenogenetic frogs brought through metamorphosis by Loeb, 15 were males, 3 females, and 2 of uncertain sex. The parthenogenetic frogs were found unexpectedly to have the normal number of chromosomes, like frogs from fertilized eggs. Apparently there had been a doubling of the chromosome number in the unfertilized egg without cell division. The presence of both sexes in these experiments requires explanation and calls for further experiments, with special attention given to the behavior of the chromosomes in the dividing cells.

In mammals, fertilization normally takes place in the oviducts—the tubes which conduct the eggs from the ovaries to the uterus. If no sperms are present the eggs pass on down the tubes, disintegrating in the lower end of the oviducts or in the uterus. In a few cases in rats and rabbits, unfertilized eggs have been found in the tubes, undergoing early cell division.¹⁸ In such cases, however, the eggs soon die. No instances of natural parthenogenetic development have been found in mammals.

¹⁸ "The Eggs of Mammals," by GREGORY PINCUS, 1936, The Macmillan Co.

Recently Dr. Pincus, an investigator in this country, removed unfertilized eggs from the oviducts of rabbits, and placed them in glass dishes containing blood plasma or serum. He found that out of 213 eggs so cultured 136 underwent cell division, some as far as the twenty-cell stage. In some way the artificial environment stimulated the beginning of parthenogenetic development. Pincus suggests that the stimulus to cell division is an increase in the salt concentration of the culture medium through the loss of water by evaporation. Such concentrated solutions are known to induce parthenogenesis in some of the lower animals. After a time, however, usually under 36 hours in the culture medium, cell division ceased and the rabbit eggs disintegrated.

Rabbit eggs have been successfully fertilized outside the body of the mother by the addition of a suspension of rabbit sperms to a culture dish containing the eggs. Under such circumstances development proceeds to a stage beyond that reached by parthenogenetic eggs. Eventually, however, all such incubated eggs die. The complete incubation of a mammal outside the body of the mother, a normal process in birds and the lower vertebrates, offers at present insuperable difficulties with respect to supplying nutriment to the embryo. The successful imitation of the uterine environment is not, however, theoretically impossible. That eggs fertilized outside the body are potentially able to continue development is proved by further experiments in which Pincus transplanted fertilized eggs into the oviducts of female rabbits. The foster-mothers that received these eggs produced from them normal litters, although such foster-mothers had nothing to do with producing the eggs and had not mated with a male.

More recently, Pincus has reported the birth of living parthenogenetic rabbits as the result of treatment of unfertilized eggs with salt solutions.¹⁹

PROBLEMS

1. Why did the earlier theories of sex determination often emphasize the environment rather than the nature of the reproductive cells?

¹⁹ PINCUS, GREGORY: The breeding of some rabbits produced by artificially activated ova, *Proc. Natl. Acad. Sci.*, Vol. 25, Oct. 4, 1939.

2. Mention a chemical analogy to the mechanism of sex determination in grasshoppers, i.e., name two chemical compounds with different qualitative properties, resulting from the presence of two atoms of some element in one compound and only one atom of the same element in the other compound.

3. How is sex determined in the following: honeybee, grasshoppers, *Drosophila*, birds, mammals, plants?

4. Would you expect to find sex chromosomes in hermaphroditic species of plants and animals? If not, what sort of factors probably determine the differentiation of the male and female reproductive organs in hermaphroditic species?

5. List the advantages that hermaphroditic species may have over species with separate sexes. (In animals most hermaphroditic species are not self-fertilizing.)

6. What advantages have species with separate sexes over hermaphroditic species?

7. On the basis of what we have learned about the relation of gene to character is it likely that the development of sexual characters depends upon one gene only or on several genes? Explain.

SEX-LINKED HEREDITY

THE SOLUTION of the problem of sex determination opened the way to the clearing up of another long-standing biological riddle. For centuries people had been puzzled by the fact that certain hereditary characteristics appeared more frequently in males than in females; and yet the males in each generation seemed to inherit the particular characteristic through their mothers and not through their fathers. The discovery of the chromosome mechanism of sex determination led directly to the explanation of this mystery.

COLOR BLINDNESS

Red-green color blindness in man is the commonest of the hereditary characteristics showing a peculiar relationship to sex. About 8.0 per cent of all white males show some lack of ability to recognize the colors red and green, while only about 0.5 per cent of white females are so affected. Such color-blind persons have normal vision with respect to black, white, yellow, and blue; reds and greens, however, in extreme cases of the defect, are not recognized as distinct colors, but are confused with yellows, blues, and grey.

Color blindness varies in degree from a moderately weakened color sense for red and green to the complete absence of the sense. Red-green color-blind persons commonly fail to distinguish between pale red, pale green, and grey, and at the same time are able to name correctly intense shades of these colors in a good light. Consequently, in most cases it is better to speak of color weakness than of color blindness. The simplest and most widely used of the tests for color blindness yet devised are the color plates invented

by Dr. Shinobu Ishihara, Professor of Ophthalmology, Imperial University of Tokyo.

A rare type of hereditary total color blindness, accompanied by day blindness, or inability to see clearly in bright light, also has been described. It is, according to some authors, inherited as an ordinary Mendelian recessive.

Those of us who have normal color vision may get some idea of the world in which color-blind persons live by observing our own sensations during advancing twilight. As the daylight diminishes in intensity, greens and reds first disappear, leaving yellows and blues still recognizable. With deepening twilight, all colors vanish until everything takes on some shade of grey. The light from the moon is usually too weak to stimulate the color sense; consequently, we are all more or less color blind by moonlight.

In all cases of congenital color blindness the cause seems to be hereditary, having nothing to do with age or training. Tests of young children of both sexes have shown the same percentage of color blindness as in adults.

The physiological cause of color blindness is imperfectly understood, as, for that matter, is the physiology of color vision itself. It is probably due to some defect of those specialized cells of the retina (the cones) which are concerned in color vision.

In its mode of inheritance color blindness is sex-linked, i.e., its gene is located on the X chromosome. Heretofore we have spoken of the X chromosome as though it had nothing to do but determine sex. There is abundant evidence, however, that the X chromosome carries a miscellaneous assortment of genes, affecting various parts of the body, in addition to the gene or genes for sex determination. The gene for color blindness, as well as the normal alternative gene, is one of these. This statement is based upon a study of the pedigrees of color blindness rather than upon observations of the cells. In the lower animals, however, particularly in *Drosophila*, sex-linked heredity of exactly the same type as in man has been shown by microscopical study to depend upon the presence of the X chromosome. The Y chromosome carries no corresponding gene, and this accounts for the difference in the percentage of color blindness in the two sexes.

To illustrate how the mechanism of sex-linked heredity

operates, let us consider the mating shown in Fig. 61. Here the gene c for color blindness is found on both of the X chromosomes of the mother; she is, therefore, color blind. The one X chromosome of the father in this mating carries the normal gene C ; hence his vision is normal. The lack of either gene C or c on the Y chromosome is represented by a dash (-).

As shown in the diagram, the reduction division produces but one kind of egg as contrasted with the two kinds of sperms. Fertilization results in the usual sex ratio of 1 male to 1 female.

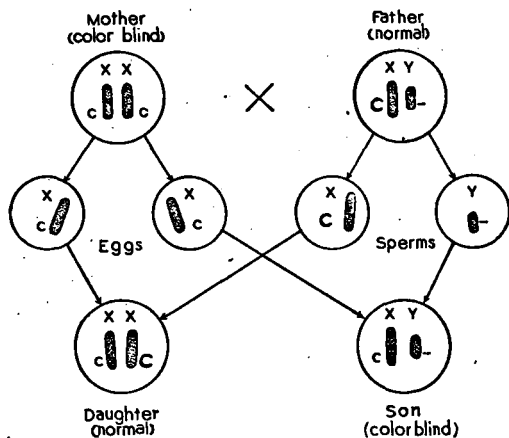


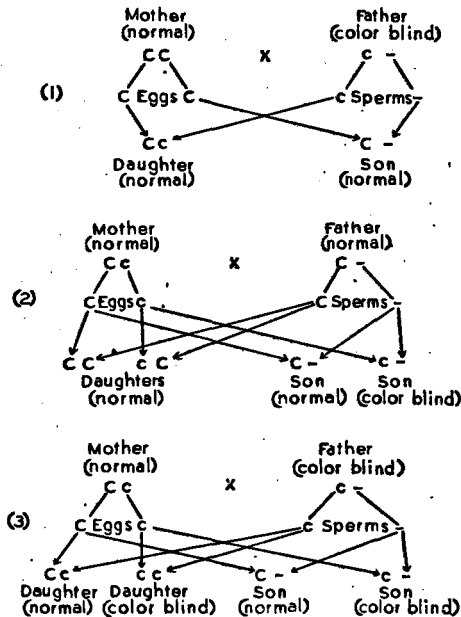
FIG. 61. Diagram showing the inheritance of red-green color blindness in man, a typical case of sex-linked heredity.

All the daughters have normal vision, since they all receive the dominant gene C from their father. All the sons are color blind, because their one X chromosome derived from their mother carries a gene for color blindness. This result is known as criss-cross inheritance, because the daughters resemble the father and the sons resemble the mother.

Whatever truth there may be in the popular belief that sons and daughters "take after" the parent of opposite sex rests entirely, so far as we know, upon this phenomenon of sex-linkage. The proportion of traits which are sex-linked in man cannot be very great because the X chromosome is only one of 24 in man (Fig. 54), and it is one of the smaller ones, at that. If the genes

are distributed equally among all 24 chromosomes, in proportion to the size of the chromosomes, less than 4 per cent of the genes should be found on the X chromosome.¹

Three other types of mixed matings involving color blindness are possible. These are as follows:



An inspection of the diagrams of the four possible mixed matings makes it clear why there are more color-blind males than females. In three of the matings color-blind sons are produced, whereas in only one of the four are there color-blind daughters, this being the last mating shown, where the mother is hybrid and the father is color blind. Nearly all color-blind women must come from the last type of mating, since the only other possible source of color-blind females is matings between two color-blind persons—naturally a rare occurrence.

¹ In animals with a smaller number of chromosomes, the proportion of sex-linked genes is, of course, higher. Thus in *Drosophila melanogaster*, which has been studied more than any other animal, there are four pairs of chromosomes, and more than one-fourth of the known genes are sex-linked.

It is interesting to note that since 8.0 per cent of all males are color blind there must be approximately twice that many women in the population who are carriers of the gene; for most color-blind males come from mothers who are carriers, and one-half of the sons of such carriers are, of course, normal.

Marriage between normal and color-blind persons is, no doubt, largely a random matter, color blindness being seldom, if ever, a deliberate factor in the choice of a mate. Natural selection probably has had little effect upon the frequency of color blindness in the population, a fact which perhaps partially explains why color blindness is so common.

Socially important consequences of color blindness appear when we consider the large number of automobiles now in use, and remember that eight men in 100 are color blind. It is more than likely, under the circumstances, that not a few accidents are due to the misinterpretation of traffic signals. Obviously, it is unfortunate that red and green were chosen as traffic signal colors; yellow and blue would have been preferable, since nearly everyone can distinguish these colors. Railway, steamship, and air transport companies, for years, have rejected color-blind applicants for certain positions, but very few states in this country have rejected color-blind applicants for automobile licenses. The most practical solution of the problem appears to be the substitution of other colors for red and green in traffic lights. Even under the existing system, greater safety undoubtedly would result from the practice of testing all drivers for color blindness, and requiring those found to be color blind to employ known methods of compensating for their deficiency.²

Interesting racial differences in the frequency of color blindness have been reported recently. Among white males the frequency (including all degrees of the defect) is about 8.0 per cent; among Chinese, about 6.5 per cent; among Negroes, about 4.0 per cent; and among American Indians somewhat less than for Negroes.³ The number of females tested in this country has not

² A method which makes use of red and green color filters attached to the wind shield has been found effective with color-blind persons by Thomas Ross of the University of Washington, who describes the method in detail in *Science*, March 13, 1936.

³ SHUEY, AUDREY M.: The incidence of color blindness among Jewish males (and previous articles therein cited), *Science*, Sept. 4, 1936.

been large enough to give very reliable estimates, but in Oslo, Norway, Waaler tested over 9,000 schoolgirls and found 0.44 per cent to be color blind. He also tested over 9,000 boys, finding 8.0 per cent color blind.

With 8.0 per cent of males color blind there should be theoretically 0.64 per cent females color blind—assuming that all color blindness is due to the same gene. The calculation of the expected percentage of color-blind females rests upon the fact that if matings are at random with respect to the gene and if there is no selection for or against it, the frequency of a sex-linked gene in both sexes should equal the frequency of the males who show the trait. Consequently 8 per cent of all genes at this locus in women should be c . This means that 8 per cent of all eggs will carry c . With 8 per cent of eggs carrying the color blind gene and with 8 per cent of X-sperms also carrying c , a union of a c sperm with a c egg should occur in 8 per cent of 8 per cent or 0.64 per cent of female-producing fertilizations.

Tests show that there are two qualitatively distinguishable types of red-green blindness. Some authors have designated these red-blindness and green-blindness, although in reality persons of both types are deficient in the red-green color sense. If two different genes occupying separate loci on the X chromosome are responsible for the so-called red-blindness and green-blindness, as has been suggested by Waardenburg and others, a female heterozygous for both of these genes will be normal, since she will possess the dominant alternative of each recessive gene. If the two genes happen to be on different chromosomes and if crossing-over does not occur all of her sons will receive either the one gene or the other; hence every son will be color blind—half of them red-blind and half green-blind. If the red-blind gene and the green-blind gene are on the same chromosome half of the sons should be both red-blind and green-blind and half should be normal, provided there is no crossing-over. If the theory of two series of alleles is correct the proportion of color-blind females should be smaller than would be expected if only a single series were involved. Thus the discrepancy between the observed and the calculated percentages of color-blind females (the difference between 0.64 per cent and 0.44 per cent) would be accounted for.

Both types of red-green blindness are variable in expression. As an explanation of this fact it has been suggested that there is a series of triple alleles for each of the two types.

OTHER SEX-LINKED CHARACTERISTICS IN MAN

Numerous other sex-linked characteristics are known in human beings but none approaches red-green blindness in frequency. In fact, some are extremely rare. Almost without exception they are recessive; only a few doubtful cases of dominants have been reported. The following list gives a few of the best known and most interesting sex-linked characteristics in man:

SEX-LINKED CHARACTERISTICS IN MAN

<i>Dominant</i>	<i>Recessive</i>
Normal.....	Red-green blindness
Normal.....	Night blindness
Normal.....	Optic nerve atrophy
Normal.....	Absence of sweat glands, defective teeth and hair
Normal.....	Hemophilia

NIGHT BLINDNESS

Night blindness is in some respects the opposite of day blindness, which, as we have seen, is one manifestation of total color blindness. During daylight, the night-blind person sees normally, but in dim light his vision is extremely defective. The trouble seems to be with those cells of the retina known as the rods, which are specially adapted for vision in dim light. Hereditary night blindness should not be confused with temporary night blindness, which has been reported recently as due to a vitamin A deficiency.

It is important to note at this point that there are two other types of hereditary night blindness which are not sex-linked: one is an ordinary dominant and the other a recessive.

OPTIC NERVE ATROPHY

A frequent cause of blindness in human beings is hereditary atrophy of the optic nerve. This condition has nothing to do with atrophy of the optic nerve which sometimes results from syphilis or other infections. According to Waardenburg, who gives a full

account of the disease, the hereditary type usually begins between the ages of 18 and 23, but occasionally appears in young children, or in adults as late as the forties. The progress of the disease is sometimes rapid, sometimes slow. In either case it leads to almost complete blindness, although slight power of vision usually remains at the boundary of the visual field after central vision is completely lost.

Optic nerve atrophy of the usual type is inherited as a sex-linked recessive, but in some families a different type seems to be inherited as a dominant. As in other sex-linked recessives, its frequency in males greatly exceeds that in females. Unlike color blindness, there is probably considerable selection against such a serious disease as this, particularly when it appears early in life.

ABSENCE OF SWEAT GLANDS, DEFECTIVE TEETH AND HAIR

Cockayne gives a good description of a striking hereditary condition which he calls "major ectodermal defect." His description, quoted in part below, is accompanied by references to numerous reported pedigrees.

The main features of this rare and interesting developmental defect are small size and delicacy of constitution, a total absence or deficient number of teeth, conical incisors and bicuspid, and molars with sharp-hooked cusps, short, fine, pale, scanty hair, chronic rhinitis with subsequent loss of smell, absence of sweat glands, and sometimes, if not always, absence of the lachrymal glands.

It has been reported among various peoples: English, German, Swedish, French, Russian, Jewish, and Hindus. It exists in the United States among peoples of various European descent.⁴

The absence of sweat glands is of special interest and importance because of the profound effect which this defect has upon heat regulation of the body under high temperatures. During hot weather the body temperature of persons without sweat glands tends to run up far above normal, resulting in considerable suffering. Victims of the defect learn to avoid extreme discomfort by staying out of the sun and refraining from vigorous exercise and hot food and drink. They also apply water to their clothing to gain the cooling effect of evaporation. A further heat loss is brought

⁴ ROBERTS, E.: The inheritance of anhidrosis with anodontia, *J.A.M.A.*, 93: 277-279, 1929.

about by the automatic speeding up of the rate of breathing, as in the case of panting dogs, these animals not being well supplied with sweat glands. Persons who have no sweat glands may be fairly active and comfortable during cool weather.

HEMOPHILIA (*Bleeder's Disease*)

Owing to its presence in the royal families of Europe, hemophilia, or the "royal disease," is the most notorious of all sex-linked characteristics. Its presence in royal families is, however, merely a coincidence, for it is no respecter of persons. Like any other hereditary trait which gains admittance to a closely intermarrying group, hemophilia has come to have a supposed importance far beyond its real importance to the population as a whole.

Hemophilia seems to have been described in detail first by John C. Otto of Philadelphia in 1803.⁵ It is, nevertheless, one of man's ancient afflictions. Albucasis, famous Arabian surgeon of the eleventh century, wrote of men in a certain village who bled to death from superficial wounds, and of boys who bled to death if their gums were rubbed harshly. The ancient Hebrews evidently knew of hemophilia for, according to Dr. Birch of the School of Medicine, University of Illinois, who has written a comprehensive illustrated monograph⁶ on the subject, there are several undeniable references to hemophilia in the Talmud, described under dispensation from circumcision.

The primary symptom of the disease is an abnormal tendency to bleed because of an extremely slow rate of coagulation of the blood. In normal individuals the blood from a ruptured vessel coagulates in from two to eight minutes; in hemophiliacs the coagulation time is greatly prolonged, varying from one-half hour to 22 hours or more, according to the severity of the disease. In some families the disease is much more severe than in others.

Clotting of the blood is a rather complex process dependent upon a number of factors, one of which is the presence in the blood of minute bodies known as blood platelets. When a vessel is

⁵ OTTO, J. C.: An account of an hemorrhagic disposition existing in certain families, *Medical Repository*, Vol. 6, 1803.

⁶ "Hemophilia: Clinical and Genetic Aspects," by CARROLL LA FLEUR BIRCH, Illinois Medical and Dental Monographs, Vol. 1, No. 4, 1937.

ruptured, these platelets normally break up and release a substance which reacts with other substances in the blood to cause the formation of a clot. In persons with hemophilia the platelets are present in normal numbers, but are highly resistant to disintegration.

Hemophilia is said to be common in certain mountainous regions of Germany, for example in the Black Forest, and in certain mountain valleys and isolated towns in Switzerland and elsewhere. Its undue prevalence in a few localities is probably due to chance mutations having occurred in certain places, coupled with a tendency of the inhabitants to remain at home and to intermarry. Although hemophilia has been reported frequently from various parts of the United States, there seem to be no reliable statistics as to its frequency for the country as a whole.

Hemophiliacs are, of course, greatly handicapped in the struggle for existence. Most affected males die young, rarely leaving offspring. There is accordingly a constant tendency for it to be weeded out by natural selection, but new mutations seem to be occurring at a rate sufficient to keep up the numbers, in spite of rigorous selection against it.

Hemophilia is inherited as a single sex-linked recessive. This means that a female can develop the disease only if she receives the gene from her father who has the gene and therefore the disease, as well as from her mother, who may be heterozygous. In view of the rarity of the disease, and the failure of most affected males to leave offspring, this coincidence would seldom happen. Thus we may explain the fact that, with a few doubtful exceptions, hemophilia has not been reported in women. Another explanation, suggested long ago and adopted by various authors, is that a female who receives the gene from both parents dies before birth, that is, that the gene is lethal when present in a double dose in females. Further studies seem to be necessary in order to establish the fate of homozygous females.

The most famous pedigree of hemophilia is that of Queen Victoria of England (Fig. 63), data for which have been assembled by Haldane.⁷ Victoria was heterozygous for the gene, perhaps

⁷ "New Paths in Genetics," by J. B. S. HALDANE, 1942, New York, Harper & Brothers.

as the result of a new mutation, since there is, according to Haldane, no record of hemophilia among her ancestors. Two of Victoria's five daughters proved also to be carriers. Her second daughter, Alice, had an affected son and two carrier daughters, and her fifth daughter, Beatrice, had two affected sons and one carrier daughter.

Among Victoria's four sons, only one, Leopold, was affected. He lived to be 31, married, and passed the gene on to his daughter, who bore an affected son.

Victoria's first daughter Victoria (II 1) was apparently free of the gene, since among her numerous children and grandchildren

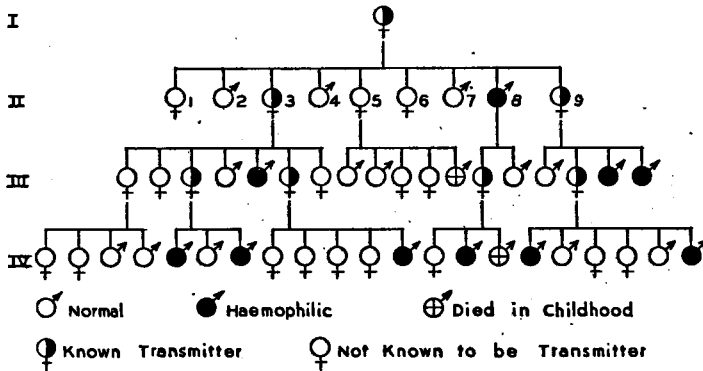


FIG. 63. Pedigree of Queen Victoria of England, showing the distribution of hemophilia among her descendants. (Redrawn, with modifications, from Haldane.)

there was no hemophilia. Victoria's first son (II 2), who became Edward VII of England, was free from it.

One of Victoria's carrier daughters, Alice (II 3), was the mother of Alexandra (III 6), who became the wife of Tsar Nicholas II of Russia. She was the mother of Alexis (IV 12), the late Tsarevitch, who suffered from hemophilia.

Victoria's other carrier daughter, Beatrice (II 9), was the mother of Victoria Eugenie (III 16) wife of Alfonso XIII of Spain. Two of her four sons, including the Spanish Crown Prince Alfonso (IV 16), were affected. It is not improbable that the existence of hemophilia in the crown princes of these two ruling families may have had an important influence in the overthrow of both dynas-

ties, thus emphasizing the far-reaching effects that a single gene may have upon the destinies of families and of nations.

Y CHROMOSOME INHERITANCE

The Y chromosome (Fig. 54) does not carry genes for ordinary sex-linked characteristics such as those just considered, but in the case of a few characteristics, pedigrees have been published which strongly indicate that their genes are located on the Y chromosome. In such cases the X chromosome carries no corresponding gene. One of these Y chromosome traits is a remarkable type of

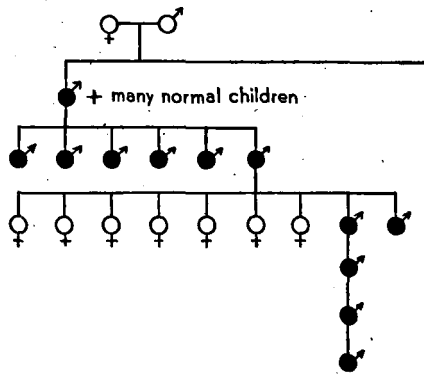


FIG. 64. Pedigree of the Lambert family showing Y chromosome inheritance of ichthyosis. (After Cockayne.)

scaly skin (ichthyosis hystrix gravior), first described more than a century ago in England. Cockayne gives a good account of the characteristic with a review of the literature relating to it. The defect first appeared in the son of a country laborer named Lambert, and the boy was shown before the Royal Society in 1731. A description written by Machin in 1732 follows:

The skin seemed rather like a dusky coloured thick case, fitting every part of his body, made of rugged bark, or hide, with bristles in some places, which case covering the whole of him excepting the face, the palms of the hands, and the soles of the feet, causing an appearance as if those parts alone were naked, and the rest cloathed. . . . It is said he shed it about once a year, about autumn, at which time it usually grows to the thickness of three-quarters of an inch, and then is thrust off by the new skin which is coming up underneath. The bristly parts, which were chiefly about the belly and flanks, looked and rustled like the bristles, or quills, of an hedge-hog, shorn off within an inch of the skin . . . his

skin was clear at birth as in other children, and so it continued for about seven or eight weeks, after which, without his being sick, it began to turn yellow, as if he had had the jaundice; from which by degrees it changed black, and in a little time afterwards thickened, and grew into the state it appeared in at present.

Both parents of this boy were normal, which indicates that a new mutation had occurred. The condition was passed on for five generations, and affected individuals were studied by some of the leading scientific men of the day. A number of articles were published describing members of later generations; all these reports agree with Machin's description. In each case it was emphasized that all affected individuals were males and that affected men transmitted the condition to all of their sons and to none of their daughters; their daughters never transmitted it to any of their children of either sex. A pedigree of the family drawn up by Cockayne is shown in Fig. 64. An inspection of this interesting pedigree shows that the characteristic is distributed exactly as it should be if the gene is located on the Y chromosome. Cockayne states that there were more children of both sexes in the later generations than he has indicated.

Webbed toes (fusion of the flesh and skin between the second and third toes) is another characteristic which is inherited in exactly the same way as the one just described. The evidence is based upon a pedigree of his own family published by Schofield,⁸ in which four generations are shown. The pedigree represents 14 affected males and no affected females. Every father transmitted the condition to all of his sons but to none of his daughters. (See pedigree p. 250.) Reports have been published of several other traits which follow the Y chromosome type of inheritance.

PROBLEMS

In *Drosophila*, the normal wing (VV) is an ordinary dominant over vestigial wing (vv). White eye (ww) is a sex-linked recessive; the normal red eye (WW) is dominant.

1. Indicate the eye color and the genotypes of the parents in the three matings which produced the following results:

⁸ SCHOFIELD, R.: Inheritance of webbed toes, *J. Heredity*, Nov., 1921.

	Red-eyed ♀'s	White-eyed ♀'s	Red-eyed ♂'s	White-eyed ♂'s
(a)	93	0	45	55
(b)	100	0	0	95
(c)	50	45	46	40

2. Show the visible ratio among the offspring of a cross between a female heterozygous for both vestigial wing and white eye, with a white-eyed male heterozygous for vestigial. (In all problems involving sex-linkage the ratio for each sex must be indicated separately.)

3. Show the results of a cross between a white-eyed vestigial female and a red-eyed heterozygous, normal-winged male.

4. Indicate the appearance and the genotype of each parent in the matings which produced the following offspring:

	Females				Males			
	Red Normal	Red. Vestigial	White Normal	White Vestigial	Red Normal	Red Vestigial	White Normal	White Vestigial
(a)	90	85	98	89	97	90	95	80
(b)	140	135	0	0	0	0	145	130
(c)	48	15	43	14	50	15	45	12

5. Show the expected ratio among the children from a marriage between a color-blind, heterozygous brown-eyed man (cBb) and a homozygous normal-visioned, blue-eyed woman ($CCbb$).

6. In the following problems assume that a certain recessive sex-linked character is present in 0.64 per cent of the women and in 8.0 per cent of the men in the entire population, and that marriages are purely at random so far as this character is concerned.

(a) Calculate the percentage of marriages in which both the man and the woman show this character.

(b) Calculate the percentage of marriages in which neither the man nor the woman shows the character.

(c) Calculate the percentage of marriages in which the man shows the character and the woman does not.

(d) Calculate the percentage of marriages in which the woman shows the character and the man does not.

7. Assume that every person who shows the sex-linked character mentioned in problem 6 fails to marry, and that this practice is continued in each generation. Assume also that 14.72 per cent of the normal women

in the first generation in the population are carriers (Cc) for the gene. Calculate the frequency of the characteristic in each of the next two generations, disregarding the occurrence of any new mutations. What will be the frequency in the tenth generation?

8. A woman whose maternal grandfather suffered from hemophilia has parents that are normal. The woman's husband is normal. What is the chance that her son will be normal? What is the chance that her daughter will be normal?

9. A woman whose maternal grandmother was a carrier of the gene for hemophilia and whose maternal grandfather was normal has parents that are normal. What is the chance that her son will be hemophilic? What is the chance that her daughter will be a carrier?

10. A certain recessive lethal gene l in man is carried on the X chromosome but not on the Y chromosome. An individual who fails to receive at least one dose of the dominant allele L dies before birth. In a mating between a normal male and a heterozygous female show the expected sex ratio of living births.

11. Construct a pedigree showing how a gene for hemophilia carried by a normal great grandmother may be transmitted through grandmother and mother to a boy, making its presence known only in this, the fourth, generation. Assume that all male ancestors of the boy are normal. Indicate the genotype of each ancestor of the boy in the direct line from his great-grandmother.

12. A boy has a great-great-grandmother on his mother's side who is known to be a carrier of the gene for hemophilia. His mother traces back to this ancestor through the female line alone. No other evidence of hemophilia has appeared among the ancestors of the boy. What is the chance that the boy inherited the gene for hemophilia?

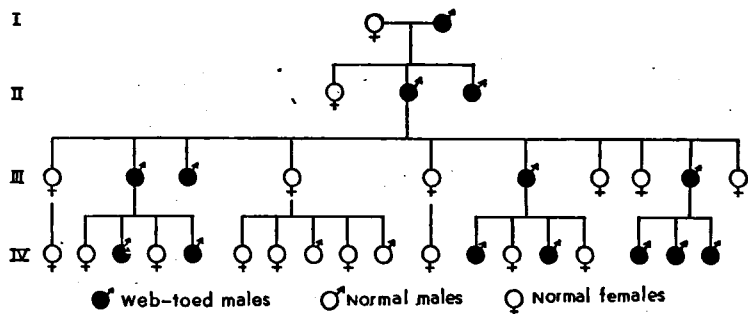
13. Assume that all hemophiliac females who are homozygous for the hemophilia gene die before birth and that in one male birth in 50,000 the child receives a gene for hemophilia from his mother. If none of these genes is the result of a new mutation, what is the proportion of women carriers in the population?

14. Explain the fact that most of the sex-linked characteristics so far discovered in man are recessive, whereas among Mendelian characteristics that are not sex-linked the majority so far discovered are dominant.

15. In Schofield's pedigree of webbed toes, shown below, if you assume that the gene for webbed toes is an ordinary non-sex-linked dominant and that the male in generation I is heterozygous for the gene, what is the probability of obtaining such a run of webbed toes in males

Sex-linked Heredity

and normal toes in females as shown here? (Assume that all parents not shown in the pedigree are normal.) Hint: The affected males produced by affected males and the normal females from affected males may be considered as two independent runs and their probabilities of occurrence calculated. The probability of the two runs occurring simultaneously may then be obtained.



Pedigree of the Schofield family indicating Y chromosome inheritance.

HEREDITY AND ENVIRONMENT

NOT SO LONG AGO, when much less was known than we know today about the relative importance of heredity and environment in the development of the individual, a favorite topic for debate ran somewhat as follows: "Resolved that heredity is more important than environment," or "Resolved that environment is more important than heredity." The debater usually held strong convictions one way or the other upon the subject, and what he necessarily lacked in valid evidence to support his thesis, he abundantly made up for in emotional fervor.

Today, considering the contribution of modern investigations in the field of genetics, all serious students of the subject realize that the question as stated above is not debatable. We now know that both heredity and environment are indispensable in the life of every organism; and if both are indispensable, neither can be considered more important than the other. In fact, the question becomes debatable only when it is limited to a single characteristic of individuals within a specified population and subject to a given environment: for example, "Resolved that heredity is more important than environment in determining the difference in height, (or weight, or I.Q.) among individuals living under the ordinary conditions found in the United States."

Let us now consider some of the facts which make necessary such limitations of the subject.

GENES INHERITED RATHER THAN CHARACTERISTICS

In the period immediately following the rediscovery of Mendel's work the rôle of heredity in the development of the organism was often overemphasized. Characteristics were looked

upon as units, and were thought to pass from parent to offspring with little regard to the environment. Further investigation soon showed the incompleteness of these ideas. As we have seen already, the discovery of the factor principle proved that the gene rather than the characteristic was the unit of heredity; and when, in turn, attention was directed to the rôle of environment, it was recognized that the genes themselves were merely factors in development. Genes, we are now aware, can do nothing by themselves; genes can work only in cooperation with the environment.

Let us now examine a few clear-cut examples of the effect of the environment on plants, on animals, and on man; afterward we shall consider a number of more complex cases in man—some of which are of the greatest importance to human welfare.

LIGHT AND ULTRAVIOLET RAYS AS FACTORS

In Indian corn we have an excellent example of the rule that what a gene can do the environment also can do. A recessive lethal mutation¹ known as albinism prevents the development of the green pigment, chlorophyll, in the corn plant. Seeds that have a double dose of this gene sprout normally, and the young albino plants grow rapidly for a time; but after reaching six to eight inches in height the food stored in the seed is exhausted, and, lacking the chlorophyll necessary for the manufacture of food, they die of starvation. Among their green neighbors the albinos present a striking color contrast, being almost pure white (Fig. 65). If normal seeds and albino seeds are planted together in a tray, which is then covered to exclude all light, all the plants, normal as well as albino, will grow up without green color; and at a little distance they cannot be distinguished from one another (Fig. 66), although on close examination the normal, unlike the albinos, are seen to be slightly yellowish in tint.

After the food in the seeds is exhausted, all the plants living in the dark will die, for the same reason that the albino plants die

¹ This effect is produced on corn seedlings by any one of a large number of genes located in at least four different chromosomes of corn. Twelve such genes are listed in "A Summary of Linkage Studies in Maize," by R. A. EMERSON, G. W. BEADLE, and A. C. FRASER, Memoir 180, Cornell University Agricultural Experiment Station, 1935.

even in the light, namely, inability to manufacture their own food. This experiment clearly demonstrates that light is just as necessary as the right genes for the normal development of green plants.

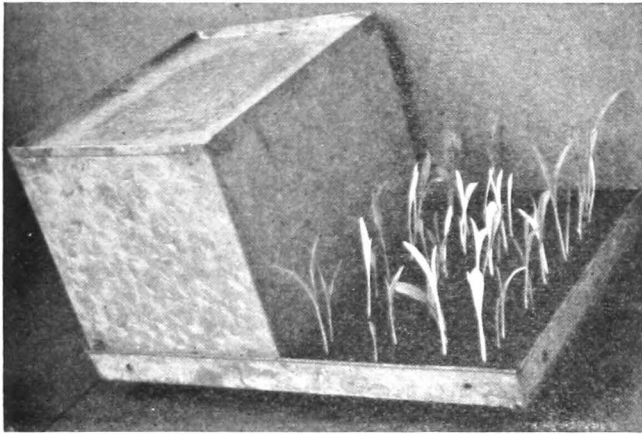


FIG. 65. Albino corn seedlings growing among normal green plants. A similar population is growing under the box in the absence of light.

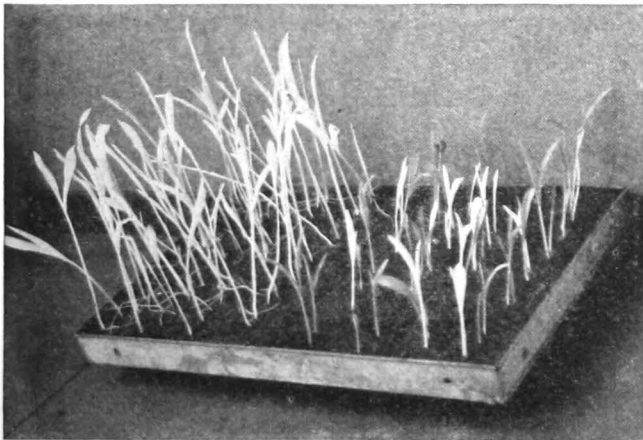


FIG. 66. Corn seedlings, all of the same age. The tall white plants at the left grew in the dark.

In order to make the above described demonstration a controlled experiment all environmental factors save the one which

is to be varied should of course be held constant. Although the apparatus does not fully meet this ideal, it is probable, considering the known facts of plant growth, that the chief effective factor in the observed differences is light. The cover shown in Fig. 65 is an open box of galvanized iron. The central region of the top is perforated in order to permit circulation of air into and out of the cover. A second iron top is fastened inside the box about one inch below the outer top. This inner top is about one inch smaller in both dimensions than the box, thus allowing circulation of air without the admission of light to the plants. As a further precaution all inside surfaces are painted black for the absorption of reflected light rays entering through the holes in the top.

The apparatus as described probably furnishes a reasonably good control of all factors in the environment except humidity. Under the box the humidity is naturally much higher than it is outside. Differences in concentration of carbon dioxide and oxygen and temperature differences are probably insignificant if the box is kept out of the direct rays of the sun.

In Fig. 66 other interesting environmental effects may be noted: the corn grown in the dark is much taller than that raised in the light; also, some of the roots of the dark-treated plants are growing above ground.

A familiar example of the effect of radiation simulating gene action in human beings is "tanning" of the skin. In the process of tanning, ultraviolet rays stimulate the development of pigment in the skin, provided there are present also the proper genes for tanning. Some persons (albinos and certain types of blondes) are unable to tan under any conditions. Brunettes, in general, tan more readily than blondes.

Since the color of the human skin depends upon genes, as well as upon the environment, it is obvious that we cannot always tell by looking at two persons whether their differences in color are due primarily to genes or to the environment. The circumstances surrounding each case must be known.

Another instance of the effect of ultraviolet rays on genetically different members of our species has to do with the deficiency disease known as rickets. This disease is characterized by imperfect development of the bones and teeth. Rickets is common

among babies and young children in northern cities, where ultraviolet rays from the sun are largely excluded by smoke, fog, and clouds for many months of the year. It is said to be extremely rare in the tropics, for exposure to the sun's rays causes the human skin to manufacture its own vitamin D, which prevents rickets.

There is good evidence, however, that heredity also is an important factor in the development of rickets. This has been shown by the study of children within the same family, where frequently some of the children develop the disease while others remain healthy. Dr. Lenz publishes a pedigree showing rickets in three generations, indicating that susceptibility may be dominant.

Recent experiments with rats in this country show that heredity is a factor in the development of rickets.² Quoting the authors of this investigation:

The animals in our experiments, after being subjected for three weeks to a rachitic diet and then X-rayed, were returned to a normal diet and reared, uninjured by the experience. Four months later they were bred. The breeders were chosen on the basis of the X-ray record of their sensitivity to the diet. Following fourteen generations of such selection and inbreeding, two strains of rats have been developed which in all appearances are alike, save in the one character that one of them reacts more severely to a rachitic diet (vitamin-D-free, high calcium and low phosphate) than the other strain. These experiments reveal the plastic nature of the growth line (epiphysis) of bones and its sensitivity to disturbances in the chemical composition of the body fluids. They also support those investigators who claim that heredity is a definite etiological factor in abnormal bone development, of the type seen in rickets. From such experiments we can thus understand why under equally unfavorable conditions the children in some families acquire rickets, while others do not.

TEMPERATURE AS A FACTOR

In plants numerous cases are known in which the effect of a change in temperature may resemble closely the effect of a change in a gene. In the Chinese primrose (*Primula sinensis*) there is one variety which produces red flowers at 20 degrees C. but white flowers at 30 degrees C. or above. By moving the plant from one temperature to another both red and white flowers may be obtained on a single plant. Another variety develops white flowers at both temperatures.

² STREETER, G. L., PARK, E. A., and JACKSON, DEBORAH: Hereditary vulnerability to dietary defects in the development of bone, *Science*, May 7, 1937, p. 437.

In animals a similar relationship between temperature and gene is shown beautifully in a breed of domesticated rabbits known as the Himalayan. Under ordinary temperature conditions these animals have a conspicuous color pattern. The skin and fur are white except on the feet, ears, nose, and tail, which are black. The eyes are pink. This pattern is a single recessive with respect to the wild color.

A simple experiment serves to show, however, that pigment formation on the extremities, without pigment formation on the rest of the body, depends upon temperature differences in the skin. If a patch of hair is plucked from the back of an adult animal and the rabbit is then placed in a cold room, the new hair coming in will be black. After the spot has become covered with new hair, and thus protected from the cold, any new hairs that appear later will be white. And as new hairs replace those lost by shedding, the dark spot gradually disappears.

Conversely, if hair is removed from one of the pigmented extremities and the bare spot protected with a bandage, thus raising the temperature of the skin, the new hairs that grow out will be white.

If the new-born animals are placed in a temperature as low as 11 degrees C. for only a few minutes and then returned to a warm room the hair as it appears will be pigmented over the entire body. It has been found that the short exposure to cold induces the formation of an enzyme in the skin which is necessary for the formation of pigment. Once the enzyme is formed it continues to function even at high temperatures. Normally pigment is not formed in these rabbits at temperatures above 33 degrees C.

It is obvious from these results that the Himalayan color pattern as such is not inherited. What is inherited is the gene which permits the development of pigment at temperatures up to a certain maximum; beyond this maximum the gene prevents the development of pigment.

The color pattern of the Siamese cat (Fig. 67) and of the albino guinea pig is subject to a temperature effect similar to that of the Himalayan rabbit. The guinea pig, however, develops much less pigment than the other two animals.

Although we know of relatively few cases in which genes are

as nicely balanced with the environment as those just considered, the principle illustrated undoubtedly applies to most genes. A series of examples could be given, beginning with those in which a change in the environment anywhere within the range tolerated

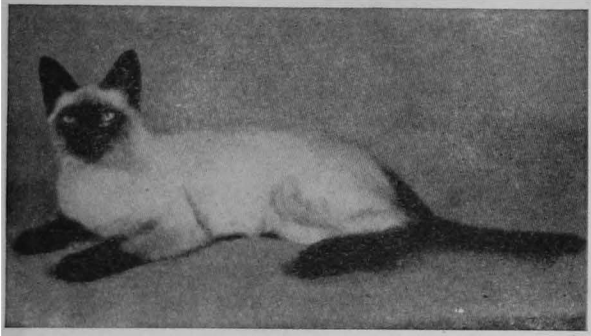


FIG. 67. Siamese cat, a color variety corresponding to the Himalayan rabbit and the albino guinea pig. Pigment develops on the extremities as a result of temperatures lower than on the rest of the body. (Courtesy, THOMPSON ET AL.: *J. Heredity*, April, 1943, p. 122.)

by the organism, produces no obvious effect on the characteristic, e.g., eye color, and ending with those in which, like the Himalayan rabbit, a moderate change in the environment produces a marked effect. Experience alone can tell us to what extent a given characteristic may be modified by the environment.

FOOD AS A FACTOR

In the chapters on human heredity we saw that genes have marked effects on size and growth. The same may be said of food. In plants and animals dwarfs can be produced at will by depriving the young of specific food substances, especially proteins and vitamins.

Because of the interaction of the two factors, genes and food, it is often hard to tell how much of the difference in stature among people is due to genes and how much to food. Measurements obtained in various countries in schools, colleges, and military recruiting offices indicate that the stature of modern man has increased during the past few generations, particularly during the

past generation. As an illustration of this, Professor Otto L. Mohr, of the University of Oslo, Norway, gives figures on the height and weight of students in the public schools of Oslo for the year 1920 compared with 1930.³ The portion of his table relating to height is shown in Table 14.

Table 14

TEN-YEAR INCREASE IN HEIGHT IN SCHOOL CHILDREN, OSLO, NORWAY

Above the double line, pupils in lower public schools. Below the double line, pupils in higher public schools (grammar school, gymnasium)

(From Mohr)

Age	Sex	Body Height in Cm.		
		1920	1930	Increase
10 Years	Boys	130.91	135.13	4.22
	Girls	130.02	134.59	4.57
14 Years	Boys	148.22	153.10	4.88
	Girls	150.60	154.94	4.34
14 Years	Boys	153.46	157.39	3.93
	Girls	154.91	158.52	3.61
18 Years	Boys	173.55	176.07	2.52
	Girls	161.64	164.69	3.05

Increases in weight were similar to those in height. Mohr states that in Norway all schools, both lower and higher, are public schools, and that his figures are from the very complete statistics collected by the municipal school physicians.

His explanation of this remarkable increase over the ten-year period is as follows:

As seen from this table there is a most remarkable general increase of stature and body weight in the course of the last ten year period. It is perfectly clear that the genotypical quality of the population cannot have changed perceptibly during so short a time. The very striking change must be due to the improvement of environmental conditions, better hygiene, better nourishment, etc. The experts in their comments upon this evidence point particularly to the fact that the widespread application of birth control has reduced the size of the family very con-

³ "Heredity and Disease," by OTTO L. MOHR, 1934, New York, W. W. Norton & Co.

siderably. The number of births in Oslo was 4,900 in 1920, 2,100 in 1933. It is a matter of course that in small families each child will have much better care, i.e., much better environmental conditions, than will be the case in large families with correspondingly limited financial opportunities.

A question might be raised as to whether the explanation is necessarily as simple as Mohr indicates. To rule out completely genetic changes it seems necessary to show that the fall in birth rate (which probably began long before 1920) was as great among tall members of the population as among short. If the fall in birth rate was less among genetically tall people, the net result of such selection would be a rise in average height of children.

A second genetic factor tending to increase stature in a heterogeneous population is the marriage of unlike types, resulting in what is known as hybrid vigor (Chapter 14).

Whether or not either of these factors has any force in the Oslo situation is not discussed, but in American cities it would seem unsafe to rule them out entirely.

Assuming that the differences shown in the table are largely environmental, we must remember that an increase in the stature of children of various ages due to improvement in the diet and other hygienic conditions does not necessarily mean an increase in the adult stature. Numerous experiments with animals have shown that diets deficient in certain respects may cause a temporary retardation of growth, but that when the diet is corrected, growth will begin again, and may continue even beyond the age at which it would normally cease. Growth may even continue until normal size is reached. On the other hand, if the diet is deficient in vitamin D and minerals necessary for bone formation, a permanent stunting and malformation may result.

An inspection of Mohr's table suggests that with the girls, at least, there was an actual increase in adult height, since girls usually reach their adult height at 18; with boys, growth may continue for several years longer.

From the preceding discussion it is evident that the solution of problems of the relative force of heredity and environment requires controlled experiments. Experimenting with man is out of the question, but fortunately nature herself has done a controlled experiment for us in the production of human twins. The study

of twins provides some of the best evidence we have on the relative importance of heredity and environment in man.

IDENTICAL TWINS AND FRATERNAL TWINS

The origin of identical twins and fraternal twins has already been discussed in some detail (Chapter 10). Briefly, it was found that identical twins come from a single fertilized egg, and therefore have identical sets of genes; whereas fraternal twins come from separate fertilized eggs, and therefore are no more alike genetically than if they had been born at different times.

The environment of a pair of twins of the same sex reared in the same family is about as uniform as can be found for human beings; hence most of the differences between them, which in the case of fraternal twins are often great, must be due to gene differences.

Assuming that the environment is equally uniform for both types of twins, a comparison of the two types tells us much about the rôle of heredity in human development. Characteristics which are usually present in both members of a pair of identical twins, if present in either one, but which are usually not present in both members of a pair of fraternal twins, must have a strong hereditary basis. Such characteristics are naturally relatively rare in the population as a whole. Nevertheless there are many examples of rare hereditary defects and diseases affecting both members of a pair of identical twins. Some of these were mentioned in the chapters on human heredity.

The comparison of the two types of twins as a means of detecting hereditary traits has been widely used in Germany, and to a considerable extent more recently in the United States. The method has been applied to all sorts of physical and mental characteristics, including the study of criminal behavior.

Since 1928 four books have been published in Germany reporting studies on crime in twins.⁴ The writers of all four books found from their investigation among prisoners that a criminal

⁴ One of these books, "Crime and Destiny," by JOHANNES LANGE, 1928, has been translated into English by CHARLOTTE HALDANE; published by CHARLES BONI, New York. For a review of the four books see POPENOE, P.: *Twins and criminals, J. Heredity*, Oct., 1936.

career in an identical twin was far more likely to be matched by a criminal career in his twin partner than is the case under the same circumstances with fraternal twins. Combining the numbers from all four studies, one obtains 66 pairs of identical twins: in 45 cases both twins were convicted of crime; in 21 cases only one was convicted. There were 84 pairs of same-sexed fraternal twins: in 32 cases both twins were convicted of crime; in 52 only one was convicted. In this country similar studies were made by Rosanoff and his associates.⁵ The results are similar to those from Germany. Among 37 pairs of identical twins both were convicted of crime in 25 cases; in 12 pairs only one was convicted. Among 28 pairs of same-sexed fraternal twins both were convicted in only 5 instances; in 23 cases only one was convicted.

In twin studies there is said to be *concordance* when both members of the pair are alike in the characteristic under study. In all five studies combined there was concordance in 68 per cent of identical twins as contrasted with only 33 per cent among the fraternal twins. If the percentage of concordance in the fraternal twins seems high, it should be remembered that these twins also have many genes in common, received from their common parents, which should tend to make them similar in behavior. Consequently we cannot say that environment alone was responsible for their criminal behavior.

In most cases the crimes were not committed by the twins in company. Nevertheless, the type of crimes committed by the pairs of identical twins, as well as the general behavior of the two individuals, showed much greater resemblances than in the case of fraternal twins. The higher degree of similarity in the behavior of the identical twins can best be explained as due to their greater similarity in heredity.

The foregoing studies strongly suggest innate differences in susceptibility to the temptation to commit crimes. It is clear, however, that the environment is an important factor in causing one to yield to the temptation or to resist it. The general conclusions from these investigations are supported by the most extensive studies of twins so far made in the United States: the work of

⁵ ROSANOFF, A. J., HANDY, L. M., and ROSANOFF, I. A.: Criminality and delinquency in twins, *J. Crim. Law and Criminol.*, 24: 923, 1934.

Professor H. H. Newman and two of his colleagues at the University of Chicago. In an extremely interesting book⁶ containing the results of more than ten years of labor the authors describe exhaustive measurements and tests of 119 pairs of twins. The monograph, containing many tables, graphs, and a carefully reasoned analysis of the data, can not be too highly recommended to those interested in the problem of heredity and environment as it applies especially to the normal physical and mental differences in man.

The first part of the book contains a comparison of paired differences of 50 pairs of identical twins reared together with 50 pairs of fraternal twins of the same sex also reared together. If one assumes that the environment of fraternal twins is about as uniform as that of identical twins the differences between the interpair differences in the two groups should be an expression of the force of heredity.

The examination given the 100 pairs of twins reared together included the following observations and tests:

PHYSICAL OBSERVATIONS AND MEASUREMENTS

Height, standing and sitting.

Weight.

Head length and width.

Cephalic index.

Hair color and texture.

Hair whorl (location and direction of twist).

Eye color and pigment pattern on the iris.

Skin texture and coloration.

Handedness.

Palm prints and finger prints.

Ears, general contour and peculiarities.

Other facial features.

Birthmarks, moles, etc.

TESTS

Standard Revision of the Binet-Simon Test of Intelligence.

⁶ "Twins: A Study of Heredity and Environment," by HORATIO H. NEWMAN, FRANK N. FREEMAN, and KARL J. HOLZINGER, 1937, University of Chicago Press.

Otis Self-administering Test of Mental Ability.

Stanford Achievement Test.

Downey Will-Temperament Test (Parts dealing with speed of decision, co-ordination of impulses, motor inhibition and finality of judgment).

Woodworth-Mathews Questionnaire.

Tapping tests for the objective determination of handedness.

Information was gathered, also, by interviews with parents and others regarding age, physical history, school history, general interests, and talents.

A comparison of the average differences in some of the traits measured is shown in Table 15.

Table 15

MEAN PAIR DIFFERENCES IN SELECTED TRAITS FOR 50 PAIRS OF IDENTICAL TWINS AND 50 PAIRS OF SAME-SEXED FRATERNAL TWINS

(After Newman, Freeman, and Holzinger)

<i>Selected Traits</i>	<i>Identical (Reared Together)</i>	<i>Fraternal (Reared Together)</i>
Standing heights.....	1.7 cm.	4.4 cm.
Weight.....	4.1 lb.	10.0 lb.
Head length.....	2.9 mm.	6.2 mm.
Head width.....	2.8 mm.	4.2 mm.
Cephalic index.....	0.016	0.028
Total finger ridges.....	5.9	22.3
Total motor score.....	19.3	29.0
Binet I.Q.....	5.9	9.9
Otis I.Q.....	4.5	9.3
Stanford Educational Age.....	6.4 mo.	11.6 mo.
Woodworth-Mathews Questionnaire.....	5.3	6.7

In the case of heights, weights, and Binet I.Q., the differences were also compared with differences among ordinary brothers and sisters of the twins. Differences among the latter were found to be almost exactly the same as among fraternal twins.

The first point to be noted is that identical twins are not absolutely identical in any of the traits listed. Evidently, environmental differences, either prenatal or postnatal, are sufficient to

produce measurable differences—in some cases fairly great ones—in identical twins reared in the same home. The differences between identical twins, however, are seen to be only about half as great as those between fraternal twins. Unlike genes obviously account for the greater differences in the fraternal twins.

Of the traits listed in the table, the one in which heredity appears to be relatively most influential is total finger ridges. This is in keeping with the finding that physical traits as a group show relatively greater influence of heredity and less influence of environment than the mental traits. The authors' explanation of this rule is as follows:

A most plausible provisional hypothesis would seem to be that behavior and mental ability are more subject to the influence of training and environment than are physical size, form, and features, such as color of eyes, color and texture of hair, etc. It is quite plausible to suppose that the nervous system, which is the physical counterpart of mental traits, of behavior, and of abilities, being more subject to influence by stimulation from the external world, is also more susceptible to variations through such stimulation and through the responses which are made to it.

But, one may ask, why should identical twins, having identical sets of genes, and reared in the same home, show even this much difference? The answer, according to the authors, is, in part at least, differences in the prenatal environment:

It is commonly believed that one member of each pair of identical twins is lacking in vitality as compared with the other. Many even believe that one member of each pair is sterile. While such views as these are incorrect, there seems to be some basis for the general impression, for in many cases one member of a pair of twins actually is physically inferior to the other in many ways from the time of birth on. It seems probable that such early differences in vigor and vitality are the result of minor inequality in the fetal blood supply of the twins, resulting from an imbalance in the placental blood exchange.

That this imbalance in blood exchange does produce marked differences in surviving twins is evidenced by the fact brought out by the extensive observations of Schatz, who found that, at about the middle period of pregnancy, size differences in monozygotic [one-egg] twins average much greater than in dizygotic [two-egg] twins. This is the opposite of what might be expected on a genetic basis. Identical twins that survive this period tend to be more nearly equal in size, but even at birth their size differences equal on the average those of dizygotic twins, many of the former showing more marked differences than the average of the latter. As has been said, such size differences frequently persist for life, and it seems probable that differences produced by this prenatal factor extend beyond mere size and involve also differences in vigor and general health. How much of the observed size and weight differences in adult identical twins

trace back to the factor under discussion we have no means of knowing, but it seems obvious that the effects of this factor are too important to be ignored. In concluding discussion of this factor it should be emphasized that it is peculiar to monozygotic twins, for there are no known cases of dizygotic twins in man in which placental anastomoses of fetal blood vessels occur.

IDENTICAL TWINS REARED APART

The really unique phase of the work on twins, as well as the part which presented the greatest difficulties, was the discovery and study of 19 pairs of identical twins separated in infancy and reared apart. In order to secure the number needed for statistical treatment the country was combed by letter, newspaper, and radio—the latter medium, incidentally, proving far the most effective.

The peculiar advantage in the study of identical twins reared apart is that they constitute a natural experiment in which one factor, heredity, is constant; while the other factor, environment, is varied. Therefore, the differences found (or rather that part of the differences in excess of the differences in identical twins reared together) should be due to the environment. By studying the differences in the environment of separated twins the effect of various factors in the environment may be discovered.

As a control on the environmental side there were already available to the authors the 50 pairs of identical twins reared together, in which the environment was as uniform as it is possible to find.

Extreme similarity was found among identical twins reared apart in the following physical traits: hair color and hair texture; eye color and pigment pattern of the iris; skin texture and coloration (except in a few cases where differences in health or exposure had produced noticeable differences); and shape and size of ears, nose, mouth, lips, chin, and teeth. In these traits environmental differences had practically no effect. In a number of other physical characteristics, however, considerable differences were found. A comparison of the differences in identical twins reared together with those reared apart is shown in Table 16.

It is obvious that the differences between the means of the two groups of twins are much greater for some traits than for others. By applying the usual statistical methods the authors

calculated that the differences were significant only for weight, I.Q., and Stanford Achievement. For traits such as height and head measurements no significant difference appears. The writers cautiously state:

These latter findings are as important as the former in that they indicate traits unmodifiable by the type of environmental change here studied. All these inferences are, of course, limited by the small number of separated cases and the small environmental difference by twin pairs for a considerable proportion of these. . . . Fifteen of the pairs had only a moderate variation in environment, whereas four pairs were reared in extremely different surroundings. If the contrast in environment had been greater for all cases, the influence of this factor would have been much larger.

Table 16

MEAN PAIR DIFFERENCES IN SELECTED TRAITS FOR TWO GROUPS OF IDENTICAL TWINS

(After Newman, Freeman, and Holzinger)

<i>Selected Traits</i>	<i>Identical (Reared Apart)</i>	<i>Identical (Reared Together)</i>
Height.....	1.80 cm.	1.61 cm.
Weight.....	9.90 lb.	4.03 lb.
Head length.....	2.20 mm.	2.59 mm.
Head width.....	2.85 mm.	2.25 mm.
Binet I.Q.....	8.21	5.35
Otis I.Q.....	8.00	4.54
Stanford Achievement.....	16.26 mo.	6.38 mo.
Woodworth-Mathews Questionnaire.....	5.00	5.48

After proper comparisons of data, it was concluded that educational and social differences in environment are effective in producing variations in such traits as intelligence and school achievement, and possibly some slight changes in temperament; while variations in physical environment are responsible for changes in weight, and to some extent in temperament.

A general conclusion as to the relative importance of heredity and environment is contained in the following quotation:

The analysis indicates that the role of heredity and environment in producing twin differences is a function of the type of environment. Thus, for twins reared together, most of the difference between members of a pair may be due to the

nature factor; whereas for twins reared under strikingly different environments, the nurture factors will have a relatively greater influence.

It is apparent from several of the comparisons made that the relative effect of hereditary and environmental differences is also a function of the type of trait. Any fixed ratio of these two factors for all traits and conditions is thus impossible. We must consider their relation always in connection with the kind of trait and grade of environmental difference.

From the viewpoint of the educator it is important to note that extreme differences in educational and social environments are accompanied by significant changes in intelligence and educational achievement as measured by our tests.

A large part of the book is devoted to detailed case studies of the 19 pairs of identical twins reared apart. The case studies suggest striking relations between certain factors in the environment and some of the characteristics. The pairs brought up under the most divergent conditions are of greatest interest, as illustrated in the four cases briefly described below.

1. *Alice and Olive*, born in London, England, were 19 years old when examined. At 18 months they were separated. Olive was brought to Canada and reared in a small town. Alice was kept in London. They did not meet for about 17 years. Then Alice came to Canada, and for one year previous to the tests had lived in Olive's home.

Olive was about 0.7 inches the taller and weighed 102 pounds; Alice weighed 92 pounds. At birth Alice was very weak and it was feared she might not live, while Olive was much stronger. Both girls had suffered from tonsillitis and bronchitis associated with rheumatism, although Olive had had a tonsillectomy at nine years of age.

The authors were unable to decide whether the rather large size difference was due to a prenatal handicap or to postnatal environmental differences.

In most of their physical traits the sisters were very similar, but, the authors state, "the tests reveal a marked and consistent difference in mental ability in favor of Olive, who probably had the better education." The differences in personality were less pronounced.

2. *Mabel and Mary* were 29 years old when examined. They were born in Ohio and separated at five months. Both lived on farms until they were six, but after that Mary was taken to a

small town where she had continued to live up to the time of the tests; Mabel stayed on the farm and lived the typical life of a farm girl.

The twins were said to be very similar as babies, and hardly distinguishable at two years of age. Even when they were 17 they were as similar physically as almost any pair of identical twins. Since that time they grew progressively more dissimilar, largely, say the authors, as the result of a very marked difference in weight, muscular development, and general health. Mary was $65\frac{1}{4}$ inches tall and Mabel $66\frac{3}{4}$ inches. Mary weighed $110\frac{3}{4}$ pounds and Mabel $138\frac{1}{2}$ pounds. The difference was largely one of muscular development, for, according to the writers, Mabel was not in the least fat.

Mary was a graduate of high school, and for a good many years had clerked in her foster-father's store, and had lived largely indoors. Mabel went through only the eighth grade in country school.

Mary had what she called "flu" almost every winter; Mabel was rarely troubled with "flu" or bad colds. With respect to health the authors state:

As a factor in the physical environment it seems to us that the active manual labor on the farm, much of it out of doors, has had much to do with Mabel's robust health: while Mary's largely sedentary, indoor life and lack of exercise have had a deleterious effect on her health and bodily vigor. This last contrast is one of considerable proportions.

Their features were still strikingly similar, except that Mabel's complexion was clearer and of a better color than Mary's, and her hair (medium brown) a little lighter in color, due probably to exposure to the sun. The teeth were nearly identical in shape and condition. Both women were farsighted and wore glasses having nearly the same correction, although Mary's were a little stronger.

What Mary lacked in physical vigor she evidently made up in mental development, for she was superior in all tests of ability. With the exception of the International Test, the difference in her favor was about twice the average difference for the 19 pairs—nearly three years in mental age and 17 points in I.Q. on the Binet Scale. Nevertheless, the writers state, Mabel did not give the impression of being at all dull, and in the International Test,

which is the least affected by education, her score nearly equaled that of her sister. "Mabel takes the lead in planning and seems to be quite competent in practical affairs," write the authors.

3. *Gladys and Helen* were both married women, 35 years old when examined. They were born in Ohio and after being separated at 18 months of age did not meet again until they were 28.

Gladys was reared in a medium-sized city in Ontario, Canada. When she had finished the second grade, her foster-father, who was a railroad conductor, went to the Rocky Mountains for his health. Gladys was taken along. There were no schools and when, after two years, the family returned to Ontario she did not reenter school, but remained at home doing housework.

At 17 she went to work in a knitting mill; at 19 she began work as a saleswoman in Detroit, working at this and at clerical work for a number of years. For the nine years preceding the tests she had been an assistant to the head of a small publishing house in Detroit, where her duties consisted of setting type, writing copy, and proofreading.

Helen's foster-parents were farmers in southern Michigan. She was not required to work hard at home, and was sent to a good Michigan college where she received a Bachelor's degree. Soon afterward she began teaching school, and for the eight years preceding the tests had been teaching in a large school in Detroit.

In weight, the sisters were almost identical, but Helen was 1.1 inches the taller. In other physical traits the two were very similar. In both twins the terminal joint of the index finger of both hands was bent toward the thumb in a curious fashion—an example of the sort of non-adaptive resemblance commonly found in identical twins, and constituting good evidence of identical heredity.

As might be expected from their differences in schooling, Helen was far superior to Gladys in all the mental tests. In the Stanford-Binet test the difference was three years, ten months, or 24 points in I.Q. The differences in test intelligence were greater for this pair than for any other pair reared apart; the difference in formal education was also greatest in this pair.

With respect to personality differences the authors make the following comment:

Observations of the overt behavior of these twins revealed some further important personality differences. Helen is a confident and suave person with rather marked charm of manner. She makes the most of her personal appearance, moves about gracefully, and is apparently conscious of making a favorable impression on men. She conversed smoothly without a trace of diffidence and always took the lead in all matters pertaining to arrangements for the trip and the stay in Chicago. One sees at once that she is by far the more aggressive in her overt acts, but the Downey test revealed about equally strong aggressiveness in the two women. Gladys made the impression upon us of a person ill at ease. This attitude may have been partly the result of a feeling of inferiority in view of the apparent certainty that she would make a comparatively poor showing on the tests. She seemed to us to be a rather staid and stolid person, distinctly diffident. She had no affectations to match those of her sister and had no charm of manner or grace of movement. She was not becomingly dressed nor did she make the best of her physique. She never volunteered any information and was difficult to draw into conversation. She made no effort to create a favorable personal impression. In general, the contrast in overt behavior during social contacts was rather extreme.

As an advertisement for a college education the contrast between these twins should be quite effective.

4. *James and Reece* were 27 years old when examined. They were born in a mountain village in southeastern Tennessee. Their mother died in childbirth and they were separated at less than one year of age, James being taken by his maternal grandparents and Reece by his paternal grandparents. Because of strained relations between the two foster-families, the twins never associated. Until their visit to Chicago they had never spent more than a few hours together.

After graduating from high school James was employed as an engineer in a sawmill and sand-and-gravel business run by his grandfather and maternal uncle, who were reported as steady and industrious people.

The paternal grandparents with whom Reece lived were "mountaineers of the more primitive sort, a type common in the mountains of Tennessee," say the authors. The grandfather, a Confederate veteran with a pension almost large enough to live on, had never worked steadily, but had tried his hand at coal mining, blacksmithing; and work on the railroad. Reece followed the custom of the family in avoiding regular work. For a short time he worked in an automobile factory, but that was "too much like slavery" to him, so he returned to the mountains. The authors state that it would not be fair to recount any of his less creditable occupations and experiences.

Reece attended a mountain school when he felt so inclined, but never for more than five months in the year, usually much less. He completed the eighth grade. The authors do not feel free to divulge the details of his social environment but state that the contrast with that of his brother was very great.

Both men were married early: James had had two children, one of whom died in infancy; Reece had none. The authors state: "Steady work, largely in the open, on the part of James, and the free life in the mountains, except when he was not so free, on the part of Reece, seem to offer no great contrasts from the purely physical standpoint."

In physical appearance these twins were as similar as the average pair of identical twins reared together, although James weighed 14 pounds more than Reece. Among their striking similarities the following are mentioned by the authors: "Both have the same peculiar iris pattern—a very dark outside ring surrounding a greenish-brown center. Both left eyes are slightly strabismic and have no image-forming power, merely reacting to light and darkness. . . . The fingernails of both have been bitten down to an extreme extent." It is interesting to note that in one other pair of identical twins reared apart (two boys of 19) the fingernails of both were bitten down in the same way.

According to the authors, "An unusual feature that is present in the pen writing of both, but does not appear in the pencil writing, is a rather marked tremor. This doubtless has a physiological basis, but we are unable to say what it is." In other respects, however, the handwriting showed marked differences.

In intelligence, James ranked 19 points above Reece in I.Q. on the Binet Scale—the second largest difference found among separated twins. The difference was as great on the International Test as on the others.

In summarizing the personality of the twins the authors write:

The facts regarding personality are not so simple. In some basic elements of temperament these brothers, brought up under such diverse conditions, are remarkably similar. This is brought out most strikingly in the Downey Test. In the tests of neurotic disposition and of emotions, also, they are rather similar. In behavior, judged from the point of view of its social productiveness and acceptability, however, the contrast is sharp. There is also a marked contrast in handwriting. While, then, a certain basic similarity in mode of reaction exists by

nature and persists in spite of differences in the environment, some rather fundamental modification has apparently been made, and marked effects in the aim, direction, and content of behavior are obvious.

The differences in behavior in this pair of twins are interesting when compared with the studies of twins in Germany, referred to previously.

AGE OF MOTHER A FACTOR IN MAMMALS

In most respects the uterine environment of mammals is well standardized; within a given species there is probably little variation in embryonic environment in such ordinary factors as temperature, light, and moisture. With respect to food and the chemical environment in general, however, there are possibilities of differences. It is therefore not surprising to find that the age of the mother may become a differentiating factor among the offspring of mammals.

There is a popular belief that many differences among children in human families are due to the age of the mother or to the father. So far as the father is concerned there seems to be no good evidence in support of such a belief, either from animal breeding or from the study of human families. The male affects the offspring only through the sperm, and a sperm seems to be little more than an animated package of genes. The genes carried by the sperms are apparently not affected by the age of the male which produces the sperms.

On the other hand, the mammalian female has an intimate relationship to the developing embryo, since substances in the mother's blood are constantly diffusing into the blood of the embryo. It is reasonable to suppose that advancing age may cause changes in the composition of the blood, thus making the environment of embryos in older mothers somewhat different from that of young mothers.

So far as is known, the only experimental studies in animals showing an unmistakable effect of age of mothers upon offspring are those reported by Sewall Wright.⁷ In an extensive experiment with guinea pigs he found that in a family of pure-bred animals

⁷ WRIGHT, SEWALL: Effects of age of parents on characteristics of the guinea pig. *Am. Naturalist*, Nov.-Dec. 1926.

having a piebald (white-spotted) pattern, the percentage of white skin and hair of the offspring increased with the age of the mother until the mother had reached her full growth.

In this same family of guinea pigs there was a hereditary tendency to produce offspring with a fourth toe on each hind foot. (Most guinea pigs have only three toes on each hind foot.) It was found that this tendency decreased to a remarkable extent with increase in age of mother. This relationship is shown in Table 17, below.

Table 17

EFFECT OF AGE OF MOTHER ON NUMBER OF TOES IN GUINEA PIGS
(After Wright)

<i>Age of Mother</i>	<i>Number of Young</i>	<i>Per Cent with Fourth Toe</i>
3-6 months.....	349	52.7
6-9 months.....	390	40.0
9-12 months.....	319	29.2
12-15 months.....	292	26.7
15-21 months.....	330	18.5
21-46 months.....	296	14.2
Total.....	1,976	31.1

The experiments on extra toes do not rule out entirely the possible effect of the age of the father, since in the great majority of the matings the father was of exactly the same age as the mother. Yet the few cases of marked difference in age of parents all pointed toward the importance of the mother in this respect. The most interesting of these cases was the birth of a litter when the female was only 100 days old. This litter was sired by an adult male 17 months old. The three offspring had fourth toes. In two the fourth toes were perfectly developed; in the other almost perfectly so.

In this family of guinea pigs only 29 cases of perfect fourth toes had been recorded among 1,976 animals; 14 of these were born before the mother reached her sixth month. The author concludes, "it can hardly be a coincidence that the most perfect

polydactylous litter in the entire body of data was produced by the youngest dam."⁸

Why should young mothers produce offspring with more pigment and more toes than older mothers? We do not know. Wright suggests that possibly some sort of competition between the growth process of the mother and the early developmental processes of the embryo may be responsible, since guinea pigs have reached only about half their mature weight at three months of age and do not reach their full growth until about fifteen months. It is possible that a decrease in the rate of metabolism in the female, with advancing age, may be a factor—a higher rate of metabolism in young mothers favoring the production of pigment and extra toes.

Whatever the cause of greater frequency of four-toed offspring from young mothers, it is clear that there is no difference between the genes transmitted by young mothers and those transmitted by older mothers: Wright found that females born to young mothers produced the same percentage of four-toed offspring as females born to older mothers. Moreover, it was found that three-toed parents produced the same percentage of four-toed offspring as four-toed parents. In this family the three-toed and the four-toed individuals were genetically alike, in both cases transmitting merely a tendency to develop a fourth toe under certain conditions. There was no evidence whatever of inheritance of an acquired characteristic: the occasional occurrence of four toes is an environmental effect that lasts for only one generation.

The extra toe in guinea pigs is an excellent example of the interaction of heredity and environment. In some pure breeds of guinea pigs the fourth toe never develops; in one breed obtained by selection by Professor W. E. Castle of Harvard University, the fourth toe always develops. Obviously we are here dealing with a clear-cut hereditary difference in the breeds. Crossing experiments between the pure three-toed and pure four-toed breeds indicate that the fourth toe depends upon several recessive genes. Incidentally, the fourth toe is not a duplication of an existing

⁸ In a later study Wright showed that the age of the father has no effect upon the frequency of fourth toes in the offspring—*Genetics*, 19: 537-551, 1934.

toe, but in structure and position corresponds to the little toe in other mammals. It is thus highly probable that it is a restoration of an ancient ancestral condition.

Suppose that we had never heard of these other families of guinea pigs, but knew only of the family studied by Wright. We would then certainly be inclined to say that the extra toe is largely an environmental difference, but from our consideration of the species as a whole, we must conclude that it is both hereditary and environmental.

If all three families had been mixed indiscriminately in a breeding pen, we would have had difficulty in deciding as to the relative importance of the two factors—heredity and environment—in determining the number of toes in the offspring. The resulting confusion of factors would be analogous to the situation in man where the heterogeneous nature of the population presents great obstacles to the study of heredity and environment. As a means of avoiding such obstacles the study of human twins has proved to be an extremely valuable method.

AGE OF MOTHER A FACTOR IN MAN: MONGOLISM

We have noted (chapter 10) that the age of the mother is an important factor in the production of human fraternal twins. This may mean simply that in older women two eggs are more often released from the ovary at one time than in younger women. The age of the mother has no permanent effect upon the offspring as individuals. There is, however, a well known case in man in which the characteristics of the individual offspring are affected by the age of the mother. This has to do with the condition known as *mongolism*, a good description of which is given by Rosanoff⁹ and which forms the basis of the following brief summary.

The name monogolism was coined by J. Langdon Down of London in 1866 for a definite kind of mental defective having as a frequent characteristic a fold of skin on the upper eyelid similar to that in Mongoloids (p. 148). Other common characteristics of monogolism are: relatively short stature and light weight; short

⁹ "Manual of Psychiatry and Mental Hygiene," by AARON J. ROSANOFF, 7th ed., John Wiley & Sons, 1938.

broad skull (brachycephalic); late and irregular eruption of teeth; tongue relatively large and often deeply fissured; hands small, broad, and stubby; low muscular tone and laxity of the joints; in infants, late development of the power to hold up the head, sit up, and walk (often unable to walk until after three years of age); mouth breathing, with a marked susceptibility to respiratory infections; congenital heart anomalies in at least 20 per cent of the cases; circulation to the extremities poor, with undue sensitiveness to extremes of heat and cold; genitalia infantile, secondary sex characters late in appearance and incomplete in development, sex interest slight or absent; failure to learn to talk in at least 25 per cent of the cases, in the others talking learned slowly and imperfectly; in intelligence about 37 per cent are classed as idiots, 61 per cent as imbeciles, and 2 per cent as morons (see p. 192); behavior difficulties are rare and patients are quiet, cheerful, and affectionate.

Very few sufferers live to be adults; the average age at death in institutions is about 14; in the majority of cases the immediate cause of death is some respiratory infection.

According to Rosanoff, "The diagnosis of mongolism presents, in general, no difficulty whatever. One who has had a chance of observing a few cases will be able to recognize the condition almost at a glance."

Mongolism is fortunately rare. During the year ended June 30, 1935 there were 59 cases among the 1789 first admissions to the New York State schools for mental defectives. This comprises 3.3 per cent of all admissions.

There have been many theories advanced as to the cause of mongolism, among them heredity. Some workers, however, have denied that heredity has anything to do with it. In the latter group is Rosanoff who takes this view because—in contrast to other forms of mental deficiency—there is rarely more than one case of mongolism in a single family.

It is now generally recognized that the age of the mother is an important factor in the occurrence of the defect, since numerous studies have shown that most cases of mongolism come from mothers well along toward the end of the reproductive period. In England L. S. Penrose found that the average age of mothers of

mongoloid defectives was about 38 years, while that of mothers of normal children was under 30.¹⁰

Penrose thinks it unlikely that mongolism is the result of a single recessive gene because among over 100 pairs of parent of mongols no first or second cousin marriages were found. With rare recessive defects the percentage of cousin marriages is usually high since cousin marriages offer an unusual opportunity for two recessive genes to come together (see Chapter 14). Penrose thinks that some kind of dominant heredity is responsible for mongolism; he suggests that susceptibility to mongolism may depend upon two dominant genes.

Table 18

SUMMARY OF CASES OF MONGOLISM IN TWINS PUBLISHED UP TO 1935

(After Rosanoff)

<i>Type of Twins</i>	<i>Number of Cases</i>	<i>One Affected</i>	<i>Both Affected</i>
Identical, males.....	3	..	3
Identical, females.....	5	..	5
Same-sex, fraternal, males.....	6	6	
Same-sex, fraternal, females.....	7	7	
Opposite-sex, fraternal.....	23	23	
Totals.....	44	36	8

The incidence of mongolism in twins is in entire agreement with the idea of defective genes. Rosanoff has summarized the recorded cases of mongolism in twins. Including only those cases where twins were diagnosed either as identical or fraternal his data are shown in Table 18.

It is noteworthy that in every case of mongolism in identical twins, both twins were affected, while in no case of fraternal twins was more than one affected. This is exactly the distribution found in other rare characteristics known to be Mendelian.

¹⁰ PENROSE, L. S.: On the interaction of heredity and environment in the study of human genetics, with special reference to Mongolian idiocy, *J. Genetics*, Vol. 25, No. 3, 1932; "A Clinical and Genetic Study of 1280 Cases of Mental Defect," by L. S. PENROSE, Med. Research Council Special Report Series, No. 229, London, 1938.

It seems probable, therefore, that the susceptibility to mongolism is inherited like the tendency to develop the fourth toe in guinea pigs, as described in the previous section. As women grow older there may be some change in the chemical condition of the blood, perhaps a hormone deficiency or the presence of certain metabolic products, which, in cooperation with certain genes, causes the development of mongolism.

ARE ACQUIRED CHARACTERISTICS INHERITED?

In considering this much-debated question it is most important to define our terms carefully. From the preceding discussion it is

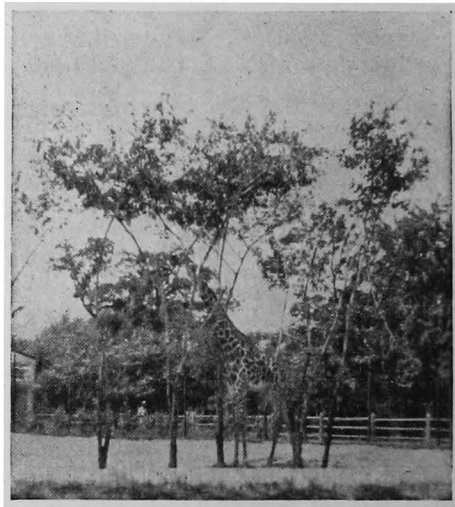


FIG. 68. This giraffe was found stretching its neck to the utmost in order to reach the leaves on the tree. Hay was available to the animal with no effort on its part. (Photograph by the author.)

clear that in one sense every characteristic of the individual is acquired, since in each generation characteristics develop anew under the combined influence of genes and the environment. It is also clear from the study of life on earth that over a period of many generations a species gradually acquires new hereditary characteristics. This is not what is ordinarily meant, however, when the expression *acquired characteristics* is used.

The inheritance of acquired characteristics has come to have a particular meaning developed especially by the French biologist Lamarck (1744–1829). Lamarck thought that individuals inherited their characteristics as such directly from their parents and that each generation began where the preceding one left off. If some parts of the organism developed in an unusual manner as the result of use or disuse, or because of the direct effect of the environment, the offspring, according to Lamarck, would show the same unusual development. Thus, according to his theory, the long neck and long legs of the giraffe (Fig. 68) are the result of many generations of stretching the neck as the animal browses on the leaves of trees.

Again, according to Lamarck's theory, the children of highly educated parents should profit directly by the special training received by the parents, and conversely the children of parents who lack opportunities should inherit poorer mentality. To take another example, if a group of white people were to migrate to a tropical country where they were exposed to intense sunlight, causing them to become deeply tanned, their children were supposed to be somewhat darker as a result. Inheritance of the effect of exposure to the sun, generation after generation, was supposed by the Lamarckians to be the explanation of the dark-skinned races of mankind.

Although Lamarck's theory was widely accepted in Mendel's day—accepted, indeed, without any valid substantiating evidence—it has now been abandoned by practically all biologists.

An outstanding weakness of Lamarck's theory is that it necessarily implies a mechanism of some sort whereby any change produced in the body cells by subjection to environmental conditions will register a specific effect in the reproductive cells in such a way that the offspring will develop the new characteristic without themselves being exposed to the original conditions.

Charles Darwin, who believed in the inheritance of acquired characteristics and considered it as one of the minor factors in the origin of species, felt the need for such a mechanism. As a purely imaginary concept he proposed what he called the "Hypothesis of Pangenesis," wherein he suggested that the cells of each part of the body liberated into the blood minute granules with the power

to multiply and accumulate in the reproductive cells. In the offspring these particles were supposed to cause the development of cells like those from which they came.

No evidence, however, was ever found in support of the Hypothesis of Pangenesis, while the evidence from subsequent discoveries relating to mitotic cell division, the process of sperm and egg formation, chromosome constitution, and genes convinces us today that the facts are essentially opposed to Darwin's theory. We now look upon development as proceeding outwardly from the genes, the genes producing their effect upon the body cells but being unchanged by them. The end result, i.e., the characteristic, may be influenced by the environment and by use and disuse, but these influences have no power to bring about a specific change in the gene.

A second important reason why the inheritance of acquired characteristics has hardly any supporters among biologists today is the negative result of countless experiments with plants and animals. Although from time to time up to recent years experimenters have thought that they got positive results in the offspring by training or specific environmental treatment given the parents, not one of these experiments has stood the test of critical examination and repetition at the hands of other experimenters. Darwin seems to have accepted Lamarck's theory on the basis of reported positive results by various experimenters. Unfortunately, he did not repeat the experiments himself and thus did not discover his error. As mentioned in Chapter 1, Mendel performed certain experiments with plants which made him skeptical of Lamarckism.

As we look at the problem from all sides today, it is perhaps fortunate for the offspring that the reproductive cells of the parents are so well protected from the effects of the activities of the parents and from the influence of the environment, and that each generation can start with a clean slate, instead of inheriting all the acquired characteristics, bad as well as good, of their parents.

But if the effects of use and disuse and the ordinary environmental factors are not inherited, how are we to account for the multitude of hereditary characteristics which complex organisms possess? How do genes change, and how are new genes added?

These are questions which we shall attempt to answer in the following chapter.

“**MENTAL IMPRESSIONS**” (*Maternal Impressions*)

Most women perhaps would like to believe that by voluntarily controlling their thoughts and actions they could influence for the better their unborn children. Many fear that mental shocks, such as the sight of some abhorrent object, received during the period of pregnancy will have specific effects upon the child. Birthmarks of various kinds as well as serious abnormalities have been attributed to such experiences. Ancient as are these beliefs, and reputable as are many of the scientists who in earlier days accepted them, there is today no reason for such fears and beliefs.

No good evidence has ever been produced to prove the transmission of mental impressions. What purports to be evidence invariably turns out to be isolated instances of abnormalities of development coupled with a recollection of some peculiar experience of the mother, supposed by her to be the cause of the abnormality. The kind of evidence needed to show the inheritance of maternal impressions—evidence which seems to be wholly lacking—is records of experiences by women made *before* the birth of the infant, with the observation of marks fitting such experiences. The belief in maternal impressions rests upon the fallacious reasoning that because one event follows another the second event must be caused by the first.

Not only is there no good evidence that mental impressions occur, but there are good biological reasons why they cannot occur. In the first place, the nervous system of the developing child is not connected in any way with the nervous system of the mother. The child is connected to the placenta of the mother by the umbilical cord only. Blood vessels, but no nerves, pass through the cord. Secondly, the blood of the mother normally does not pass directly into the blood vessels of the embryo; the vessels of the two merely lie side by side, permitting substances from the mother's blood to diffuse through the walls of the blood vessels into the blood of the embryo. It is only those influences which alter the mother's blood that are proved to have an effect on her

unborn child. In the latter category of course come poisons of various kinds, a diet deficient in vitamin D, antibodies (a striking example of which we have seen in the case of the Rh blood factor) and at least one parasite, the spirochete of syphilis, which is known to pass from the mother into the blood of the child. As a result of vitamin D deficiency and of syphilis in the mother babies are frequently born with rickets or congenital syphilis, respectively, contracted during embryonic life.

Other changes in the blood of the mother of a more subtle nature are no doubt responsible for a few variations in individuals. As an example we have already considered the age of the mother as a factor in the development of mongolism.

Many abnormalities of development such as birthmarks, harelip, abnormalities of the hands and feet, and so on, are, as is well known, influenced by heredity. Others for which no evidence of heredity has been shown are regarded as "accidents of development" and are probably due to some factor in the environment.

PROBLEMS

1. If the effect of environmental factors in determining differences is to be studied what should be the genetic make-up of the individuals used in the study?

2. If the effect of alternative genes in determining differences is to be studied what should be the nature of the environment of the experimental individuals?

3. In human beings, the external environmental factors such as light, temperature, and food have no obvious effect upon the color of the eyes. Does this mean that the development of the eye color in the individual is independent of all environmental factors? Explain.

4. Give several reasons why in mammals it is more difficult to demonstrate hereditary differences in behavior patterns than hereditary differences in physical traits.

5. Why are identical twins reared apart especially favorable material for the study of the rôles of heredity and environment?

6. The statement is sometimes made that differences in intelligence in man are not due to heredity if the individuals compared are normal and healthy. Analyze critically this statement and state your own conclusions on the question of the relationship between heredity and intelligence.

7. Assuming that all the cells in the body contain identical sets of genes (the evidence available indicates that this is true) to what may we attribute the differentiation of the cells into muscles, glands, skin, brain cells, etc.?

8. If the genes in all parts of the body are identical how may we account for the fact that paired structures on opposite sides of the body, e.g., finger-print patterns, shape of ears, etc., are never absolutely identical?

9. Aside from humanitarian reasons, and purely for genetic reasons, why should the environmental conditions for all the people be made as favorable as possible, under a program designed to improve the hereditary qualities of a people?

10. What human characteristics are clearly influenced by environmental differences, judging by the results of the studies of Newman and his associates of identical twins reared apart?

THE GENE AND MUTATION

HUGO DE VRIES, famous Dutch botanist, remembered as one of the rediscoverers of Mendel's work, brought into general use the word "mutation." He did this by writing a book entitled, "*The Mutation Theory*," published in 1901. His views are summarized in the following quotation:

These saltations, or mutations, of which the so-called sports are the best known instances, constitute a distinct province in the study of variability. They occur without transitional gradations and are rare; whilst ordinary variations are continuous and always present . . . Mutations give rise not only to species but also to varieties.

In thus emphasizing the discontinuous nature of mutations and the difference between mutations and ordinary variations (by which he meant environmental variations), de Vries made a significant contribution to the study of evolution. His experiments, observations, and writings aided much in discrediting the theory of the inheritance of acquired characteristics.

But, according to Professor Thomas Hunt Morgan, pioneer and leader in the study of heredity in the United States,

it was not so much the idea that variation is a discontinuous process that makes de Vries's contribution significant. It was rather, as he thought, his detection of the process of mutation at work, and his demonstration that it is playing a rôle in the evolution of certain forms living today. Here, if de Vries was correct, was a chance to study by direct observation and controlled experiment the processes by which evolution of animals and plants comes about. . . . The sequel has, I think, justified the expectation. . . .¹

De Vries observed that mutations are often indifferent, neither helping nor hindering their possessor, and he pointed out that indifferent mutations as well as beneficial ones might become fixed

¹ "The Scientific Basis of Evolution," by THOMAS HUNT MORGAN, 2d ed., 1935, New York, W. W. Norton & Co.

in the population. He thus correctly accounted for the fact that closely related species frequently differ in nonadaptive characteristics; these cannot be accounted for by natural selection, since natural selection changes species in adaptive ways.

The cause and the physical basis of de Vries's "mutations" were unknown; de Vries, therefore, used the term mutation to include all hereditary changes. Usage today is tending toward the restriction of the meaning of the word mutation to a change in a single gene. Other kinds of hereditary changes—of which there are many, such as duplications or losses of entire chromosomes or chromosome sets or pieces of chromosomes, or gross reorganization of chromosomes—are designated chromosome changes. As a matter of fact, some of these chromosome changes are transmitted in the same way as gene mutations. Consequently, many supposed gene mutations may turn out to be chromosome changes, as some actually have in the past. In general any Mendelian change is regarded as a gene mutation until it is shown to be the result of some gross chromosome change. Most of the so-called mutations which de Vries observed proved later to be chromosome changes.

De Vries looked upon mutations as changes which cause large and conspicuous effects (as most chromosome changes are known to do); but as more refined methods for the study of mutations were developed, it became clear that the fundamental thing about the phenomenon is the change in the gene—not the size of the effects. Gene mutations may produce effects varying all the way from large and conspicuous ones down to those that are barely perceptible, and perhaps even imperceptible by our present methods of observation. This is easily illustrated in man: the mutant genes for albinism and for amaurotic idiocy, to choose two examples, produce gross changes in various parts of the body, while some other genes, such as those responsible for the almost unlimited number of slight differences in the shade of the hair, produce small effects. Although it has not been proved that albinism and amaurotic idiocy are due to gene mutations rather than to chromosome changes, the principle holds good, nevertheless, since many examples could be cited for plants and animals in which the effects of gene changes are either great or minute.

Recent investigations in several directions indicate that small

mutations are the most numerous of all. In agreement with this conclusion, the analysis of related species in plants and animals, by crossing and otherwise, shows that their differences depend upon many mutations, each of which by itself has only a slight effect. Consequently, Darwin's formula for the origin of species by the "accumulation of innumerable slight variations" is perhaps not far from the truth in the great majority of cases.

On the basis of what has been said above we may define a mutation as a sudden and discontinuous change in a gene, occurring rarely for any particular gene, and capable of producing a change—great or small—in some part of the body. Mutated genes possess in general the same degree of permanency as the original genes from which they came.

THE NATURE OF THE GENE

Genes occupy a position today similar to that occupied by vitamins and hormones a few years ago; that is, we know that genes exist, we know where they can be found, we know much about their effects, but we are not yet able to isolate and analyze them chemically or to produce them synthetically.

In the past few years, one after another of the vitamins and hormones has been isolated, analyzed, and synthesized in the laboratory. Will this history be repeated for the genes? Time alone can tell. At present the problem is being actively attacked in the laboratories of the biochemists.

The theory most widely accepted at present is that genes are specific chemical substances having certain physical, chemical, and physiological properties in common. One of the most interesting of their properties is the ability to speed up specific chemical reactions without themselves being used up in the process, i.e., they act like enzymes. In some cases, as in the Himalayan rabbit (Chapter 12), it has been shown that a gene causes the formation of an enzyme which in turn produces a specific effect.

Chemically, genes are regarded by many investigators as large protein molecules (Fig. 69). This idea is an attractive one in view of two recent discoveries: first, that certain disease-producing viruses are large protein molecules, and second, that

genes and viruses show a number of interesting properties in common.

As to their common properties, both genes and viruses are minute bodies of comparable size (Fig. 70); both multiply only in living cells (unlike bacteria, viruses cannot be cultivated on dead culture media); both produce their specific effects only in definite

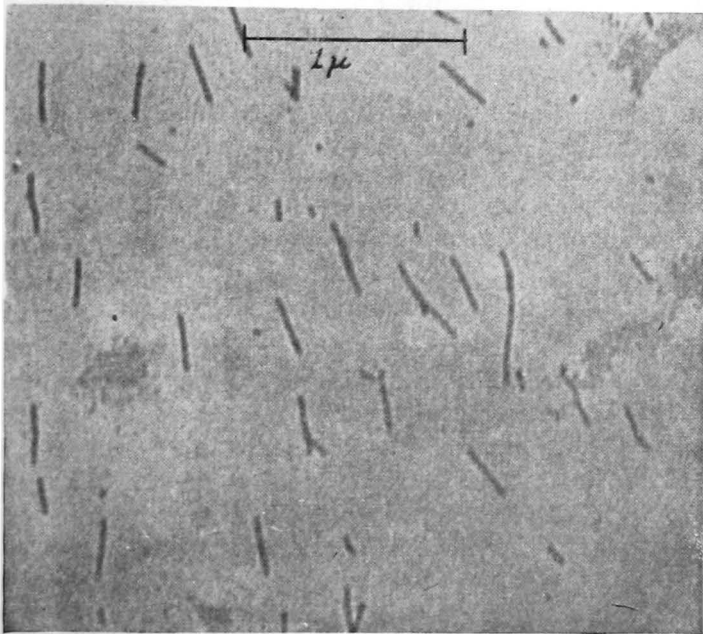


FIG. 69. Photograph by means of the electron microscope of molecules of tobacco-mosaic virus. $\times 34,000$. Compare size of this virus with that of a gene (Fig. 70). (Courtesy, STANLEY AND ANDERSON: *J. Biol. Chem.*, 139: 325, 1941.)

types of cells and tissues (in animals, viruses most often affect epithelial and nervous tissue); both may have a stimulating effect on cells (as the virus which causes warts) or a destructive effect (as the virus which causes infantile paralysis); and finally, both can be caused to mutate by means of x-rays, and both may undergo spontaneous mutation.

There are, however, some notable differences between viruses and genes. (1) In all but a few of the simplest one-celled organ-

COMPARATIVE SIZES OF VIRUSES

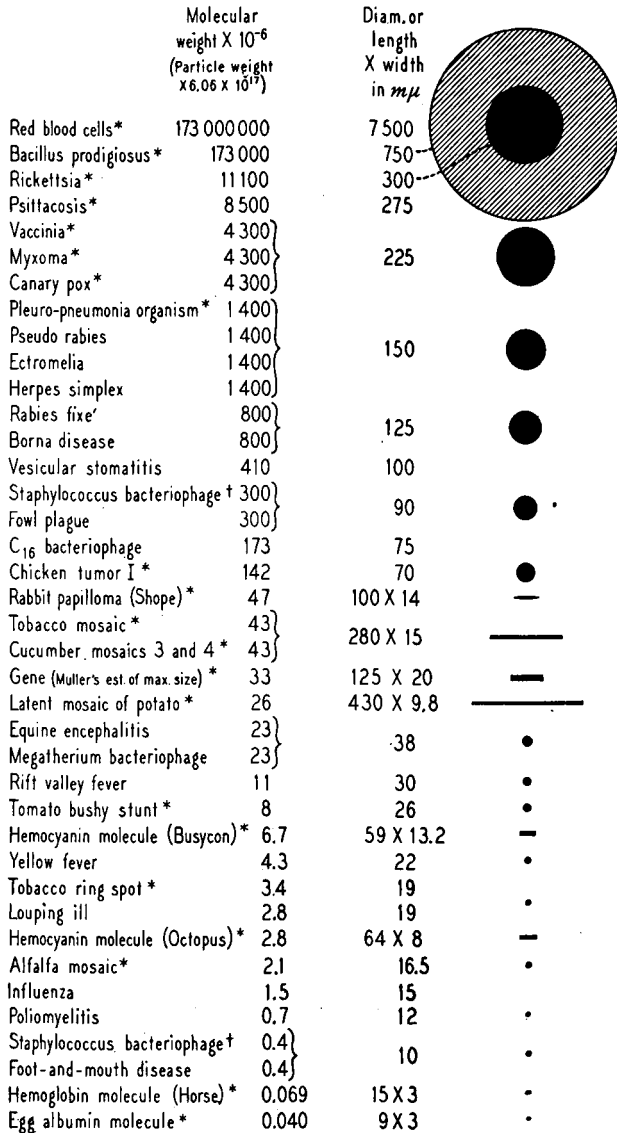


FIG. 70. Chart showing the relative sizes of several viruses as compared with those red blood cells, a large bacillus, a gene,

(For remainder of legend see opposite page.)

isms, genes are aggregated in chromosomes where they are arranged in a definite linear order, whereas viruses have no such organization. (2) Except for a brief period during mitosis, genes are retained within the nuclear membrane of the cell, while some viruses are found in the cytoplasm of the cell as well as in the nucleus. (3) Genes ordinarily reproduce themselves only once for each cell division, whereas viruses, judged by the amount of virus obtainable from infected cells, must reproduce on a large scale. (4) Most genes in a given organism are distinctly beneficial and even necessary to the life of the organism as a whole (owing no doubt to countless generations of trial and error by mutation and selection), while most viruses so far discovered are lawless invaders which injure or kill the host, although a few (the so-called latent viruses of plants) may be carried by a healthy plant of one species to another species in which they cause disease. The potato plants raised in the United States, for example, in most cases carry a virus which has no apparent effect upon the potato, but which produces disease in Turkish tobacco, as can be shown by inoculating the tobacco plant with juice from the potato plant. Certain cherry trees and plum trees, although themselves healthy, carry a virus which produces disease in peach trees. Several species of lily are known to carry a virus disease of tulips. In the healthy plant they may be neither beneficial nor injurious, although it is possible to imagine cases of mutual benefit (symbiosis) between a virus and the host.

There is, with respect to the effects produced, a distinct parallelism between a virus and the usual newly-mutated gene in that both tend to be injurious to the cell, often in strikingly similar ways. Thus if one did not know the cause of infantile paralysis and certain types of hereditary muscular atrophy, respectively, he might not be able to tell from the effects produced that the former was due to a virus and the latter to a gene; since in both

and protein molecules. * indicates that evidence regarding shape is available. † indicates large size from filtration and sedimentation of concentrated solutions and small size from diffusion of dilute solutions. (Courtesy, STANLEY AND KNIGHT: *Cold Spring Harbor Symposia on Quantitative Biology*, 9: 255, 1941.)

diseases there is a destruction of the motor cells in the spinal cord leading to paralysis of certain muscle groups.

W. M. Stanley² and his co-workers at the Rockefeller Institute for Medical Research have made many important discoveries regarding the structure of viruses, all of which have great interest for the student of the gene. On the chemical side they have identified 13 different amino acids, the building blocks of proteins, in tobacco mosaic virus. Four other amino acids have been ruled out as not present in this virus. They have gone further and have calculated the percentage of each amino acid in the virus. Among the several distinct strains of tobacco mosaic virus they have found a difference in amino acid composition; and, most important of all, have shown that the mutation of a virus may be accompanied by the introduction of an entirely new amino acid into the virus structure. It has not, however, been demonstrated that any given structural change is responsible for the new biological properties of the mutated virus.

What chemical change takes place when a gene mutates? Regarding this question we can do little more than speculate. One of the well-established facts, however, is that reverse mutations are possible. Many cases are known in which a normal gene has mutated to some new recessive type, and later by reverse mutation the normal gene has returned. This has led most students of mutation to the view that recessive mutations are not merely losses of genes. In regard to this question, Wright points out that many recessive mutations are probably inactivations of dominant genes.³

CAUSES OF MUTATIONS

If the Lamarckian theory of the inheritance of acquired characters—plausible and attractive as it is to many—must be given up, what is there left as the cause of hereditary changes? Do mutations occur from causes residing within the organism, or are they caused by forces from without? This question appears to be an ideal one for experimental testing.

An attempt to induce mutations directly by changing the

² "Virus Diseases," Rockefeller Institute for Medical Research, Cornell University Press, 1943.

³ WRIGHT, SEWALL: Evolution in mendelian populations, *Genetics*, March, 1931.

environment is not at all the same thing as an attempt to obtain a Lamarckian effect. In the Lamarckian experiments the environment or activities of the organism are first used to change some characteristic of the organism—such, for instance, as the use of ultraviolet rays to stimulate pigment formation—with the idea that the new characteristic will produce a specific change in the hereditary material of the organism. Followers of Lamarck thus assume a one to one relationship between the change in the bodily characteristic and the supposed change in the hereditary material. In the experimental induction of mutations, on the other hand, the

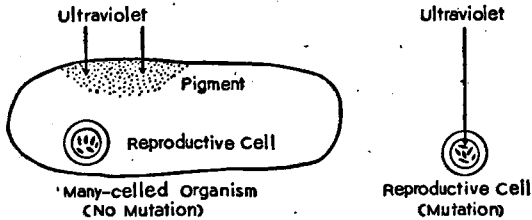


FIG. 71. Diagram showing the difference between the supposed inheritance of an acquired characteristic and the direct induction of a mutation.

environmental agent is so applied that it will reach directly the reproductive cells and there bring about a change. The contrast between the two types of experiment is shown graphically in Fig. 71.

In the case represented on the left the surface of the organism is exposed to ultraviolet rays. As a result pigment is formed near the surface, but the rays fail to reach the reproductive cells, and no mutation results. In the case shown on the right the rays are applied directly to the reproductive cells, with the result that mutations are induced.

In experiments on direct induction of mutations there is no assumption whatever as to the type of mutation that may result. Experience shows that the type of mutation has no direct relationship to the kind of environmental agent used. A mutation induced by ultraviolet rays may have nothing whatever to do with pigment formation.

A wide variety of chemical and physical agents have been used in the attempt to induce mutations. Among these are alcohol, lead,

arsenic, ammonia, iodine, manganese, acids, alkalis, alkaloids, neutral salts, ether and other anesthetics, foreign proteins, antibodies, lack of oxygen, high temperatures, low temperatures, centrifugal force, ultraviolet rays, x-rays, radium, and neutrons. The list is not complete.

Most of the agents listed are distinctly poisonous or injurious to living cells and produce permanent changes when applied in the proper concentrations. Positive effects upon the offspring of treated plants and animals, however, have been demonstrated with only a few of the agents used. Aside from radiations and high and low temperatures, not one has yielded a satisfactory series of gene mutations in the hands of a number of investigators. Individual successes have been claimed for many of the agents listed at one time or another, but unless an experiment can be successfully repeated by other competent workers, there is always grave doubt as to the adequacy of control or technique.

It is true that no amount of negative evidence is sufficient to prove a universal negative, and for this reason there is always the possibility that some experimenter may hit upon a new or different method which will yield positive results where other investigators have failed. This is strikingly illustrated in the case of x-rays.

MUTATIONS FROM X-RAYS AND OTHER SHORT-WAVE RADIATIONS

Prior to 1927 numerous experimenters had used x-rays in an attempt to produce mutations in insects and mammals. Most of the experiments gave negative results, although in a few cases there were strong suggestions of positive results. A satisfactory demonstration of the induction of mutations by means of x-rays had not been accomplished.

In 1927 Professor H. J. Muller, at that time of the University of Texas, announced that by the use of special methods which he had developed over a period of years for the detection of spontaneous mutations (mutations in untreated animals) he had at last been able to demonstrate the induction of true gene mutations by means of x-rays.⁴ He used the fruit fly *Drosophila* and obtained mutations in a high proportion of the sperms and eggs of treated

⁴ MULLER, H. J.: Artificial transmutation of the gene, *Science*, July 22, 1927.

flies. Comparison of the mutation rates under the two sets of conditions showed that heavy x-ray treatment had caused a rise of about 15,000 per cent in the mutation rate over that in the untreated flies.

The mutations were for the most part similar to or repetitions of those that had been previously observed in untreated flies, although some were different. Lethal mutations greatly outnumbered mutations producing a visible effect. Dominant lethals were about as numerous as recessive lethals. The great majority of the visible mutations were recessive, just as they are in untreated flies. Chromosome breakages and chromosome rearrangements also were frequent.

At about the same time as Muller's work, L. J. Stadler of the University of Missouri, working independently, obtained positive results with barley and corn. During the next few years the results of Muller and Stadler were abundantly confirmed by numerous investigators using insects and plants. Radium was found to give the same results as x-rays, and the number of mutations was found to vary directly with the dosage. To date mutations have been induced by x-rays in several dozen species of plants ranging in complexity from bacteria to seed plants and in a somewhat smaller number of animals, ranging from one-celled species to mammals.

The earlier experiments with ultraviolet rays gave negative results, owing perhaps to the low penetrating power of ultraviolet rays; but when insect eggs or pollen from plants were rayed, mutations resulted. Visible light, supersonic waves, and electrostatic fields have been tried with negative results.⁵

Naturally we are most interested in the effects of x-rays and radium on human beings. Experiments on mammals have therefore, a special interest. Unfortunately, the results here are not nearly so conclusive as with plants and insects. The reason probably has to do with the greater difficulty of treating and rearing large numbers of mammals, there being no reason to suppose that mammals are fundamentally different from other forms of life in their susceptibility to radiation.

⁵ For an excellent review of the various experiments on radiations, with extensive literature citations, see "Biological Effects of Radiations," edited by BENJAMIN M. DUGGAR, Vol. 2, McGraw-Hill, 1936.

Early experiments with x-rays on mice by several independent investigators yielded results that were inconclusive. A recent well-controlled experiment with a highly inbred and homogeneous strain of guinea pigs (Figs. 78 and 79) has been done by H. H. Strandkov of the University of Chicago.⁶ Males were treated with heavy doses of x-rays sufficient to bring about atrophy of the testes and temporary sterility. Seventy-one treated males produced 173 offspring, conceived before the onset of sterility, or after recovery of fertility. There were no visible mutations among these 173 offspring of treated males, nor among the two succeeding generations from these offspring. The only effect which the author considered as probably due to the treatment was a decrease in size of litter. The controls produced on the average 2.69 offspring per litter as compared with 2.04 from the treated males. This decrease was attributed to the production of dominant lethal mutations.

The question naturally arises, are all mutations, including the mutations that occur in nature, due to penetrating radiations? High temperatures have been found by several workers to increase somewhat the rate of mutation, but it is not certain that the mutations which occurred in the heat experiments would have taken place in the absence of short-wave radiations. The critical experiment of rearing organisms completely protected from all extraneous radiations offers such great practical difficulties that it has not yet been carried out.

As might have been expected, experiments to test the natural radiations from radioactive minerals in the earth's crust have given positive results. All organisms on the earth, man included, are probably exposed to natural radiations, radiations coming either from the earth or from cosmic rays from outer space. The proportion of spontaneous mutations due to such radiations is of course unknown. There remains the possibility that mutations take place under ordinary conditions at a low rate, because of interaction of chemical and physical forces within the organism itself; and that radiation and high temperatures merely serve to increase the rate.

⁶ STRANDSKOV, H. H.: Effect of x-rays in an inbred strain of guinea-pigs, *J. Exp. Zoology*, Aug. 5, 1932.

ALCOHOL AND LEAD

As mentioned above, a great many chemical substances have been used on animals in an attempt to produce mutations. In general these attempts have given negative results. Among such substances, two—alcohol and lead—have special importance on account of their relationship to man. Alcohol is important because of its widespread use as a beverage; and lead, because in our industrial civilization it is the cause of a large amount of poisoning.

In the medical and sociological literature there are many statements based on isolated cases and, in some instances, on more elaborate studies, to the effect that the excessive use of alcohol by one parent or both parents causes the birth of defective offspring. Lenz, in a book previously cited, states that in Germany about one-third of all epileptics, imbeciles, and idiots are the offspring of hard drinkers; and that among the parents of schizophrenic patients there is an unusually large number of alcoholics. He gives it as his opinion that the abuse of alcohol produces considerable effects on the hereditary material. As one reason for this opinion he cites the fact that alcohol causes atrophy of the testes and sterility in man just as x-rays are known to do; and that probably some of the surviving sperms are injured.

The human data, however, will not bear critical analysis. Even though it be admitted that the children of an alcoholic parent are more likely to show certain defects than the children of sober parents, this does not prove that alcohol has caused a change in the hereditary material transmitted to the child. In the first place, the alcoholism in the parent is likely to be a symptom of the parent's own defective heredity; and if the child shows certain mental and physical defects, it may simply mean that the defective genes of the parent have been passed on to the child. In the second place, the defects of the child may be due in part to a defective environment such as commonly is found in families with alcoholism. The study of twins, it may be recalled, showed that mental traits in particular depend in part upon the environment. The question of the effect of alcohol on the child of an alcoholic father is different from the question of its effect on the child of an alcoholic mother. In the mother there is an opportunity for a

poison circulating in the blood to reach the embryo directly and cause injury to it, although the egg itself may have escaped injury.

A definite answer to the problem of alcohol as a racial poison in man must wait on more adequate human data. In the meantime, some conclusions may be drawn tentatively from the results of animal experimentation.

A large number of experiments have been performed in which laboratory animals were treated with alcohol in order to study the possible effects upon their descendants. Many of the experiments were carried out in this country between the years 1910 and 1930. Among those most often cited as indicating positive effects in the offspring are the experiments of Dr. C. R. Stockard of Cornell University Medical School, who published a series of papers on the effects of alcohol on guinea pigs.⁷ Both male and female guinea pigs were exposed to alcohol fumes for one to three hours per day to the point of intoxication, six days per week, in some cases for several years. No permanent injury was induced in the animals treated, aside from the production of opaque corneas and blindness. None of the characteristic lesions of stomach, heart, liver, and nervous system, which are often found in chronic human alcoholism, was produced. The testes and ovaries showed no atrophy.

Nevertheless, among the offspring of treated animals, even where males only were treated, defective offspring were reported, whereas no defects were observed among the untreated controls. The defects included abnormally small eye on one side, cataract, deformed limbs, paralysis of the limbs, and tremors. None of the defects was shown to be Mendelian in character. The size of litter was smaller from treated males, and the number of abortions was higher from treated females.

Obviously, in an experiment of this sort the use of a homogeneous group of animals of known genetic constitution is of supreme importance. Otherwise one cannot be sure that any differences that appear are due to the treatment, rather than to the reassortment of genes already present in the stock. In this respect Stockard's guinea pigs were not all that could have been desired.

⁷ STOCKARD, C. R.: Experimental modification of the germ plasm and its bearing on the inheritance of acquired characters, *Proc. Am. Philosoph. Soc.*, 62: 311-325, 1923. This paper gives references to earlier work by Stockard and others.

Doubt as to the value of Stockard's experiments is increased by the negative results obtained by Durham and Woods,⁸ who repeated the experiments for the Medical Research Council of Great Britain.

Durham and Woods found no evidence that exposure to alcohol injures the reproductive cells. Guinea pigs of both sexes were treated, in some cases for as long as five years, and for four successive generations. Only ten abnormal individuals were obtained among 6,309 animals from the alcoholic stock; one abnormal guinea pig was found among the 674 controls. The percentage of abnormals in the two groups is thus almost identical.

Fertility and the sex ratio were unaffected by alcohol. Stillbirths and deaths of young under three weeks were somewhat more frequent in the alcoholic stock, especially where the parents were treated for more than two years. No exact controls, however, were available with respect to such mortality rates.

In the beginning of the experiment the animals were not closely related; later in the experiment, however, some inbreeding was practiced. The authors suggest that since all the abnormalities were in related families, these abnormalities may have resulted from genes already present in the stock.

In several experiments with alcohol on white rats and white mice, performed by careful workers in the United States, no mutations or defective offspring have been reported. With respect to other characteristics (mortality rates of young, litter size, and sex ratio) the results also have been either negative or are so conflicting that their significance is doubtful. In view of all the evidence, therefore, it seems wise to withhold judgment as to racial effects of alcohol on mammals.

Lead poisoning is a constant source of danger to human beings in civilized countries such as the United States—even to people not employed in any of those industries involving a special hazard, such as the manufacture of paints, pottery, and storage batteries, or the trades of house painting, printing, plumbing, and so on. We are all exposed to a certain amount of lead in the foods we eat, the

⁸ DURHAM, F. M., and WOODS, H. M.: Alcohol and inheritance: an experimental study, (Great Britain) Medical Research Council Special Report, Series No. 168, 1932.

liquids we drink, and the motor exhaust gases which we breathe. Poison sprays and dusts containing lead are widely used for the destruction of insects and fungi growing on fruits and vegetables, and a certain amount of these poisons is always left on such produce when it reaches the consumer. Refined foods are frequently contaminated with lead during their processing.

The question of the effect of lead on the offspring in man has, accordingly, come in for a good deal of consideration by physicians and geneticists. It has been widely accepted by the medical profession that a man's children may be injuriously affected by lead absorbed by the father.

Several experimenters have administered lead salts by mouth to chickens, rabbits, and guinea pigs, and have interpreted their results as indicating positive effects on the offspring. A review of these animal experiments, however, as well as of the literature on human lead poisoning, convinced the writer a number of years ago that positive effects had not been demonstrated. Accordingly, the privilege was accepted of working in the laboratory of Professor Sewall Wright, of the University of Chicago, and of repeating the lead experiments with guinea pigs.⁹

For the first time highly inbred and homogeneous mammals of known genetic constitution were used (Fig. 80). The guinea pig experiments were carried out on a much larger scale than any of the earlier experiments by other workers. Three generations of descendants of poisoned male guinea pigs were studied. Although the treated males themselves showed highly characteristic and constant symptoms of lead poisoning, the offspring and their descendants, numbering 1145 animals, were in all essential respects indistinguishable from the controls. In a few of the experiments there was a significantly higher percentage of offspring from treated males stillborn or dying under one month of age; but when certain complicating factors were taken into consideration it was doubtful that lead poisoning in the sire was to blame. At present, therefore, lead as a possible racial poison seems to the writer to be in the same category as alcohol—not demonstrated.

⁹ COLIN, E. C.: A comparison of the descendants of lead-poisoned male guinea-pigs with those from untreated animals of the same closely inbred strains, *J. Exp. Zool.*, Nov., 1931.

It is interesting to note that Muller was unable to obtain any effect on *Drosophila* with lead, using the same materials and methods with which he had obtained positive effects with x-rays.

Why have the experiments with chemicals so consistently failed to show positive effects, while those with short-wave radiations have been successful? One may hazard a guess that it is due to the inability of the chemicals to reach the genes without killing the cell. Short-wave radiations are highly penetrating. Evidently they are able to reach and change the genic material without serious injury to the rest of the cell. Chemicals, however, can act on the chromosomes only after penetrating more slowly through the cell membrane and through a layer of cytoplasm. Perhaps the cell as a whole is killed or inactivated before the chemical can reach and change the genes. Nevertheless, chemicals have been found capable of producing gross chromosome changes, as we shall see in a later section.

THE CONTROL OF MUTATIONS

The induction of mutations by radiations has been compared to firing a gun at a target in the dark. In both cases the chance of making a hit is small. If the hit occurs, there is no predicting what the effect will be, though it is most likely to be harmful.

In using radiations—even the strongest dosage that can be used without killing the organism—the great majority of the genes seem to escape being struck. The occasional hits result in mutations of the same types as occur naturally. But precisely what these mutations will be cannot be predicted. There is as yet no way of producing a desired mutation to order, and any artificial induction of mutations is sure to produce a great majority of undesirable ones.

In one respect, however, the results are predictable: experience teaches that certain mutations occur again and again, and some with greater frequency than others. This means that some genes are more stable than others. Furthermore, there is a limit to the variety of possible mutations—a limit set by the nature of the organism itself. For example, among the millions of *Drosophila* that have been bred in experiments during the past decades, dozens of mutations have occurred changing the normal red eye

color to darker shades, such as purple or brown, or to lighter shades, grading down to white. Most of these mutations have occurred again and again, but a mutation causing the eyes of *Drosophila* to become green has never been observed, notwithstanding that green is the eye color of some other insects, for example, certain mosquitoes and dragon flies. This means that the nature of *Drosophila* sets a limit to the kind of mutations that can take place in the animal.

Similarly, in man and many other mammals numerous mutations have occurred affecting hair color, but the color is always black or white or some shade of brown or red—never green. Evidently something in the chemical nature of the organism limits the possible color mutations.

CHROMOSOME CHANGES

Under this head are included all changes in the normal number of chromosomes, additions and losses of parts of chromosomes, changes in the arrangement of genes along the chromosomes, and in fact all gross changes that are visible under the microscope. The genes themselves are not affected.

POLYPLOIDY

One of the earliest examples of a chromosome change was given by de Vries in his book on mutations, already mentioned. He stated that he observed the origin of a new species of primrose (*Oenothera gigas*) from the common primrose (*Oenothera Lamarckiana*) which appeared suddenly in his cultures in 1895 and which he said "possessed, at its first origin, all the attributes of a new species, including constancy and even a double number of chromosomes in its nuclei."

De Vries had no idea what caused this plant to double its chromosome number, just as he had no explanation of the cause of other hereditary changes. Experiments within the past few years, however, have shown several methods of inducing chromosome doubling. The most striking results have been obtained with a drug known as colchicine (kól'-kĩ-šín). This chemical ($C_{22}H_{25}O_6N$) is an extremely interesting substance. It is classed as an alkaloid poison, and is extracted from the seeds of a plant known

as meadow saffron. Incidentally, it is one of the drugs used as a remedy for arthritis in man.

Only recently the discovery was made by two groups¹⁰ of American investigators working independently that colchicine was almost a specific for the induction of chromosome doubling without cell division in plants. When growing tips or buds of plants were wet with a weak solution of the drug, say one per cent, cells were formed with double the normal chromosome number. Frequently there was a redoubling, occasionally as many as three times. What happens in these experiments is that cell division is inhibited by the drug, while chromosome splitting goes on as usual. After the effect of the drug has abated, the cells with doubled chromosome numbers divide normally, and from the tissues so produced seeds and embryos with double chromosome numbers develop. There is thus a permanent change in the plant, just as there is in nature as a result of doubling from unknown causes. All such cases in which among related organisms there is a series of chromosome numbers that are multiples of a basic number are examples of *polyploidy* (*poly*, many; *ploid*, fold). An organism with a single complete set of chromosomes, like the male honeybee and numerous plants, is a *haploid* (*haploos*, single), and contains the basic number, (n) of chromosomes. Most sexually reproducing organisms have a double set of chromosomes and are known as *diploids* ($2n$). A doubling of a diploid set results in a *tetraploid* (*tetra*, four).

Several other drugs have more recently been found effective in inducing polyploids, while similar results have been obtained in plants—though in a much smaller percentage of treated individuals—by the use of x-rays, high temperatures, low temperatures,¹¹ centrifuging, and by merely cutting off the end of the growing tip. In one case, for example, the growing tip of a tomato plant was cut off, thus preventing the formation of normal shoots.¹²

¹⁰ BLAKESLEE, A. F., and AVERY, AMOS G.: Methods of inducing doubling of chromosomes in plants by treatment with colchicine, *J. Heredity*, Dec. 1937; NEBEL, B. R., and RUTTLE, M. L.: The cytological and genetical significance of colchicine, *J. Heredity*, Jan., 1938.

¹¹ DERMEN, HAIG: A cytological analysis of polyploidy induced by colchicine and by extremes of temperature, *J. Heredity*, June, 1938.

¹² JORGENSEN, C. A.: The experimental formation of heteroploid plants in the genus *Solanum*, *J. Genetics*, 19: 133-211, 1928.

Under the scar tissue which formed, irregular shoots developed: some of these had the doubled chromosome number. Subsequent cell division was normal, so that all the cells on the growing branch, including the flowers, had the doubled chromosome number. Eggs and sperms produced by such plants have twice the number of chromosomes possessed by eggs and sperms in the original plant. If self-fertilization occurs, the double condition is thus perpetuated.

The ease with which a great variety of plants may be artificially induced to double their chromosome number explains perhaps why the process is so common in nature. One investigator, Müntzing, concludes that more than half the species of flowering plants (including many of our economically useful plants) in which the chromosome number is known have doubled or redoubled chromosomes. For example, in wheat, species are known with 14, 28, and 42 chromosomes; in chrysanthemums, species with 18, 36, 54, 72, and 90; and in *Solanum*, the genus to which the potato belongs, species with 24, 36, 48, 60, 72, and 96 chromosomes. The regularity of these series of numbers, consisting as they do of simple multiples of some lower number, clearly indicates the origin of new species from other species by polyploidy. Whether the chromosome doubling in series like those above arose within a single species or was the result of the crossing of two related species, is often difficult to decide. Both types of polyploidy are known to be of frequent occurrence in plants. The second type which results from hybridization is considered in Chapter 15.

A typical example of a spontaneous tetraploid in plants is reported by Bamford and Winkler of the University of Maryland.¹³ As shown in their excellent illustration (Fig. 72) the stems, flowers, leaves, stomata, and even the pollen grains, are larger in the tetraploid than in the diploid plant. The authors mention the fact that tetraploid snapdragons had previously been induced by colchicine treatment by Nebel and Ruttle (see footnote, p. 301) and that such tetraploids were similar to the spontaneous one.

Plants that have doubled their own chromosome make-up are known as autotetraploids. They often differ in many ways

¹³ BAMFORD, RONALD and WINKLER, FRED B.: A spontaneous tetraploid snapdragon, *J. Heredity*, Aug., 1941.

from diploids. They are usually larger, have thicker stems, thicker and relatively broader leaves, and a darker green color. The

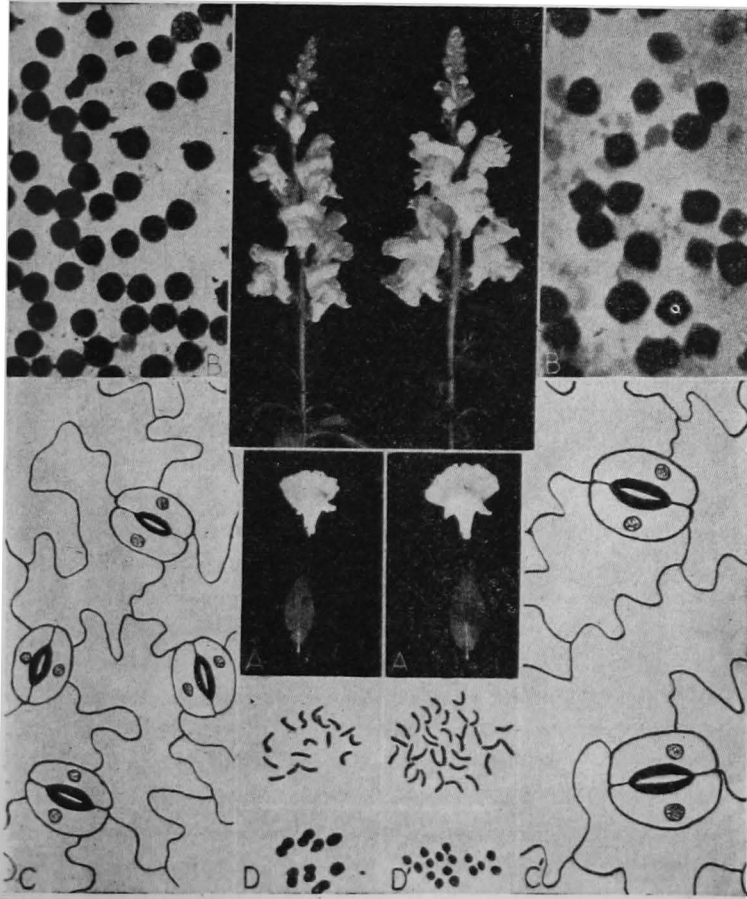


FIG. 72. A spontaneous tetraploid snapdragon (shown on the right half of the figure) in comparison with a diploid (on the left). Structures in the tetraploid (A'-C') are larger than in the diploid (A-C). A, A' plants; B, B' pollen; C, C' stomata; D, D' chromosomes. (Courtesy, BAMFORD, RONALD AND WINKLER, F. B.: A spontaneous tetraploid snapdragon, *J. Heredity*, Aug., 1941.)

flowers and seeds also are usually larger. The differences, however, are largely quantitative and are not usually such as to cause taxonomists to class the diploids and the tetraploids as distinct

species. Sometimes, in fact, there are no visible external differences between the two. As examples of the latter condition may be cited two species of spiderwort, in both of which there grow side by side diploid and autotetraploid races. In the spiderwort of eastern meadows (*Tradescantia canaliculata*) and in the one of western prairies (*T. occidentalis*) these chromosomal races cannot be distinguished by any other character.¹⁴ Tetraploids develop more slowly, take longer to reach maturity and are often hardier than the diploids. Tetraploid tomatoes have been found to contain about double the usual concentration of vitamin C,¹⁵ and tetraploid yellow corn has a higher concentration of vitamin A than diploid corn. Tetraploid ornamental flowers of superior types have been obtained. We thus see something of the possibilities of developing new varieties of plants which are economically superior because of their doubled chromosomes.

In animals, in contrast to plants, polyploidy in natural species is rare, and few polyploid animals have been produced experimentally. In only two phyla of animals do the chromosome numbers suggest polyploid series. These two are the flatworms and the annelids, in both of which hermaphroditism is common. The fact that in most species of animals the sexes are separate is no doubt one of the chief reasons for the rarity of polyploid series in the animal kingdom. In bisexual species polyploidy can become established only in case the doubling in chromosome numbers is present in both a male and a female which subsequently mate. The improbability of this happening reduces the chance of perpetuating the condition.

An added difficulty in bisexual species is the regular presence in one sex or the other of an X and a Y chromosome or of an unmated X. A tetraploid individual with unpaired sex chromosomes is likely to produce sterile offspring because of failure of the two X's or the two Y's to go together in gametogenesis.

¹⁴ "Experimental Studies of the Nature of Species. II. Plant Evolution through Amphiploidy and Autoploidy with Examples from the Madiinae," by JENS CLAUSEN, DAVID D. KECK, and WILLIAM M. HIESEY, Carnegie Institution of Washington Publication, 564, 1945.

¹⁵ SANSOME, F. W., and ZILVA, S. S.: Polyploidy and vitamin C, *Biochem. J.* 27: 1935-1941, 1933.

Fertile individuals require the normal balance between the sex chromosomes and the autosomes.

That polyploids do appear spontaneously in animals with fair frequency is evident, however. Fankhauser,¹⁶ of Princeton University, during a period of four years examined 1302 larvae of the newt *Triturus viridescens* raised in his laboratory. About 2 per cent of the individuals were found to be polyploids. Among these were 17 triploids, 1 tetraploid, 4 pentaploids, and 1 haploid. The amphibians seem to be the only group of vertebrates in which polyploidy has been studied.

Among the invertebrate animals polyploid races and species are found living successfully in nature in only a few groups. In all cases the polyploids are parthenogenetic. A crustacean known as the brine shrimp (*Artemia salina*) is represented by a diploid bisexual form and by parthenogenetic tetraploid and octoploid races. A similar case is that of the sow bug *Trichoniscus elisabethae*, likewise a crustacean. In the south of Europe a diploid race occurs, with the sexes in equal numbers. In Northern Europe this race is replaced by a parthenogenetic triploid race, in which males are practically absent. The eggs of the parthenogenetic race lack a reduction division and develop without fertilization.

In two groups of insects polyploidy has been described by European workers. A tetraploid race of the moth *Solenobia triquetrella* ranges widely in Central Europe. Females only are found and reproduction is parthenogenetic. It is probable that this race was derived from a diploid bisexual race which occupies a restricted region in Germany.

The other group of polyploid insects are members of a family of beetles known as weevils (*Curculionidae*), in which nine parthenogenetic species have been reported. One of these is diploid, five are triploid, and three are tetraploid. In all of them females alone exist; the eggs develop without fertilization after a single meiotic division. In the same group four bisexual diploid species are found; in these maturation of the gametes is normal.

Examples of polyploidy as a result of the crossing of two distinct species, which seems to be especially important in the origin of species in plants, will be described in Chapter 15.

¹⁶ FANKHAUSER, GERHARD: Induction of polyploidy in animals by extremes of temperature, in "Biological Symposia," Jaques Cattell Press, 1942.

CHROMOSOME REARRANGEMENTS: LOCATING THE GENE

As we have seen, the evidence from crossing-over (Chapter 7) indicates that the genes lie on the chromosome, arranged in a definite linear order from one end to the other. This evidence, however, is indirect, and while convincing to those most familiar with it, has been received with skepticism by some competent biologists in other fields because of the lack of visual proof.

In many species, including *Drosophila*, investigators had discovered that the chromosomes were not homogeneous throughout their length, but were made up of a series of granules or bands of varying sizes, resembling beads strung on a string. The pattern of these bands in a given chromosome showed great constancy throughout a species, and during synapsis of homologous chromosomes preceding meiosis there was specific pairing of the particular granules. The natural conclusion was that these granules or bands represented the genes. What was needed, however, was the simultaneous study of the chromosomes and of the breeding results in order to identify positively distinct structures along the chromosome as particular genes.

In 1933, Professor T. S. Painter of the University of Texas published the first of a series of articles announcing the development of a new technique which seemed to provide just what was lacking. So successful has this method been in locating the genes that it is rapidly doing for the gene theory what the chromosome theory did for Mendel's laws.

The essentials of the method, as well as the early discoveries made under it, were summarized by Painter in 1934.¹⁷ Painter comments that ever since the formulation of the chromosome theory of heredity cytologists and geneticists had dreamed of the day when someone would find an organism in which the chromosomes were so large that it would be possible to see qualitative differences along their length corresponding to the different genes known to reside there.

Recalling that in various species of flies, including *Drosophila*, the cells of the salivary glands of the larvae contained unusually

¹⁷ PAINTER, THEOPHILUS S.: Salivary chromosomes and the attack on the gene, *J. Heredity*, Dec., 1934.

large chromosomes, and that the chromosomes showed conspicuous bands or disks of deeply staining material, alternating with clearer regions, Painter began the reexamination of the salivary

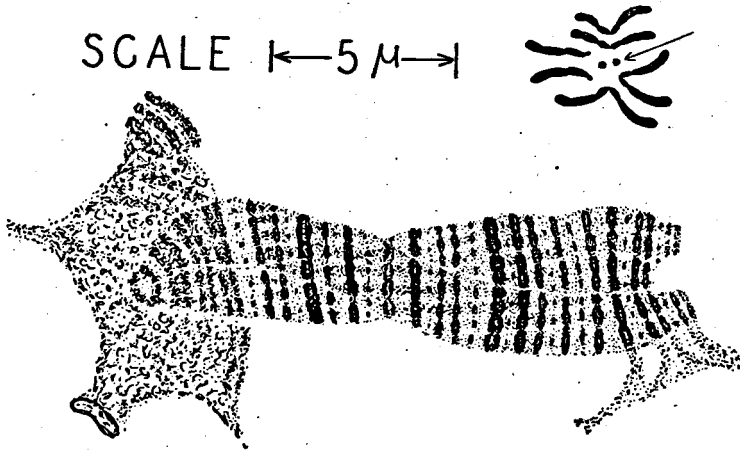


FIG. 73. Drawings of chromosomes of the fruit fly, *Drosophila melanogaster*: (upper right) as they appear in pairs in the ovaries before the reduction division; (below) on the same scale, the pair of dot-like chromosomes as they appear in the salivary glands of the larva. Scale, $5\mu = \frac{1}{5000}$ inch. (Courtesy, BRIDGES: *J. Heredity*.)

gland chromosomes in *Drosophila*. He developed an improved technique for spreading out the coiled chromosomes so that they might be more easily studied. From his own observations he gave the following description:

The chromosome consists of an elongated more or less cylindrical rod made up of lightly staining material, while running apparently across each may be seen a great variety of "bands," some broad and deeply staining, others narrow or made up of a series of dots. A study was begun at once to determine if the patterns of bands and lines, which are so conspicuous, were constant morphological characteristics of a given element. It turned out that the landmarks are constant to a most extraordinary degree so that we were able to recognize the same element in the nuclei of different individuals and ultimately to follow any characteristic bit of a chromosome as it is shifted here and there to other chromosomes through the agency of irradiation.

A drawing of a pair of the tiny dot-like chromosomes from *Drosophila*, made by Dr. Bridges of the Carnegie Institution of Washington, is shown in Fig. 73.¹⁸

¹⁸ BRIDGES, CALVIN B.: Salivary chromosome maps with a key to the banding of the chromosomes of *Drosophila melanogaster*, *J. Heredity*, Feb., 1935.

In order to represent the other three chromosomes on the same scale (as is done by both Bridges and Painter) a page several times the width of this one would be needed. The same wealth of detail is found in the other chromosomes.

In the salivary glands, the chromosomes remain in an elongated condition; the one shown in the figure is nearly 100 times as long as the corresponding chromosome in the contracted state of an ordinary cell, as drawn in the upper right. Note that the members of the pair of salivary gland chromosomes lie side by side, slightly twisted about one another. For some reason somatic synapsis is the rule in salivary gland chromosomes. The identity of structure of the two mates is striking. From end to end Bridges counted 34 separate bands on this one tiny chromosome.

More recently Slizynski¹⁹ of the University of Edinburgh has studied the same chromosome in *Drosophila*. By making use of especially favorable preparations in which the salivary chromosomes were well stretched he was able to identify 137 bands (Fig. 74). His drawing shows the elaborate method that has been devised for identification of the bands and for relating these to particular genes. The symbols for about a dozen genes are shown above the heavy horizontal line in the figure.

The fact that individuals of the same species ordinarily have identical chromosome patterns even though they may differ genetically indicates that ordinary gene differences are not associated with any visible difference in chromosome pattern. But with chromosome changes, as heretofore defined, the situation is quite opposite. Any gross change, such as the loss of a piece of a chromosome (deficiency), a duplication of a piece (duplication), a shifting of a piece from one chromosome to another (translocation), an end for end reversal of a piece (inversion), can at once be identified by the altered pattern of the bands. All these changes occur occasionally in untreated animals; they can also be induced readily by x-rays and by other means.

The study of chromosome changes under the microscope, in connection with breeding results from flies showing such chromosome changes, gives the most convincing evidence of the location

¹⁹ SLIZYNSKI, B. M.: A revised map of salivary gland chromosome 4 of *Drosophila melanogaster*, *J. Heredity*, pp. 323-324, Nov., 1944.

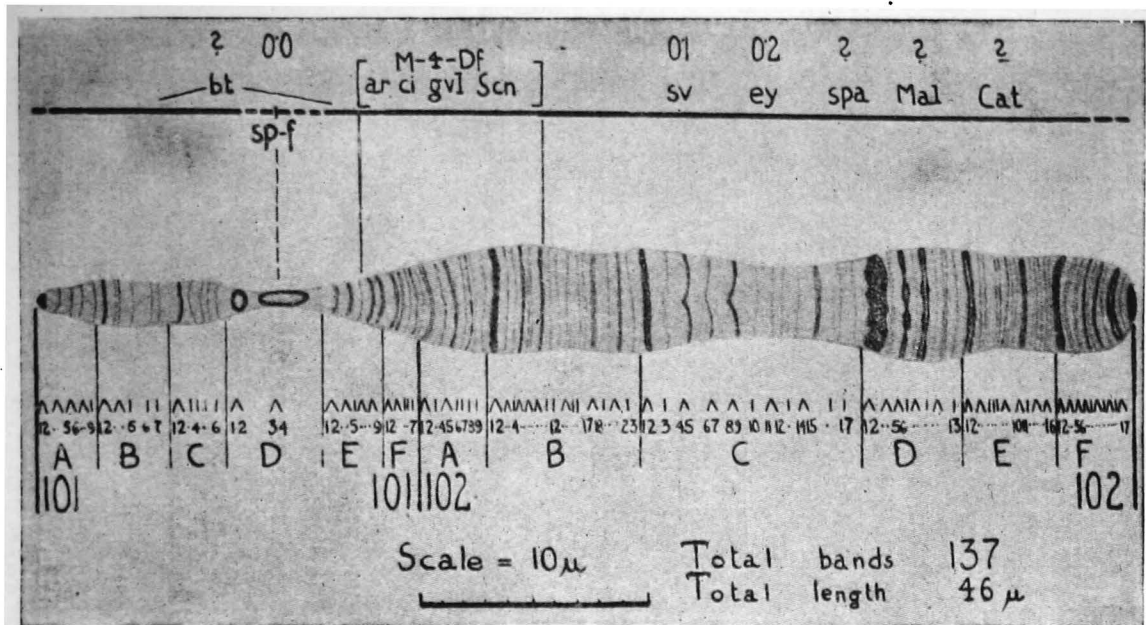


FIG. 74. Drawing of salivary gland chromosome IV of *Drosophila melanogaster*, with a map above the chromosome indicating the position of the better known genes. (Courtesy, SLIZYNSKI, B. M.: A revised map of salivary gland chromosome 4 of *Drosophila melanogaster*, *J. Heredity*, Nov., 1944.)

of the genes. The two lines of independent facts thus obtained are in perfect agreement with one another, and both support the theory of the linear arrangement of the genes along the chromosomes. Moreover, the combination of breeding experiments and microscopic studies of the salivary chromosomes points to an arrangement of the genes in the chromosomes of the reproductive cells identical with that in the cells of the salivary glands. We have already seen that mitotic cell division insures that all the cells of the body shall have identical chromosome sets. Additional evidence of this uniformity is supplied by the recent discovery that certain cells of the intestine in the fungus fly, *Sciara*, have large chromosomes, showing bands identical with the salivary gland chromosomes in this fly.²⁰

In examining more closely Figs. 73 and 74, it is evident that the dark bands are really represented as rows of dots or loops. Are these dots or loops the genes? The consensus at present is that the gene is within the dot or loop. The stained material itself (chromatin) is thought to be made up of nucleic acid, a common constituent of the nuclei of cells, the chemistry of which is fairly well known. The gene, which is regarded by some as a large protein molecule, is presumably associated with a definite mass of chromatin—whether actually enclosed in the chromatin or not is undetermined. Investigations have now reached the point where it is possible to look at a salivary gland chromosome and to state confidently, in some cases, that a given gene lies within a region covered by a single band.

Bridges originally counted a total of 2,650 dark bands in all four chromosomes of *Drosophila*. This number agreed well enough at the time with the estimated total number of genes in *Drosophila*, but subsequently Bridges made a more exhaustive study of the X chromosome with improved technique, and found that there are many other faint bands which escaped detection before. His revised map of this chromosome shows 1024 cross lines as compared with 725 on his 1935 map.²¹

²⁰ BERGER, C. A.: The uniformity of the gene complex in the nuclei of different tissues, *J. Heredity*, Jan., 1940.

²¹ BRIDGES, CALVIN B.: A revised map of the salivary gland X-chromosome of *Drosophila melanogaster*, *J. Heredity*, Jan., 1938.

More recently map revisions have been made of the long chromosomes II and III by C. B. Bridges and Philip N. Bridges. The latter author²² has summarized the maps of all four chromosomes and finds a total band count of 5,072. He obtained this number by considering each double band as two. There is some evidence, however, that each double band is a gene locus. He therefore counted each double as one and obtained a total of 3,795. This is not far from the present estimate of 3,000 genes for *Drosophila*.

As to the number of genes in organisms other than flies, we have no very reliable estimates. No other animal has had more than a small fraction of the study that *Drosophila* has received. So far, the only animals known with large banded salivary chromosomes are insects of the order Diptera, which includes the flies. How many genes does man possess? Perhaps as many as *Drosophila*, maybe more.

The origin of complex chromosomes containing thousands of genes arranged in a definite order presents an intriguing problem. It seems necessary to suppose that during past ages, as life has progressed from the simple to the complex, new structures being added step by step, new genes must have been added also. Bridges offered the interesting suggestion that one type of chromosome change (duplication) may be the answer to the origin of new genes, since in certain sections of the salivary chromosomes he found blocks of bands duplicated in all their detail. He argued that the genes in such duplicated blocks might subsequently mutate into genes having effects quite different from the original. The net result would be the addition of new genes. So far, however, there is no evidence that this has actually happened, and the manner of origin of new genes must for the present remain speculative.

THE PHYSIOLOGY OF THE GENE

As already mentioned the best evidence today indicates that the gene is a large protein molecule or an aggregation of such molecules. No technique is known for separating genes from the nongenic material of the chromosomes. No progress has been

²² BRIDGES, PHILIP N.: A new map of the salivary gland 2L-chromosome of *Drosophila melanogaster*, *J. Heredity*, pp. 403-408. Nov., 1942.

made therefore in the chemical analysis of the gene to compare with that made by Stanley and his associates in the analysis of viruses. We can only guess as to the nature of the change that takes place when a gene undergoes mutation. By analogy with the viruses a mutation may involve a loss or gain or rearrangement of the amino acids making up the molecule. The nature of the bond that holds the genes together in linear order in the chromosome

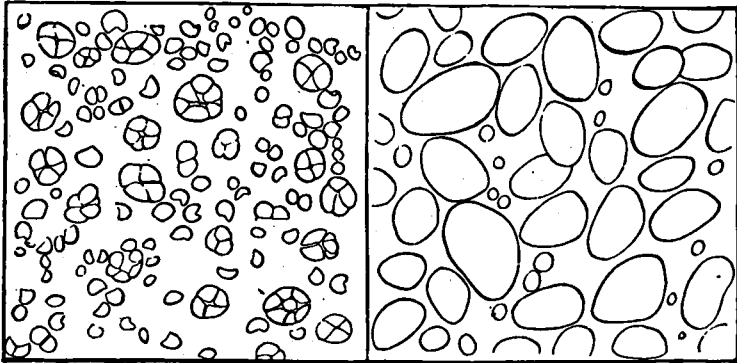


FIG. 75. Outlines of starch grains in peas, showing the simple form (*right*) present in round peas and the compound grains (*left*) from wrinkled varieties. (Courtesy, BATESON: "Mendel's Principles of Heredity," after Gregory.) Magnification the same in both figures.

also is undetermined, as is the nature of the differences among the various genes along its length. One thing is certain, however, and that is that the gene has the power of taking substances from the environment and of synthesizing from them its own likeness. In addition to this power of autocatalysis, which normally is exercised only once for each cell generation, genes act as catalytic agents in cell growth and differentiation. Without this property, of course, we would not know of the existence of genes.

In most cases the effect of a gene on the development of a character is probably indirect. As described in the preceding chapter, the development of pigment in the skin of certain mammals rests upon the formation of an enzyme under the influence of a particular gene. Here the end product is only two steps removed from the gene.

In peas and maize we have interesting examples comparable to the one in animals just referred to; these are the recessives

wrinkled in peas and *sugary* in corn. In both cases the starch grains formed in the cells of the plant are very different in appearance from the grains in round peas and starchy corn, respectively. Fig. 75 shows in outline the two types of starch grains in peas, as drawn by R. P. Gregory, who first reported the existence of this difference in 1903. Its demonstration is very simple. All that one needs to do is to mount a bit of the crushed cotyledon (preferably after soaking) in a drop of water on a microscope slide, and examine under moderate power. It will be noted that the grains from both varieties are variable in size but that those from the round seeds are on the average larger, and are ovoid and *simple* in outline. Those from wrinkled seeds are irregular in shape and often *compound*.

In 1908 A. B. Darbishire added the interesting observation that the starch grains from a heterozygote of round and wrinkled peas are intermediate in shape: many grains are large and simple, but round instead of ovoid, with a mixture of compound grains. The microscope thus enables us to demonstrate lack of dominance in a case where the naked eye classes the homozygote and the heterozygote together.

Fig. 76 represents a comparable drawing of the starch grains in two types of corn. As in peas, the variety which is smooth-seeded has the simple grains, and the sugary whose seeds are wrinkled when ripe has the compound grains.

The starch grains in plants, of course, are derived from sugar which has been produced by photosynthesis. The sugar is converted into starch under the influence of enzymes. It seems probable, therefore, that the alternative genes in peas and corn act through the production of specific enzymes. Here the end product is only two steps removed from the gene.

In the development of most characters there are probably several intervening steps between gene and character. On the other hand, the formation of specific agglutinogens in the blood corpuscles may be the direct effect of the specific blood group and blood type genes acting within the cell during its differentiation into a corpuscle.

The action of genes, naturally, is always dependent upon the substances which surround them in the cell and upon the physical

factors, such as temperature, that compose the physical environment. Hence the net result—the character—is always the product of the interaction of genes and environment. This point was emphasized in Chapter 12. One further illustration may be given here. Some varieties of rabbits have yellow fat and others white fat. The difference depends upon a single gene; yellow fat is

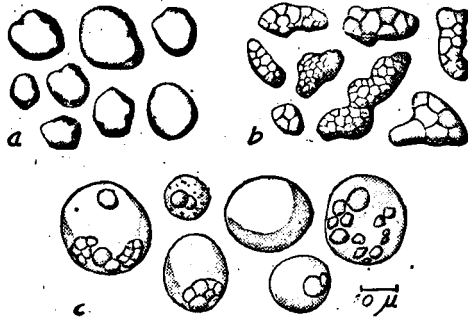


FIG. 76. Starch grains in endosperm of maize 50 days after pollination: (a) simple grains from starchy maize; (b) compound grains from sweet maize; (c) globules of liquid dextrin from sweet maize, some of which contain simple and compound grains. (Courtesy, SHARP: "Introduction to Cytology," McGraw-Hill Book Co., 1934, after Lampe.)

recessive. If the rabbits are deprived of green feed, from which the yellow pigment is derived, both varieties will be alike in possessing white fat. The dominant gene here seems to work by conditioning the development of a specific enzyme which prevents the storage of yellow pigment in the fat. The recessive yellow-fatted rabbit is unable to produce the enzyme; hence the yellow substance xanthophyll supplied in the green feed is stored in the fatty tissue.

THE POSITION EFFECT. For the most part genes function as independent units. They do not work as men on an assembly line where the failure of one man halts the whole line. A much better analogy would be to compare the chromosome to a row of independent chemists in a laboratory: Each one independently is producing some product which is then at the proper time mixed with

the products of the other chemists to produce certain compounds. This conclusion is based upon the fact that most chromosome reorganizations such as an end to end inversion of a section of a chromosome or a translocation of a piece of a chromosome to a chromosome of another pair do not alter the effects of the genes, even though in the process some genes are found to be displaced from their normal position. In *Drosophila* a number of exceptions to this rule have been found—cases in which a modified physiological process results from altering the position of the gene through gross chromosome changes. This is known as the position effect. Apparently it has not been reported in any other animal. In plants one case has been described in the evening primrose, *Oenothera*, and a recent case in maize.²³

There are several hypothetical explanations of the position effect, but so far no method has been developed for testing the correctness of any of them. This remains a problem for future research.

PROBLEMS

1. Is it possible to distinguish a gene mutation from a chromosome change by the type of the effect produced? Give an example.
2. Mention one type of chromosome change that may be inherited in the same manner as a gene mutation.
3. How do you account for the fact that beneficial mutations are rare as compared to injurious mutations?
4. What is the presently held hypothesis as to the chemical nature of the gene?
5. Give the various classes of evidence for the linear arrangement of the genes on the chromosomes.
6. What agents have been shown to increase the frequency of gene mutations? How do you account for the negative effects of other agents?
7. In what respects is mutation not an entirely random process, i.e., to what extent is the type of mutation predictable?
8. Why is polyploidy in animals rare as compared to its frequency in plants?
9. Is it possible to control the production of a specific type of mutation?

²³ JONES, DONALD F.: Growth changes in maize endosperm associated with the relocation of chromosome parts, *Genetics*, 29: 420-427, 1944.

INBREEDING AND CROSSBREEDING

THE TERM INBREEDING usually refers to the mating of two closely related individuals, such as first cousins or nearer of kin, while crossbreeding usually refers to the mating of unrelated individuals, each from a different variety or different species. Strictly speaking, however, any two individuals are related if they have even one ancestor in common. Obviously, various degrees of inbreeding and crossbreeding exist. The number of common ancestors and their recency furnish a measure of the degree of inbreeding.

Two important questions are bound up in any discussion of inbreeding and crossbreeding. First, why does the former automatically tend to make a population homogeneous or pure-bred—as it is known to do—while the latter tends to make a population less homogeneous? Second, how are we to explain the well-known fact that inbreeding tends to bring about a decline in vigor, while crossbreeding tends to increase the vigor of a race or species? Thanks to a knowledge of Mendel's laws we now have the answers to both questions.

Long before Mendel's time, animal and plant breeders came to the definite conclusion that close inbreeding usually was detrimental to the offspring, and that a certain amount of crossbreeding was beneficial. Nevertheless, the leading breeders of domestic animals at times practiced close inbreeding because they found from experience that this was the easiest way of fixing a desired type.

Likewise, the lawmakers in most human societies—if we correctly judge the motives behind the laws—came to the conclusion that inbreeding was detrimental to the race, for the laws

In the first generation the hybrid parent has given rise to offspring of which 50 per cent are pure-breeding and 50 per cent hybrid. In the next generation of self-fertilization we obtain the following result (assuming that each plant produces the same number of offspring):

T T	T t	T t	t t
↓	↓	↓	↓
4 T T	1 T T	1 T T	4 t t
	2 T t	2 T t	
	1 t t	1 t t	
Totals 6 T T 4 T t 6 t t			

Twelve individuals in this generation are pure-breeding, and four are hybrids (75 per cent to 25 per cent). Thus in the second generation the percentage of hybrids has been reduced again by one-half.

In the third generation the percentage of hybrids will be still further reduced by one-half, resulting in 87.5 per cent pure-bred to 12.5 per cent hybrid. This process will continue until by the tenth generation 99.9 per cent will be pure-bred, and only 0.1 per cent (one in a thousand) hybrid. As the process continues, it is obvious that the percentage of hybrids in the population will soon become infinitesimally small. For all practical purposes, the self-fertilizing organism will be 100 per cent pure-bred (homozygous) (Fig. 77).

It could readily be shown, if space permitted, that the same rule holds good if two, or any other number of pairs of genes, are chosen for observation simultaneously. In each generation of self-fertilization the percentage of hybridity as a whole is halved. Theoretically, in the absence of selection there will always be a few hybrids left. But if selection accompanies the breeding—as it naturally does in breeding domesticated varieties—the plant can be made 100 per cent pure-breeding for any desired characteristic. Self-fertilization plus selection are no doubt the explanation of the purity of Mendel's varieties of peas.

This theoretical result agrees well with the practical results of self-fertilization in plants. During the first few generations of inbreeding, in plants that normally cross-fertilize, there is a

striking effect apparent in the reduction in vigor and the increase in homogeneity; but after about seven to ten generations, little further change is noted.

A great many plants, such as corn and clover, as well as all the higher animals, are normally cross-fertilizing. This is true

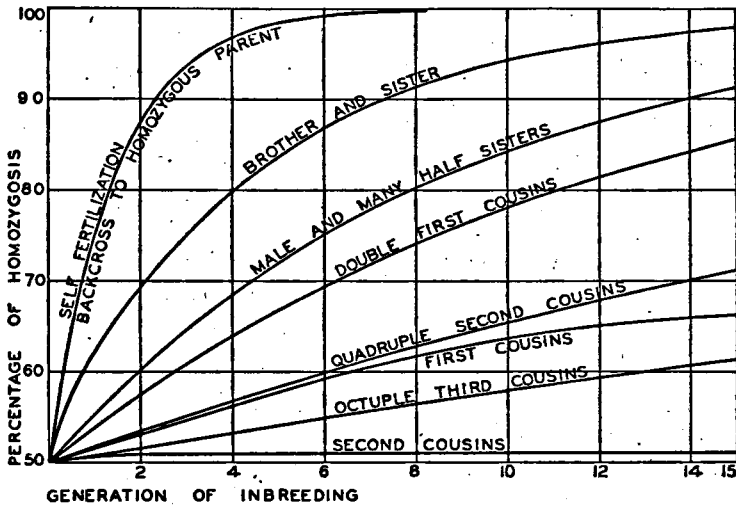


FIG. 77. Curves showing increase in homozygosity as a result of inbreeding in successive generations under various systems of mating, starting with individuals that are 50 per cent homozygous. The percentage reduction in heterozygosity per generation in the various types of mating are: self-fertilization, 50 per cent; brother-sister, 25 per cent the first generation and 19.1 per cent thereafter; male and many half sisters, 11.0 per cent; double first cousins, 8.0 per cent; quadruple second cousins, 3.6 per cent; first cousins, an increasingly slow approach toward fixation; octuple third cousins 1.7 per cent; second cousins, to 98 per cent of the initial value after any number of generations. (Courtesy, WRIGHT, SEWALL: The effects of inbreeding and crossbreeding on guinea pigs, Bulletin No. 1121, U.S. Department of Agriculture, 1922.)

even in most of those that are hemaphroditic. The advantages of cross-fertilization over self-fertilization, to the organisms themselves, are several. The chief of these is greater opportunity for new and better combinations of genes to appear. A necessary consequence of cross-fertilization—in the absence of close inbreeding—is that injurious recessive mutations tend to accumulate in the species, because recessives are usually concealed by normal

dominant genes. It is only when the recessive gene happens to be present in both parents that the offspring show it. The general rule is, as we have noted, that recessive genes are injurious. Consequently, when a normally cross-fertilizing species, for example corn, is self-fertilized, opportunity is at once opened for these accumulated recessives to show their presence. The result is more likely to be injurious than beneficial.

On the contrary, in a self-fertilizing plant such as peas, there is a constant process of self-purification in every generation. As new recessive mutations arise they are at once exposed in one-fourth of the offspring; and if the mutants are not fit, they perish. Only in the hybrids will the recessive persist, and as noted above, in a constantly decreasing percentage of individuals. For this reason, in an organism that is normally self-fertilizing, the process of self-fertilization causes no harm.

We may conclude, therefore, that inbreeding in itself is not detrimental. It is hazardous only to the extent that undesirable recessive genes are present in the original stock. If the stock is free from these, inbreeding of the closest possible type may go on indefinitely without causing harm. The conflicting results from inbreeding in species that are self-fertilizing as compared with those that are cross-fertilizing are thus readily explainable. An example from mammals will illustrate further the points here considered.

BROTHER-SISTER MATINGS IN GUINEA PIGS

Among the most interesting and extensive experiments on the effects of inbreeding and crossbreeding in mammals is a series of experiments on guinea pigs, begun in 1906, by the United States Department of Agriculture,¹ Washington, D. C. Thirty-five healthy and vigorous females were selected from general breeding stock and mated with a smaller number of similarly selected males. The matings were numbered separately, and the offspring of each mating were kept separate and mated exclusively brother to

¹ U.S. Department of Agriculture Bulletins: 1090 and 1121, The effects of inbreeding and crossbreeding on guinea pigs, 1922, by SEWALL WRIGHT; Technical Bulletin 103, The persistence of differentiation among inbred families of guinea pigs, 1929, by SEWALL WRIGHT and O. N. EATON.

twigs grow into large branches with many sub-branches and twigs. In any generation, however, only a few are destined to have living descendants a number of generations hence. This is well shown in the partial pedigree of one of these inbred families (Fig. 78). Note that the pedigree shows all the animals descended from a single pair in the twenty-third generation of brother-sister mating.

Two striking results followed the close inbreeding of guinea pigs. First, each family gradually became more homogeneous.

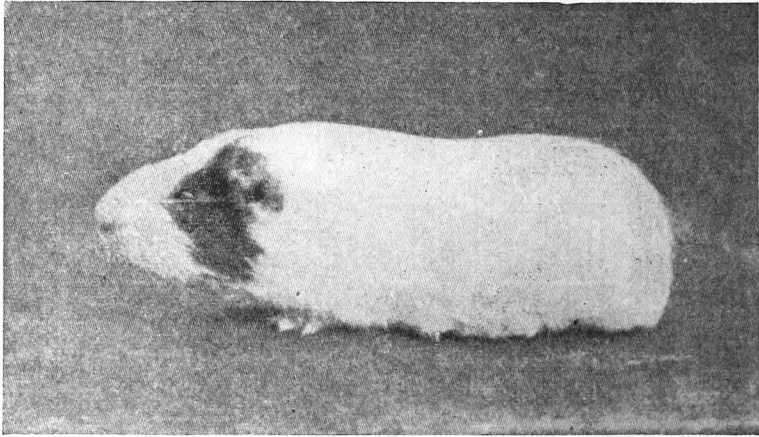


FIG. 79. Male of Family 13, belonging to the eighteenth generation of brother-sister mating. The heaviest animals and the largest litters came in this family. It was above the average in most other respects but was next to the poorest in resistance to tuberculosis. The large amount of white is characteristic. (Courtesy, WRIGHT, SEWALL: The effects of inbreeding and crossbreeding on guinea pigs, Bulletin No. 1090, U.S. Department of Agriculture, 1922.)

While this process was going on there was a gradual elimination of sub-branches, as shown in Fig. 78. The increasing homogeneity within each family was accompanied by a notable differentiation among the families as described below. Second, there was a decline in vigor during the first nine years, covering about 12 generations. This decline applied to weight, fertility, and vitality of the young.

During the second nine years of inbreeding there was no further decline in vigor of the inbred animals as a group. This stability was taken to indicate that after 12 generations the families had become essentially pure-bred, i.e., no longer heterozy-

gous with respect to many genes (Fig. 77). New mutations were apparently not frequent enough to have much effect.

There was found no evidence of heredity of general vigor as a unit. The vigor of a family in one respect was largely independent of its vigor in other respects. Thus Family 13 (Fig. 79), which had the heaviest animals and the largest litters, was next to the poorest in resistance to tuberculosis. The animals in Family 2 (Fig. 80) were the lightest in weight; there were frequent but rather small litters, heavy mortality at birth, but great vitality and longevity thereafter. This family was second in resistance to tuberculosis.

As a result of the inbreeding, each family came to be extremely homogeneous with respect to such characteristics as color of hair, eye color, prominence of eyes, body conformation (one family was decidedly sway-backed, Fig. 81), and even temperament (Family 2 was noticeably more nervous and active than Family 13). Differentiation of the inbred families was by no means limited to external characters. Strandkov² has made a study of internal organ differences in Family 2 and Family 13. The liver, lungs and heart were significantly heavier in Family 13 than in Family 2, but this seemed to be correlated with the greater body weight of Family 13. The thyroids, adrenals, and spleen of the two families were found to differ not only in size but in shape (Fig. 82). The author makes the reasonable suggestion that these organs may be affected by genetic factors which are independent of those which determine general body size. He points out that if no other differences had been found between Family 2 and Family 13 the two families could readily have been distinguished by the differences in size and shape of the adrenals. Those of Family 2, although the lighter of the two families, are significantly heavier than those of Family 13. The left adrenal of Family 2 is thick and triangular in cross-section as shown in Fig. 82, whereas that of Family 13 is thin and flat. That of Family 13 has a characteristic indentation on its mesial side. It is tempting to speculate upon the possibility of there being physiological differences in these and

² STRANDKOV, H. H.: Inheritance of internal organ differences in guinea pigs, *Genetics*, 24: 722-727, 1939.

other glands, correlated with differences in growth and behavior of the two families.

In a further study Strandskov³ made a comparison between 16 skeletal measurements of 20 males and 20 females of Family 2 and Family 13. He found significant differences in the families in ten of the 16 measurements. There was evidence that some of the

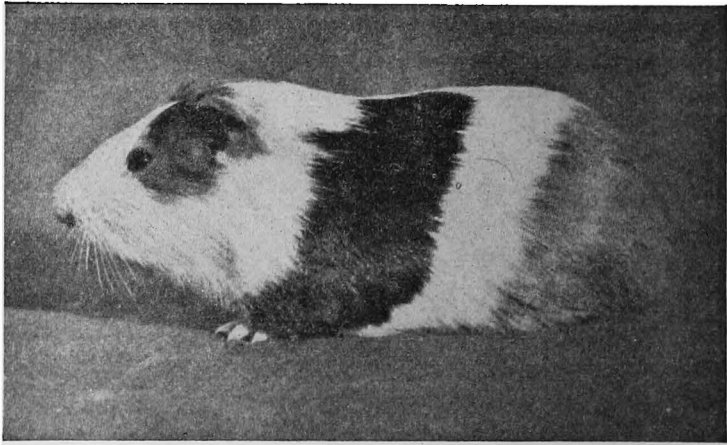


FIG. 80. Male of Family 2, belonging to the twelfth generation of brother-sister mating. This family was characterized by frequent but rather small litters, heavy mortality at birth but great vitality and longevity thereafter. It was second in resistance to tuberculosis. (Courtesy, WRIGHT, SEWALL: The effects of inbreeding and crossbreeding on guinea pigs, Bulletin No. 1090, U.S. Department of Agriculture, 1922.)

differences were due to general growth factors and some to specific factors that act on local parts. The humerus, the femur, the tibia, and some of the cranial bones seemed to be especially affected by local factors.

In all respects in which each inbred family came to be distinguished, the mechanism which brought about uniformity probably was the same, namely, the segregation and independent assortment of genes and the gradual increase in the proportion of genes in which the inbred family was homozygous.

³ STRANDSKOV, H. H.: Skeletal variations in guinea pigs and their inheritance, *J. Mammalogy*, 28: 65-75, 1942.

The theoretical rate at which continued brother-sister matings increase homözygosity has been calculated by a number of investigators. According to recent calculations made by Wright the reduction in the proportion of heterozygous gene-pairs closely approximates 19.1 per cent per generation after the first generation, in which the reduction is 25 per cent (Fig. 77). Although this rate is much slower than the 50 per cent per generation found in self-fertilization, it is still so rapid that after ten generations of



FIG. 81. Male of Family 39, belonging to the thirteenth generation of brother-sister mating. The small amount of white and the sway back are characteristics fixed in this family. Other characteristics are the greatest success in bearing young alive, but lack of success in rearing them, irregularity in producing litters, and the greatest susceptibility to tuberculosis. (Courtesy, WRIGHT, SEWALL: *The effects of inbreeding and crossbreeding on guinea pigs*, Bulletin No. 1090, U.S. Department of Agriculture, 1922.)

such inbreeding, starting with organisms that are 50 per cent homözygous, about 94 per cent of all gene-pairs are homozygous. We see, therefore, why such inbreeding produces its greatest effect during the earlier generations, and relatively little effect if continued beyond ten or 12 generations.

The results of the guinea pig inbreeding experiments are in good agreement with those from other mammals, and from *Drosophila*. The decline in vigor, including the extinction of certain lines, follows largely from the segregation and fixing of recessive genes, which are on the whole injurious to the species. But along with the fixing of such recessives there may also be a

fixing of gene-pairs which are indifferent or beneficial. It is a matter of chance as to what combination of gene-pairs a family finally comes to possess, except that selection is always at work weeding out combinations that are not well adapted to the conditions of life.

There is a common belief that inbreeding causes the production of monstrosities and defectives. In the guinea pig experiments relatively few of these were produced, either by the inbred families or by the controls. It was found, however, that the tendency to produce a given type of monstrosity was characteristic of certain families, but such a tendency had no connection with the vigor of the family in other respects. The two feeblest families were almost free of abnormalities, while the most vigorous family (Family 13) produced 30 per cent of the cyclopean (one-eyed) monsters, 5 per cent of births in this family being monsters of this type. Another family produced most of the eyeless young, and still another had several young with rudimentary legs. There was evidence of hereditary tendencies within the families toward the production of these abnormalities. On the question of the relation of inbreeding to the origin of monstrosities Wright states, "There was no evidence that inbreeding has any specific causal connection with the origin of the monsters. Inbreeding seems merely to have brought to light genetic traits in the original stock."

HYBRID VIGOR

The classic example of hybrid vigor is the mule. This animal is a species-hybrid produced by crossing the horse (*Equus caballus*) with the ass (*Equus asinus*). The mule combines some of the superior qualities of both species: it has much of the size, speed, strength, and spirit of the horse, along with the sure-footedness, lack of excitability, endurance, and ability to thrive on poor food which are characteristic of the ass. This combination of traits gives to these hybrid animals a unique value for certain types of work. For instance, at the Grand Canyon of the Colorado River in Arizona, herds of mules are maintained for carrying tourists over the trail from the rim to the river, one mile below. Horses are not used for this work because of the danger of their becoming frightened by falling rocks or other disturbances and going over a

precipice. Because of their superior quality as work animals mules bring a higher price than horses.

The mule is rather an exceptional case, however, since there are very few species-hybrids of economic importance among

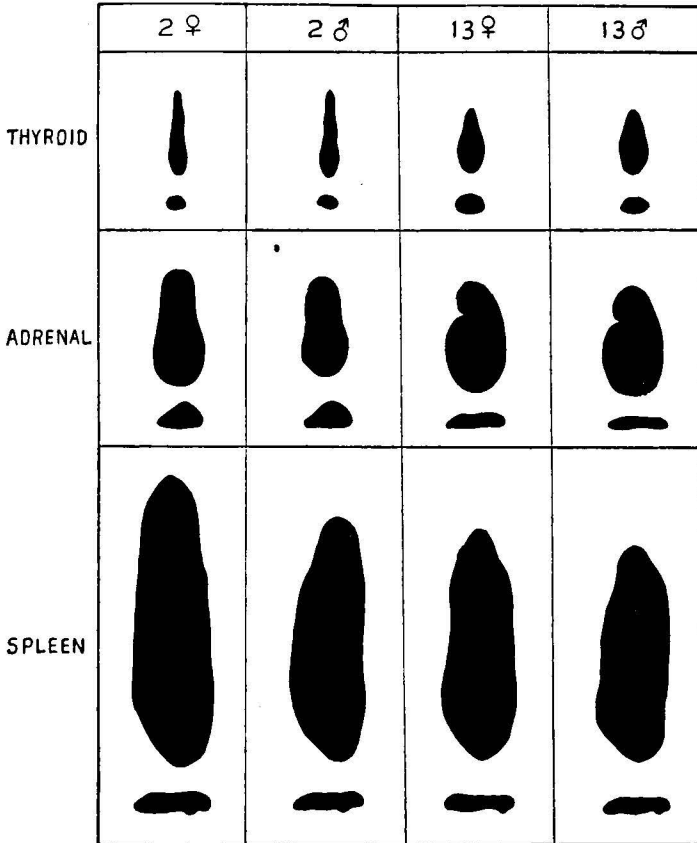


FIG. 82. Drawings showing differences in the size and shape of thyroid, adrenal, and spleen of two highly inbred families of guinea pigs (Families 2 and 13). (Courtesy, STRANDSKOV, H. H.: Inheritance of internal organ differences in guinea pigs. *Genetics*, 24: 722-727, 1939.)

domesticated mammals. Like most species-hybrids the mule is sterile because normal reproductive cells fail to develop. Among mammals, it is usually impossible to obtain a hybrid by crossing

one genus with another. Such wide crosses as the cat (*Felis domestica*) with the dog (*Canis familiaris*) or the jackrabbit (*Lepus californicus*) have never been obtained.

As mentioned in Chapter 1, the term hybrid is properly applied also to the offspring of two subspecies or two varieties of the same species. Such varieties may differ in only one gene or, as is commonly the case, they may differ in a number of genes, but no hard and fast distinction can be drawn between a subspecies and a species, since the difference between them is one of degree.

As a result of breeding experiments with plants and animals, it is now generally accepted that hybrid vigor, in certain cases at least, has a simple explanation in the operation of Mendel's laws. The experiments with guinea pigs,⁴ described in the previous section, included an investigation of hybrid vigor. The results are very clear-cut in their demonstration of the increase in vigor following the crossing of two pure breeds. Crosses were made among five of the inbred lines or breeds of guinea pigs produced by brother-sister matings. It will be recalled that in these experiments continuous mating of brothers with sisters was accompanied by a decline in all of the elements of vigor which were studied. These elements of vigor included the percentage born alive, the percentage raised to weaning, the birth weight, the rate of gain in weight, adult weight, size of litter, and number of litters per year. The inbred animals as a group came to be distinctly inferior to the random-bred control stock, a stock in which matings closer than second cousins were not made (see Fig. 77), in all these respects, as well as in resistance to tuberculosis. Two of the five inbred families, however, were more resistant to tuberculosis than the controls.

It was found also that the various elements of vigor and weakness were inherited independently of each other, and that these had become fixed in almost all of the possible combinations in the various families; though there was no evidence of hereditary differences in general vigor.

In addition, a conspicuous differentiation was evident among the families in such characteristics as color, number of toes, and tendency toward the production of particular types of monsters. Each family came to be characterized by a particular combination

of traits, usually involving strength in some respects and weakness in others. These results were interpreted in accordance with Mendel's laws of heredity.

Crosses between different inbred families showed marked improvement in the offspring over both parental inbred families, in every respect. In the case of adult weight and resistance to tuberculosis the improvement appeared to its full extent in the offspring of the first cross. The hybrid young were at least as resistant to tuberculosis as the more resistant parental family. In some cases the young were more resistant than either parental family. Resistance was dominant over susceptibility.⁴

The improvement in the various elements of vigor affecting the number of young raised to weaning per year added up to produce an increase of over 80 per cent in the number of young raised, so that the hybrids from inbred family crosses were considerably superior to the random-bred controls in this respect.

Wright concluded from his analysis of the various crosses, that the results just described were all the direct or indirect consequence of the Mendelian mechanism of heredity; that the fundamental effect of inbreeding is the automatic increase of homozygosis; and that an average decline in vigor is the consequence of the observed fact that recessive genes are more likely to be injurious than are their dominant alternatives. He concluded further that the differentiation among the families is due to the chance fixation of different combinations of the genes present in the original crossbred stock, and that crossing causes an improvement because each family supplies some dominant genes lacking in the other.

Wright suggested that the method of close inbreeding, followed by crossbreeding, would have important applications in the improvement of livestock. The method had in fact been used by the pioneer breeders more than a century earlier on a less intensive scale in the founding of many of the pure breeds of livestock. The most remarkable results of the method thus far, however, have come from its application to crop plants such as corn and sugar

⁴ WRIGHT, SEWALL, AND LEWIS, PAUL A.: Factors in the resistance of guinea pigs to tuberculosis, with especial regard to inbreeding and heredity, *Am. Naturalist*, 55: 20-50, 1921.

cane, in which phenomenal increases in yields have been obtained from hybrids.

William Crocker, one of the leaders in plant research in the United States, gives the following striking example of the possibilities of increasing the yield of crops by making use of hybrid

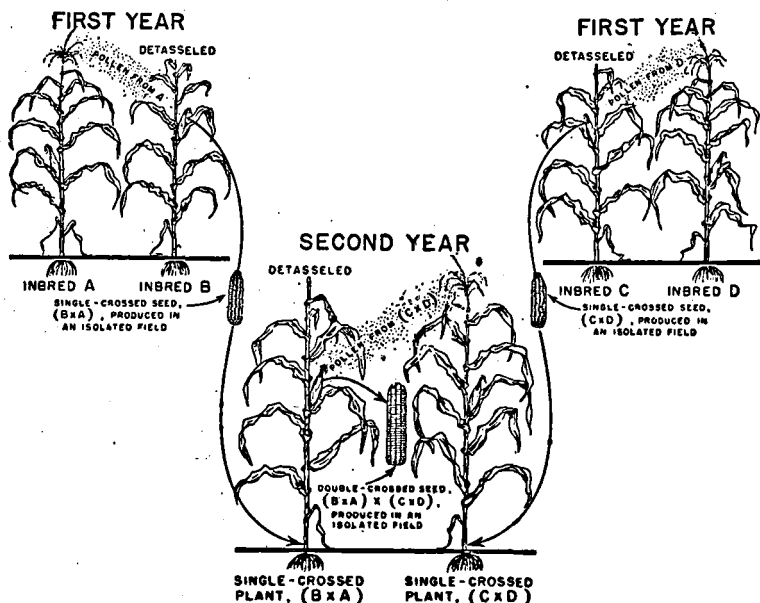


FIG. 83. Method of producing double-cross commercial hybrid seed corn. (Courtesy, SPRAGUE, G. F.: Production of hybrid corn, Bull. P48, Agric. Exp. Station, Iowa State College, 1942.)

vigor. In the island of Java the breeding of sugar cane over a period of more than 20 years has resulted in new types which

under identical cultivation methods, produce three times as much sugar per acre as any of the canes entering into the original crosses. More than 15 tons of sugar per acre per crop have been produced. With these new canes and with improved methods of cultivation now known, two islands, Cuba and Java, besides growing much other food for their people, can produce with profit all the sugar the world can eat at two cents a pound at the mills.⁵

In the United States during the past few years, we have seen an astonishing increase in the yield of corn per acre as a result of the production of hybrid seed. The breeding methods used are

⁵ CROCKER, WILLIAM: Botany of the future, *Science*, Oct. 28, 1938.

essentially the same as in the guinea pig experiments previously described: numerous inbred lines of corn are produced by self-fertilization. In these inbred lines there is a rapid decline in vigor, because corn is largely cross pollinated; but out of many inbred lines a few give fair yields. By crossing the better lines, commercial seed is produced.

In actual practice the production of commercial hybrid seed usually is carried out in the following manner: Four superior inbred lines are chosen. Let us call these lines A, B, C, and D. Line A is crossed with line B; and line C is crossed with line D. The two resulting hybrids are then crossed; the seed from the latter cross becomes the commercial seed (Fig. 83). The first generation hybrids are not used for crop production because the amount of such hybrid seed is small since the parent lines are inbred. The crossing of the two hybrids, however, produces a large amount of seed as a consequence of hybrid vigor. These second generation hybrids are, of course, quite variable because their parents are hybrids; any disadvantages in their variability, however, are more than offset by the abundant yield (Fig. 84).

The development of the inbred strains and the production of hybrid seed from them is naturally an expensive process. Nevertheless, the results more than justify the labor, since it is not uncommon for hybrid corn to yield 25 to 30 per cent more per acre than ordinary open-pollinated corn. At present about three-fourths of all corn grown in the United States is from hybrid seed; in 1934 it was a curiosity.

MARRIAGE LAWS PREVENT CLOSE INBREEDING IN MAN

In the United States, legislation on marriage is a function of the several states. All of the states prohibit marriages between blood relatives closer than first cousins; a majority prohibit marriages of first cousins. Those states that permit cousin marriages are all in the South and East except one (California) in the Far West. The newer states in the Middle West and Northwest without exception prohibit cousin marriages. A few states extend the prohibition to first cousins once removed, and one (Oklahoma) prohibits the marriage of second cousins.⁶

⁶I am indebted to Mrs. A. C. BUCHANAN, Director of Research Service, "En-

Nearly half the states prohibit a man's marrying certain classes of relatives-in-law such as his wife's daughter, his wife's mother or his stepmother. The same prohibitions apply to women within corresponding degrees. Strange as it may seem, in general these are the same states which permit cousin marriages. Whatever the reasons for prohibiting the marriage of relatives-in-law, such reasons, of course, have nothing to do with the hereditary qualities of expected offspring. The model for such statutes is no doubt the Mosaic law as contained in the eighteenth chapter of Leviticus. The Mosaic law makes no provision against cousin marriages, but prohibits marriages between various classes of relatives-in-law, as well as blood relatives nearer than first cousins.

In most European countries the marriage laws appear to be patterned after the Mosaic law. All, save a few of the smaller countries in the south of Europe, permit cousin marriages, as do also the British Dominions, Japan, and countries which follow Mohammedan law. China, on the other hand, prohibits the marriage of cousins. China forbids marriages between persons having the same surname, as did some of the tribes of North American Indians and the aborigines of Australia.

Ideas condemning the marriage of near of kin must have had a very ancient origin since the customs of most primitive tribes enforce certain restrictions. There is no unanimity on the question of cousin marriages, for among some primitive peoples cousin marriages are prohibited, while among others they are highly favored. Curious exceptions regarding marriages of the nearest of kin are found among certain primitive tribes. According to Bronislaw Malinowski,⁷ marriages between mother and son or daughter and father are reported from certain tribes in Malaysia, in the Islands of the South Pacific, and in Africa. Even better attested, according to this anthropologist, are the marriages between brother and sister in the Marshall Islands and Hawaii and, in ancient times, in the royal families of Egypt, Ireland, and the Inca Empire of South America.

cyclopaedia Britannica," for furnishing a compilation of the laws and statutes concerning consanguineous marriages in the United States and foreign countries, compiled from the latest available sources.

⁷ "Encyclopaedia Britannica," article on Marriage.

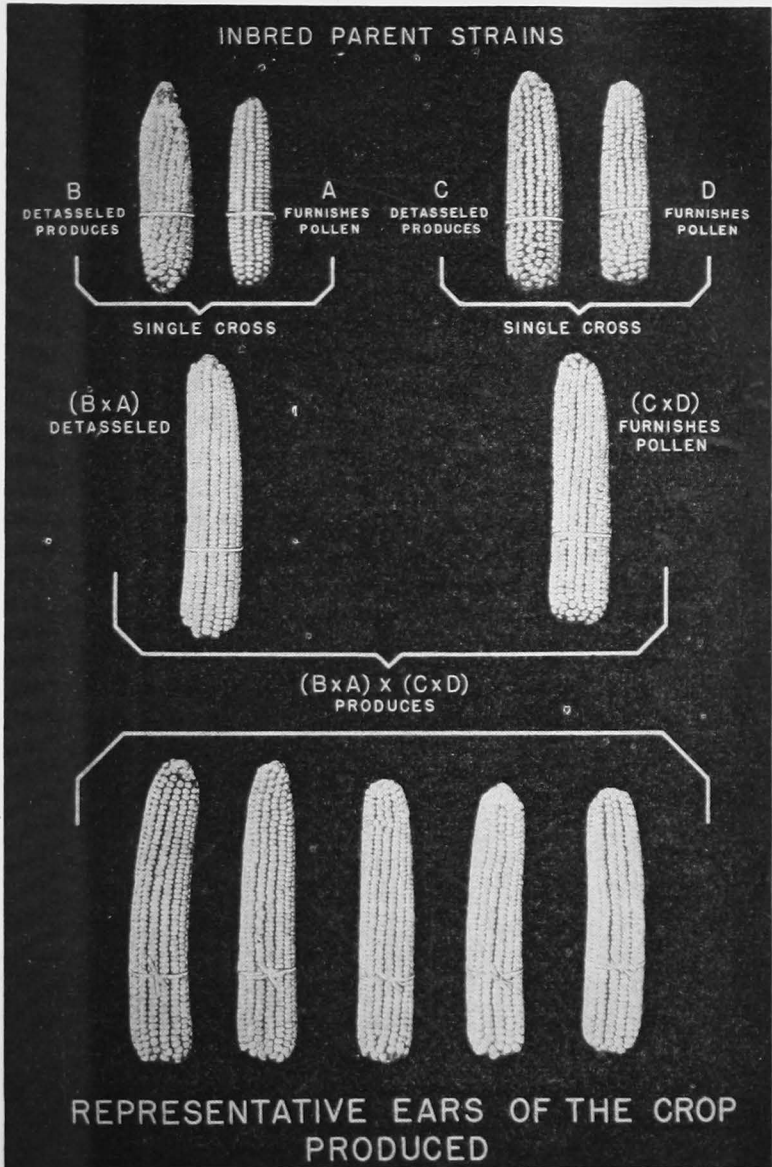


FIG. 84. Hybrid vigor illustrated in the crossing of inbred strains of maize. (Courtesy, POOLE, C. F.: Improvement of Sweet Corn, "Yearbook of Agriculture," U.S. Department of Agriculture, 1937.)

COUSIN MARRIAGES AND DEFECTIVES IN MAN

There is a widespread popular belief that the marriage of first cousins is likely to result in defective offspring. On what evidence is this based? The question can best be answered from the examination of a concrete case.

Amaurotic idiocy was described (Chapter 9) as a single recessive defect in man. Torsten Sjögren has made an exhaustive study of the juvenile form of this disease in Sweden, where he visited

Generation

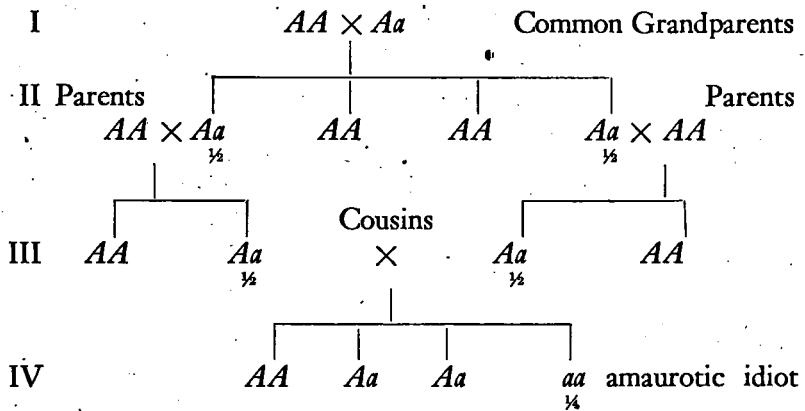


FIG. 85. A typical pedigree covering four generations showing the path of a recessive gene from a single grandparent of two cousins to its expression in a child of the cousins. The probability of the appearance of the recessive trait in an individual of generation IV is found by multiplying together the five fractions ($\frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{4} = \frac{1}{64}$).

all the schools for blind children in search of cases.⁸ The fact that in Sweden family records have been kept in the churches for generations enabled him to prepare more than 50 pedigrees.

Approximately one case of juvenile amaurotic idiocy was found for every 30,000 children. In the population of Sweden as a whole only about one per cent of marriages were between first cousins, yet this one per cent was responsible for about 15 per cent of all the amaurotic children in Sweden. Marriages between

⁸ SJÖREN, TORSTEN: Die juvenile amaurotische Idiotie. Klinische und erblichkeitsmedizinische Untersuchungen. *Hereditas*, 14: 197-425, 1930-1931.

relatives other than cousins produced another 10 per cent of the amaurotics.

Clearly the marriage of cousins has something to do with the appearance of this rare recessive defect. The relationship seems to be as follows. All cases of amaurotic idiocy come from normal parents who are heterozygous for the gene, since defectives invariably die young and never reproduce. Cousins have two grandparents in common, and are hence much more likely to carry the same rare recessive gene than are any two unrelated persons. With respect to any recessive gene present in a single grandparent of two cousins, there is a chance of one in 16 that both cousins will carry it. The demonstration of this relationship is shown in the accompanying example of a typical pedigree (Fig. 85). Let *a* stand for the gene for amaurotic idiocy and let *A* stand for the normal alternative gene. One grandparent on one side is shown as a carrier of the gene; the other grandparents are assumed to be free from it.

The fraction beneath the gene formula in each case indicates the chance of occurrence of that particular gene combination in the generation shown. Applying the law of probability (Chapter 2) it is seen that the chance of a person in generation II being a carrier (*Aa*) is one in two. The chance of a person in generation III being a carrier (provided a parent in II is a carrier) is also one in two. Hence the chance of a grandchild such as one of the cousins being a carrier is one in four ($\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$). The chance of both cousins simultaneously being carriers is one in sixteen ($\frac{1}{4} \times \frac{1}{4} = \frac{1}{16}$).

Two cousins who are both carriers have a chance of one in four of producing at each birth a child who is recessive (*aa*). Multiplying this probability by the probability that both cousins shall be carriers we get $\frac{1}{4} \times \frac{1}{16} = \frac{1}{64}$ (one in 64). This represents the chance of a child's showing any recessive trait, the gene for which was present in the heterozygous state in one, and only one, of the common grandparents of the two cousins.

In Sweden, approximately one child in 40,000 from unrelated parents is amaurotic. The frequency of carriers of gene *a* must, therefore, be about one in 100, because the chance of two such carriers marrying is only $\frac{1}{100} \times \frac{1}{100}$ or $\frac{1}{10,000}$; and if such a

marriage occurs the chance is one in four that the first child born will be defective.

The chance that one or the other of the two common grandparents of cousins will carry the recessive gene *a* is $\frac{1}{100} + \frac{1}{100} = \frac{1}{50}$ (one in fifty). The chance that a cousin marriage chosen at random will produce an amaurotic child as the result of genes derived from a common grandparent is therefore $\frac{1}{50} \times \frac{1}{64} = \frac{1}{3200}$. There is also a very slight chance that both cousins will receive the gene for amaurotic idiocy from their other grandparents not held in common or from one of the two possible combinations of common grandparents with noncommon grandparents. Without presenting the calculations of this chance we may say that by combining all of the chances mentioned above we obtain one chance in 3,061 as the probability of the birth of an amaurotic child from a cousin marriage chosen at random in Sweden. This chance is approximately 13 times the chance of birth of such an individual from unrelated parents.

Although the risk of this particular recessive showing up is rather small, even in cousin marriages, it must be remembered that there are hundreds of other rare recessive defects in man, and the gene for one or more of these will probably be present in a common grandparent. The rarer a recessive gene is in the population the greater is the effect of a cousin marriage in increasing the frequency of the trait as compared with its frequency from unrelated parents.

Among other rare recessive defects known to have a much higher frequency in children from cousin marriages than in children from unrelated parents are the following: albinism, xeroderma pigmentosum, total color blindness, Friedreich's disease, and congenital ichthyosis. Obviously, the popular prejudice against cousin marriages is based on sound facts so far as the increased risk of defective offspring is concerned.

The picture of cousin marriages which we have just drawn has another side. If inbreeding as exemplified by cousin marriages tends to bring into expression injurious genes which are already present in the stock it likewise tends to bring into expression beneficial genes, since the mechanism of heredity is the same in both cases. One famous example of superior traits passing on to

the children of cousins is found in the family of Charles Darwin. Darwin, who came from a distinguished English family, married his first cousin, also from a distinguished family. Of five sons who survived him, four became distinguished far above the average, and in ways that clearly indicate superior hereditary capacities.

This family may also illustrate the outcropping of recessive defects, since according to one of Darwin's daughters,⁹ in the family of ten children many were delicate and difficult to rear, and three died. She states that the last child, a son, was born without his full share of intelligence and died at about a year and a half of age, never having learned to walk or talk.

All things considered it seems that we are not justified in laying down a hard and fast rule against cousin marriages. In special cases the opportunity of preserving or concentrating superior qualities in the offspring may warrant taking some of the risks that naturally accompany such marriages.

PROBLEMS

1. Why does inbreeding in species that are normally crossbred usually lead to a decline in vigor?
2. How is it possible for species that normally are self-fertilized to continue indefinitely with no decline in vigor?
3. Why does crossbreeding two distinct varieties or species usually result in a hybrid more vigorous than either parent?
4. What is usually the nature as to vigor and variability of the offspring produced by F_1 hybrids?
5. In his experiments with garden peas Darwin found that a cross between two individuals of the same variety resulted in no increase in height or fertility of the offspring. Give an explanation of this result in terms of the gene theory.
6. Darwin found that a cross between two varieties of peas resulted in a marked superiority in the growth and vigor of the offspring over the self-fertilized plants of the same varieties. Explain this by the use of the gene theory.
7. Explain by diagram, using two pairs of genes, how inbreeding in mammals, accompanied by rigorous selection, may result in no appreciable decline in vigor.

⁹ "Emma Darwin, A Century of Family Letters, 1792-1896," edited by her daughter HENRIETTA LITCHFIELD, Appleton-Century, 1915.

8. Show by diagram, using two pairs of genes, why the hybrid offspring of two pure-bred varieties or of two species is usually no more variable than the parent varieties or species themselves.

9. In some of the crosses between inbred families of guinea pigs the hybrids were larger than either inbred line and larger than the ordinary random-bred stock. Explain this result by means of a diagram of matings and hypothetical genes.

10. Show by diagram, choosing hypothetical characters and genes, how to obtain, by crossing homozygous races, and selection, a race of organisms that is homozygous for a *combination of traits* superior to that of either parental type.

11. Represent by means of the usual histograms or bargraphs the range of variability in some quantitative character such as skin pigmentation in man in the offspring of hybrids. Show separately the range, assuming (a) that the difference between the original types depends upon a single gene pair, (b) that the difference depends upon two pairs of genes, and (c) that it depends upon three pairs of genes.

12. If among the offspring of F_1 hybrids the two original pure types are seldom obtained, what can be said regarding the probable number of gene differences between the original types?

13. What method of breeding is necessary in order to produce a pure breed of mammals? Explain.

14. Mention some important problem in biology which might be solved by the use of a completely homozygous stock of animals.

HEREDITY AND EVOLUTION

AS USED IN BIOLOGY the term *evolution* denotes the process of origination of the various kinds of plants and animals by descent from other kinds through the interaction of natural forces. In contrast to the theory of evolution there is the theory of the separate creation of each species.

The earlier writers on evolution sharply separated the question of evolution from the problem of the origin of life. As to the origin of life, Darwin himself, who did more to establish the truth of evolution than any other man, publicly took a thoroughly orthodox view, as expressed in the closing sentence of his book "The Origin of Species":

There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a few forms or into one; and that, while this planet has gone circling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved.

But in a letter to his closest scientific friend, the famous English botanist Sir J. D. Hooker, in 1863 he writes,

I have long regretted that I truckled to public opinion, and used the Pentateuchal term of creation, by which I really meant "appeared" by some wholly unknown process. It is mere rubbish, thinking at present of the origin of life; one might as well think of the origin of matter.

Although the problems of the origin of life and the evolution of life are perhaps logically distinct, it seems probable, on the basis of recent researches on the filterable viruses, that the two problems will eventually merge into one. In Chapter 13 we considered the interesting resemblances between the viruses and genes, and found that in some respects viruses appear to be intermediate between the living and the nonliving. Further intensive study of

the gene may well result in important contributions to the problem of the origin of life.

MENDEL AND EVOLUTION

In Darwin's day very few people, biologists included, had come to accept evolution as a fact. Darwin therefore felt it necessary to devote much of his energy to the marshaling of evidence in support of the fact of evolution. The case he made out was so convincing that most biologists—as well as many of the laity—were converted to the idea of evolution as a fact. Mendel, as mentioned earlier, was a close student of Darwin's writings, and undoubtedly accepted the existence of evolution, for in the introduction to his paper on peas he writes:

It requires indeed some courage to undertake a labour of such far-reaching extent; this appears, however, to be the only right way by which we can finally reach the solution of a question the importance of which cannot be overestimated in connection with the history of the evolution of organic forms.

Near the end of Mendel's paper is the following statement:

The opinion has often been expressed that the stability of the species is greatly disturbed or entirely upset by cultivation, and consequently there is an inclination to regard the development of cultivated forms as a matter of chance devoid of rules; the coloring of ornamental plants is indeed usually cited as an example of great instability. It is, however, not clear why the simple transference into garden soil should result in such a thorough and persistent revolution in the plant organism. No one will seriously maintain that in the open country the development of plants is ruled by other laws than in the garden bed. Here, as there, changes of type must take place if the conditions of life be altered, and the species possesses the capacity of fitting itself to its new environment.

And finally, in his concluding remarks, while discussing hybrids in certain plant groups which are known to breed true in the same way that pure species breed true, he writes: "For the history of the evolution of plants this circumstance is of special importance, since constant hybrids acquire the status of new species."

Although the quoted statements indicate that Mendel accepted evolution as a fact, he was, according to his biographer Iltis, critical of some of the theories proposed to explain the process of evolution. In particular he was skeptical of the theory of the inheritance of acquired characters, developed by Lamarck and

adopted in part by Darwin. This skepticism, which was based upon Mendel's own experiments, has been fully justified by subsequent developments. Although Darwin never knew of Mendel's

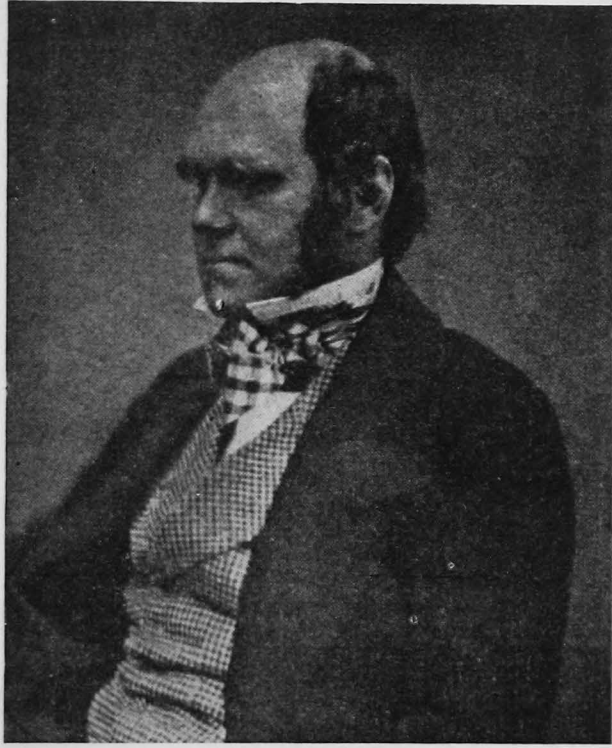


FIG. 86. Charles Darwin in 1854. (Courtesy, DARWIN, FRANCIS and SEWARD, A. C.: "More Letters of Charles Darwin," New York, D. Appleton & Co., 1903.)

work, the application of Mendel's laws has had a profound influence in recent years in confirming and extending the theory of natural selection, proposed independently by Darwin and his British contemporary A. R. Wallace in 1858.

NATURAL SELECTION

Since natural selection constitutes the core of our modern theories of evolution let us quote a summary of it by one of the originators of the theory as found in the introduction to "The Origin of Species" by Darwin.

As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be *naturally selected*. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form . . . I am convinced that natural selection has been the most important, but not the exclusive, means of modification.

The statement is sometimes made today that biologists have abandoned the theory of natural selection. Nothing could be farther from the truth. Those in the forefront of research in heredity and its application to evolution are the staunchest supporters of natural selection—as witness the following statement from Professor Sewall Wright of the University of Chicago:

The conclusion seems warranted that the enormous recent additions to knowledge of heredity have merely strengthened the general conception of the evolutionary process reached by Darwin in his exhaustive analysis of the data available 70 years ago.¹

In the same vein is the following quotation from Professor Theodosius Dobzhansky of Columbia University:

During the years that have elapsed since the publication of the theory of natural selection, it has been the subject of unceasing debate. The most serious objection raised against it is that it takes for granted the existence, and does not explain the origin, of the hereditary variations with which selection can work. Those who advance this objection fail however to notice that in so doing they commit an act of supererogation: the origin of variation is a problem entirely separate from that of the action of selection. The theory of natural selection is concerned with the fate of variations already present, and the merits and demerits of the theory must be assessed accordingly . . . It is hardly necessary to reiterate that the theory of mutation relates to a different level of the evolutionary process than that on which selection is supposed to operate, and therefore the two theories cannot be conceived as conflicting alternatives. On the other hand, the discovery of the origin of hereditary variation through mutation may account for the presence in natural populations of the materials without which selection is known to be ineffective. The greatest difficulty in Darwin's general theory of evolution, of the existence of which Darwin himself was well aware, is hereby mitigated or removed.²

Other leading investigators might be quoted to the same general effect. It is fair to state that natural selection is more firmly established now than ever before as one of the factors of evolution.

¹ WRIGHT, SEWALL: Evolution in Mendelian populations, *Genetics*, 16: 97-159. 1931.

² "Genetics and the Origin of Species," by THEODOSIUS DOBZHANSKY, 2d ed., 1941, Columbia University Press.

although there is considerable difference of opinion as to its relative importance as compared with other factors.

Let us now consider in more detail the theory of natural selection and its relationship to the principles of Mendelian heredity. Referring back to Darwin's summary, we note that he there states several biological laws, which upon examination prove to be almost self-evident. These laws are: (1) the geometrical ratio of increase of all organisms; (2) the struggle for existence; (3) hereditary variations; and (4) the survival of the fittest.

1. THE GEOMETRICAL RATIO OF INCREASE. By this is meant the tendency of every organism to reproduce itself at such a rate that if all its offspring survived, and in turn reproduced their kind, the single species would soon come to occupy all available space on the earth. Some striking examples of this tendency may be cited.

Among the many-celled plants a group of higher fungi known as puffballs have perhaps the highest rate of reproduction. Some puffballs are said to reach several feet in diameter. They are filled with tiny reproductive cells known as spores, which in a single individual, according to estimates, may reach the stupendous total of one-million million (1,000,000,000,000). If each of these spores were to develop into a puffball only one inch in diameter they would cover a combined area of 250 square miles, growing side by side in physical contact. If in turn each of these individuals produced only 500,000,000 spores, all of which developed into one-inch puffballs, they would cover in close contact a surface of 125,000,000,000 square miles, or more than 2,700 times the total land area of the earth.

Again, in the wood-eating insects known as termites, the queen grows to an enormous size and becomes a veritable egg-laying machine. She is then incapable of locomotion and is zealously tended by the workers in the colony. Professor Alfred E. Emerson, of the University of Chicago, an authority on termites, who has in preserving fluid the largest termite queen ever reported, has kindly supplied the following facts. The queen referred to (a member of the species *Macrotermes natalensis*) was collected by Lang in the Belgian Congo in 1913. Her dimensions are: length 101 mm., width 31 mm. When taken from the termite hill, according to Lang, she laid about one egg a second. Since egg-

laying seems to be a continuous process in these insects, in the course of a year the single queen would lay more than 30,000,000 eggs.

Man has a relatively slow rate of reproduction, and yet during the past century or two we have seen his potentialities in this respect amply demonstrated. For example, according to the *Encyclopaedia Britannica*, the population of Japan has grown as follows (using round numbers):

POPULATION OF JAPAN	
1846.....	27,000,000
1872.....	33,000,000
1893.....	41,000,000
1913.....	53,000,000
1923.....	60,000,000
1930.....	64,000,000
*1939.....	73,000,000

* *Japan Year Book, 1940-41*, New York: Columbia University Press, 1941.

The writer of the article in the *Encyclopaedia Britannica* states that "birth control is advocated in some quarters, but has not been seriously considered, nor is it likely to be." The opinion expressed in the last clause may, perhaps, be taken with a grain of skepticism. The spread of birth control within the past two or three decades makes one doubt that any race is immune. As a matter of fact, according to Japanese reports in 1939, the annual growth in population was highest in 1932, but since then a gradual decline in rate of increase has been observed.

The history of population increase in the United States is even more remarkable, although it is complicated by a large amount of immigration. Official United States Census figures (to the nearest 100,000) are as follows:

POPULATION OF CONTINENTAL UNITED STATES	
1790.....	4,000,000
1800.....	5,300,000
1820.....	9,600,000
1840.....	17,100,000
1860.....	31,400,000
1880.....	50,200,000
1900.....	76,000,000
1910.....	92,000,000
1920.....	105,700,000
1930.....	122,800,000
1940.....	131,700,000

Between 1920 and 1930 only 2,823,000 immigrants entered—a marked reduction over previous years. From 1930 to 1940 46,518 more persons left the United States than entered. Since 1880 the rate of increase in the population of the United States has fallen rapidly, though irregularly, from 30.1 per cent for the decade 1870–1880 to 7.2 per cent for the decade 1930–1940, in spite of the fall in the death rate during this period. The decrease in rate of growth is largely due to voluntary limitation of size of families. Between 1915 and 1933 there was a rapid downward trend in the birth rate. Since 1933 the trend has been slowly and irregularly upward, with a decided increase during the war years. This recent increase is probably a temporary phenomenon. Considering the various factors in the situation some of the leading experts on population anticipate a stabilization of the population of the United States within a few decades corresponding to that now existing in a number of the European countries.

2. **THE STRUGGLE FOR EXISTENCE.** This expression was used by Darwin in a metaphorical sense to describe the complex relationships of organisms one to another, as well as to their physical environment. For example, a desert plant must struggle to conserve water, and man must struggle to obtain food and shelter, and to resist the attacks of parasitic diseases. The struggle may be among members of a given species as well as among distinct species. Even though it were possible to have complete cooperation within a species there would always be potential enemies and dangers from without against which a struggle would be necessary.

3. **HEREDITARY VARIATIONS.** Our study of heredity has shown us that each individual is unique (identical twins, triplets, etc. excepted) and that much of this uniqueness is due to a difference in the gene make-up of the individual. Although Mendel's laws of heredity and the gene concept were unknown to Darwin, he recognized that there were two types of variations—those due to environmental differences (which he called environmental modifications) and those due to hereditary differences (hereditary modifications). Darwin's greatest error as we view it today was in considering that certain changes induced by the environment or by exercise were converted into hereditary changes (the inheritance of acquired characters). But as already pointed out, the

existence of such hereditary variations is the important fact, and for the purposes of natural selection it makes no difference how the variations are produced.

4. **THE SURVIVAL OF THE FITTEST.** This expression was first used by the famous British philosopher Herbert Spencer and later adopted by Darwin. As Darwin pointed out, the word fittest has no moral connotation, but means simply the degree of adaptation of the organism to its environment. For example, in a desert plant the individuals with best drought resisting tissues are most fit, other things being equal. In animals, fitness may depend upon a variety of characteristics, such as speed, strength, weapons, defensive armor, well-developed sense organs, intelligence, and (among the most important of all) resistance to invading parasites. In man, in modern times, fitness depends much more on the two traits last mentioned than on the first two.

In the struggle for existence, chance, as we all know, plays a part. But in the long run chance cancels out, and those individuals which are best fitted to the environment survive in larger numbers than those not so well fitted. The surviving individuals are therefore naturally selected, and in so far as their differences from those that perish are hereditary, they will tend to transmit these differences to the next generation. If this process is continued over many generations the result, according to Darwin, may be a new species. In "The Origin of Species" he illustrates the principle in the case of the giraffe in the following words.

The giraffe, by its lofty stature, much elongated neck, fore legs, head and tongue, has its whole frame beautifully adapted for browsing on the higher branches of trees [see my Fig. 68, p. 278]. It can thus obtain food beyond the reach of the other Ungulata or hoofed animals inhabiting the same country; and this must be a great advantage to it during dearths. . . . So under nature with the nascent giraffe, the individuals which were the highest browsers and were able during dearths to reach even an inch or two above the others, will often have been preserved; for they will have roamed over the whole country in search of food. That the individuals of the same species often differ slightly in the relative lengths of all their parts may be seen in many works of natural history, in which careful measurements are given. These slight proportional differences, due to the laws of growth and variation, are not of the slightest use or importance to most species. But it will have been otherwise with the nascent giraffe, considering its probable habits of life; for those individuals which had some one part or several parts of their bodies rather more elongated than usual, would generally have survived. These will have intercrossed and left offspring, either inheriting the

same bodily peculiarities, or with a tendency to vary again in the same manner; while the individuals less favored in the same respects will have been the most liable to perish.

We see here that there is no need to separate single pairs, as man does, when he methodically improves a breed: natural selection will preserve and thus separate all the superior individuals, allowing them freely to intercross, and will destroy all the inferior individuals. By this process long-continued, which exactly corresponds with what I have called unconscious selection by man, combined, no doubt, in a most important manner with the inherited effects of the increased use of parts, it seems to me almost certain that an ordinary hooved quadruped might be converted into a giraffe.

The process of natural selection is evidently similar to the method practiced by man in improving his domesticated animals and plants, if instead of selection by a human agency we substitute selection by the forces of nature. As an example of man's power of directing the adaptation of animals to particular functions let us compare two widely used breeds of horses—the Belgian, a draft breed, and the thoroughbred, a breed used for running races. The former (Fig. 87) was developed on the continent of Europe, the latter in England. The Belgian was probably derived from the wild horses of Europe which existed down into Medieval times. From all the available evidence these wild horses were much smaller and lighter in weight than the Belgian, although in Western Europe there existed a forest type of wild horse with large bones and feet. During the Middle Ages the heavy horse was bred for riding, since such a type was required to carry a knight in full armor. Later, horses were used for pulling heavy loads; and here again size and strength were most important. The Belgian is among the heaviest of modern breeds. Stallions commonly weigh from 2,000 to 2,500 lbs. The body is broad, deep and heavily muscled and the legs are short and strong. The neck is short and heavily arched. The height is about 17 hands or 68 inches. The Belgian illustrates well what can be done by man in modifying an animal in a specific direction. The contrast between the Belgian and the thoroughbred (Fig. 88) is striking. Here the whole force of selection has been directed toward increased speed. Stallions that have outstanding records on the track are retired after a few years to the stud where they often continue to sire colts for many years. Selection of females that are of superior speed likewise is practiced. As mentioned above, the thoroughbred was developed in England for the specific

purpose of racing. Its ancestry is a mixture of native English horses crossed with horses imported from Arabia, Turkey, and North Africa about 1700. By combining the good qualities of both types the size and speed of the breed was increased, until today the average height is about 16 hands and the speed superior to that of the Arabian. The Arabian is about 15 hands and the original

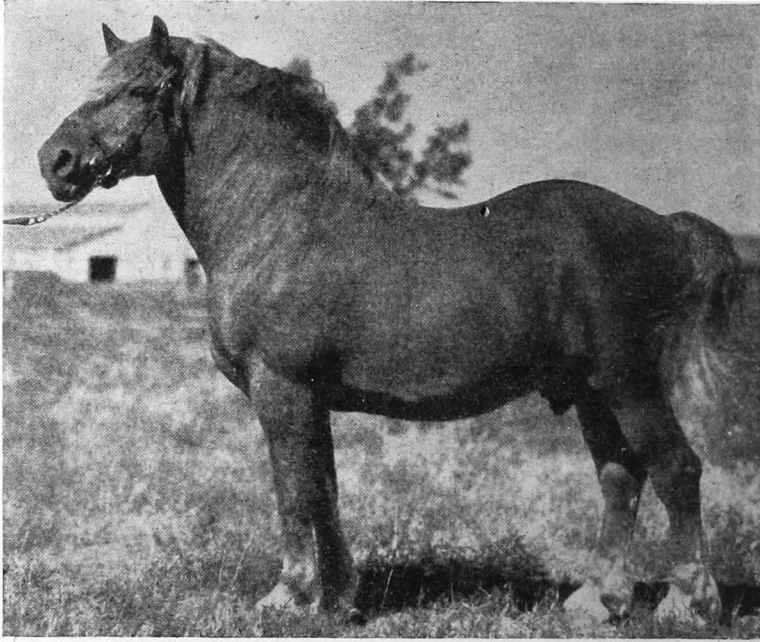


FIG. 87. Belgian stallion, representative of a breed especially adapted for pulling heavy loads. Compare the heavily-muscled and relatively short and thick body, neck, and legs with the slender proportions of the race-horse shown in Fig. 88. (Courtesy, U.S. Department of Agriculture: Breeds of draft horses, Bull. No. 619, 1941.)

English running horses were still less. Thoroughbreds are about half the weight of the Belgian. From the foregoing it is evident that the theory of natural selection accounts only for the preservation and perfection of adaptive traits; it does not attempt to explain the origin of nonadaptive differences. The problem of the origin of such differences has remained to be solved by later workers making use of modern principles of genetics.

Hereditary variations are of three types so far as fitness is concerned, namely, good, bad, and indifferent. Observation shows that the most frequent type is the bad variation, i.e., the one making the organism less fit. The least frequent type is the good variation, which increases the fitness. Completely indifferent muta-

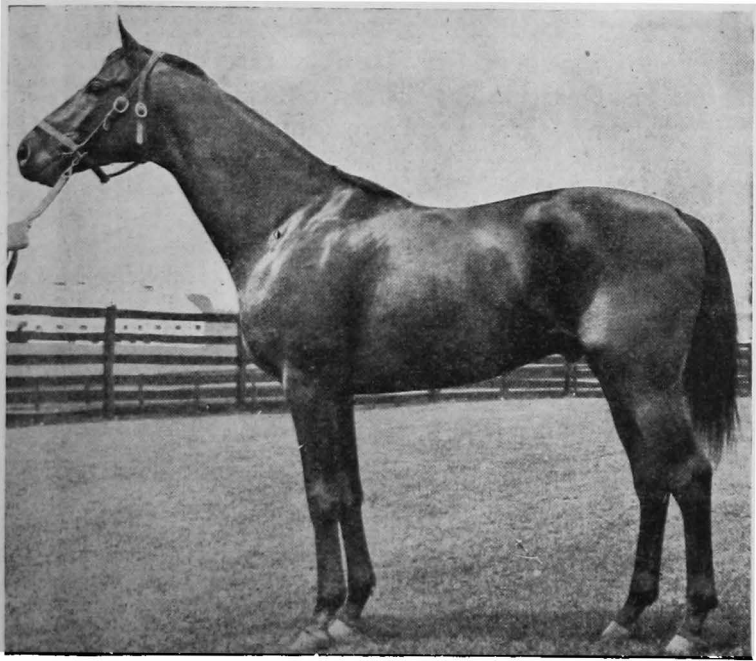


FIG. 88. Thoroughbred stallion, Kentucky Derby winner *Twenty Grand*, as a four-year-old. Note how in every way the body is admirably adapted for speed: long slender neck and legs, small feet, deep chest, thin flanks, and well-muscled thighs and shoulders. (Courtesy, ESTES, J. A. and JOE H. PALMER: *An introduction to the thoroughbred horse, The Blood-Horse*, 1942.)

tions are probably very rare, owing to the tendency of genes to have manifold effects; the conspicuous effect may be indifferent while the concealed effects may be either good or bad. The tendency for most mutations to be injurious may come as a shock to one who has given it no thought, and he may wonder how any species can survive for long under such conditions. Selection is the answer. Some selection is necessary in order to prevent

deterioration, while rigorous selection is necessary in order to obtain positive improvement. Every plant and animal breeder is familiar with this fact, and acts accordingly. We have every reason to think that these same principles apply to man just as to the lower organisms.

SEXUAL SELECTION

In "The Origin of Species" Darwin discussed briefly a special case under natural selection which he called sexual selection. This was developed in great detail in one of his later books, "The Descent of Man and Selection in Relation to Sex." Quoting from the former work:

This form of selection depends, not on a struggle for existence in relation to other organic beings or to external conditions, but on a struggle between the individuals of one sex, generally the males, for the possession of the other sex. The result is not death to the unsuccessful competitor, but few or no offspring. Sexual selection is, therefore, less rigorous than natural selection. Generally, the most vigorous males, those which are best fitted for their places in nature, will leave most progeny. But in many cases victory depends not so much on general vigor, as on having special weapons, confined to the male sex. A hornless stag or spurless cock would have a poor chance of leaving numerous offspring . . .

Among birds, the contest is often of a more peaceful character. All those who have attended to the subject, believe that there is the severest rivalry between the males of many species to attract, by singing, the females. The rockthrush of Guiana, birds of paradise, and some others, congregate, and successive males display with the most elaborate care, and show off in the best manner, their gorgeous plumage; they likewise perform strange antics before the females, which, standing by as spectators, at last choose the most attractive partner. Those who have closely attended to birds in confinement well know that they often take individual preferences and dislikes . . .

Thus it is, as I believe, that when the males and females of any animal have the same general habits of life, but differ in structure, color, or ornament, such differences have been mainly caused by sexual selection: that is, by individual males having had, in successive generations, some slight advantage over other males, in their weapons, means of defense, or charms, which they have transmitted to their male offspring alone . . .

Among many species of birds and mammals in which the males fight for the possession of the females, polygamy is the rule; and since the sex ratio is usually close to 1:1 this means that the defeated males are deprived of mates, leaving the more vigorous males to become the sires of the next generation. The effectiveness of this type of selection is generally recognized by

biologists today. There can be little doubt that it has played a part in the evolution of the Primates, including early man.

The second type of sexual selection, involving a display of charms by one sex and selection by the opposite sex, is not so generally accepted by biologists. It is argued that if the sexes are numerically equal and polygamy is not practiced (as we find in some birds and mammals) all individuals will eventually find mates. But as Darwin pointed out, the less attractive individuals may be seriously delayed in finding mates, and will therefore not leave so many offspring as their more attractive competitors; this will result in the gradual perfection of those characters which make for attractiveness. Furthermore, those lowest in the scale of attractiveness, the grossly malformed and defective, may never succeed in finding mates; and this will have the same general effect.

From what has been said it seems that sexual selection has a limited application among the higher animals. It probably has been and still is an important factor in the evolution of the human species, and for the future would seem to offer almost unlimited possibilities for the continued improvement of mankind,

ISOLATION AS A FACTOR IN EVOLUTION

From the foregoing discussion it is evident that a species may gradually change under the impact of natural selection until it comes to be something quite different from the original. If the species is a single unit, with perfectly free opportunities for interbreeding among all the individuals of the species, any new advantageous characteristic that arises will spread throughout the population; thus the whole species will change as a unit. This transformation of the species as a whole, however, seems to be contrary to the usual course of events. A study of the two great kingdoms, the plant kingdom and the animal kingdom, convinces us that most species have arisen by a process of splitting up of preexisting species. There is no other explanation of the complex branching relationships found in these two kingdoms. How are we to explain this splitting up of species? The answer is the presence of some factor which prevents free and random mating. This factor is isolation.

There are two principal types of isolation: *geographical isola-*

tion and *reproductive isolation*. In the former, the species is divided into two or more subgroups by physical barriers so that communication between the groups is difficult or impossible. For example, at one time several millions of years ago the marine animals of the Caribbean Sea and those of the Pacific Ocean were free to migrate back and forth through a neck of water which extended across what is now the Isthmus of Panama. Later the land was elevated, forming a continuous land bridge between North and South America, and cutting off means of communication. As a result, the marine animals on the two sides of the Isthmus gradually diverged until many of them became distinct species, although separated by only a few miles. Among the fishes the species today usually occur in pairs, one on either side of the isthmus. Numerous similar examples could be given for animals as well as for plants.

Barriers to migration such as mountain ranges, deserts, and oceans undoubtedly played an important rôle in the production of the major divisions and races of mankind. Wright³ has recently developed the theory that *distance* alone may constitute an effective isolating agency. Merely as a result of their remoteness populations may become differentiated from one another. The tendency today is obviously toward the breaking down of such barriers through the improvement of modes of transportation, accompanied by a reduction in the cost of travel. Whether there finally comes an amalgamation of all the races into one is doubtful, however, because of the strength of the second type of isolation—reproductive isolation.

Under reproductive isolation we should include, in the higher animals and man, psychological isolation. Reproductive isolation may cause groups living in the same region to remain distinct even though there is no physical barrier to prevent their mixing. Differences may prevent or discourage mating, as they do to a certain extent among the major races of man. If mating occurs the offspring may be few, nonviable, weak, or sterile.

When two groups are isolated, whatever the means, they gradually tend to diverge. This follows partly as a result of natural selection operating somewhat differently in the two groups.

³ WRIGHT, SEWALL: Isolation by distance, *Genetics*, 28: 114-138, 1943.

Adaptive differences may thus be accounted for; but nonadaptive characters require a different explanation.

THE ORIGIN OF NONADAPTIVE DIFFERENCES

Adaptive characteristics have always claimed the major attention of students of evolution, but it is also recognized that probably every species has certain distinguishing characteristics which have had no selective value and are hence nonadaptive in nature. In man the blood groups or the shape of the skull may be cited as examples of nonadaptive characteristics. No one has ever shown that any one of the four major blood groups has any advantage over the others or that a brachycephalic skull has any advantage over a dolichocephalic skull, or *vice versa*. Natural selection has no power to increase or to decrease the frequency of such characteristics. How then have they become a fixed part of populations?

During the latter part of the last century various attempts were made to account for evolution in the absence of selection by postulating an innate force or tendency within the organism causing it to evolve along some particular line, more or less irrespectively of the external conditions. The botanist Nägeli was one of those who held such views, and there were paleontologists with similar hypotheses, sometimes associated with a belief in the inheritance of acquired characters. To these theories the term *orthogenesis* has been applied.

As pointed out in our discussion of mutation in Chapter 13 there are limitations to the directions in which mutations may go, set by the nature of the organism itself. To this extent there is an inherent directing force within the organism. But since in all species studied intensively there has been found a great variety of mutations affecting all parts of the body the exact course of evolution must be directed by forces outside the organism. Orthogenesis as a theory of evolution is therefore no longer seriously considered by most students of the problem of evolution.

Darwin recognized the existence of nonadaptive characteristics although he regarded them as less numerous than did many of his contemporaries. Some of the alleged cases he ascribed to our ignorance of the uses to which many structures may be put by

the possessor. For example, unless one knew something of the mode of reproduction in seed plants and the part played by insects in pollination of flowers, he would not be able to see any advantage to the plant in the beautiful colors and complex structures of flowers.

Many cases of nonadaptive differences were attributed by Darwin to "correlated variation." By this he meant that a change produced in one part of the organism was often accompanied by changes in other parts, due to interactions in growth and development. As an example he refers to the fact that white cats with blue eyes are usually deaf. We would today class such cases under the head of multiple effects of a single gene (Chapter 5) since we know that in cats the character white with blue eyes is a Mendelian dominant over colored normal. Deafness develops in homozygous animals.

There are undoubtedly many genuine cases of nonadaptive differences such as those cited above in man. Applying the known principles of heredity including the mechanism of hereditary changes by mutation and chromosome changes we are now able to give a fairly simple explanation of such cases.

Imagine a species from which a small group is split off by some sort of barrier. Because of repeated mutations no species is ever made up of absolutely identical individuals. The two groups will therefore differ somewhat in the frequency of certain nonadaptive genes. Following the split, each group will breed only among its own members, thus preserving such original differences. If a separated group is quite small, so that inbreeding takes place, some nonadaptive genes will be preserved and others eliminated merely as the result of chance. The experiments on inbreeding in guinea pigs, described in an earlier chapter, constitute a good demonstration of how this occurs under extremely close inbreeding. With inbreeding of a less extreme type the same effect follows, but more slowly.

Mutations will of course continue to occur in each group, but will not follow identical patterns in both; for, as we have seen, mutation is to a certain extent a random matter. This will increase still further the differences between the groups. Thus by the

chance distribution of genes, one group comes gradually to differ from the other group in nonadaptive characteristics.

It is probable that some of the nonadaptive differences that distinguish the modern races of mankind have arisen in the manner just described, although of course some of these differences such as hair form, thickness of lips, and facial features, may have arisen in part through sexual selection.

HYBRIDIZATION AND THE ORIGIN OF SPECIES

There is much evidence that many new species of plants have arisen in nature as a result of the crossing of two distinct species. With animals, this seems to have occurred with much less frequency than with plants. There are two chief reasons for this difference between plants and animals: in the first place, the great majority of animals show a strong preference for mating with members of their own species; in the second place, for reasons that will be brought out below, a new species can be founded by hybridization much more readily in an organism which is hermaphroditic than in one with separate sexes. The great majority of plant species are hermaphroditic, whereas the great majority of animal species have separate sexes. If the hermaphroditic species is self-fertilizing—as are many of the plants—the chances are greatly increased for the establishment of a new species by hybridization.

Within recent years, taking advantage of the newer knowledge of genetics, experimenters have been able to produce by hybridization, synthetic new species of plants which meet all the tests of separate species in nature. Thus the criticism, formerly leveled at biologists, to the effect that if new species originate in nature under natural forces, experimenters should be able to duplicate the process in the laboratory, has been finally answered. The following example will illustrate the method.

Successful crosses have frequently been made between the radish and cabbage. These two plants belong to distinct species, and are not even members of the same genus, although they are distantly related. Each is a diploid with nine pairs of chromosomes (Fig. 89). The hybrid also has 18 chromosomes, 9 derived from the radish and 9 from the cabbage. The F_1 hybrid is usually sterile,

but occasionally produces seeds. The F_2 plants raised from such hybrid seeds are variable, in accordance with the general rule of variability in the offspring of hybrids. Some of these F_2 offspring which resemble their hybrid parents are entirely fertile; further-

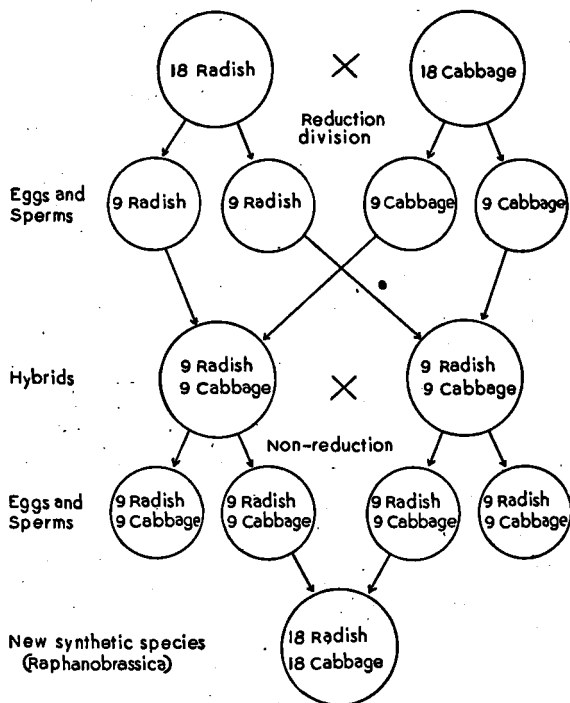


FIG. 89. Diagram showing distribution of the chromosomes in the crossing of the radish (*Raphanus sativus*) with the cabbage (*Brassica oleracea*) resulting in the experimental creation of the distinct new species (*Raphanobrassica*). (Each original species has 18 chromosomes.)

more, unlike ordinary diploid hybrids, they breed true to type. When their cells are examined they are found to possess 36 chromosomes, just twice the number in their hybrid parents and in the original cabbage and radish ancestors.

The explanation of this result lies in the failure of the reproductive cells in the hybrid to undergo a reduction division, thus leaving the eggs and sperms with 18 chromosomes each instead of the usual nine. Of the 18 chromosomes in the eggs and sperms, nine

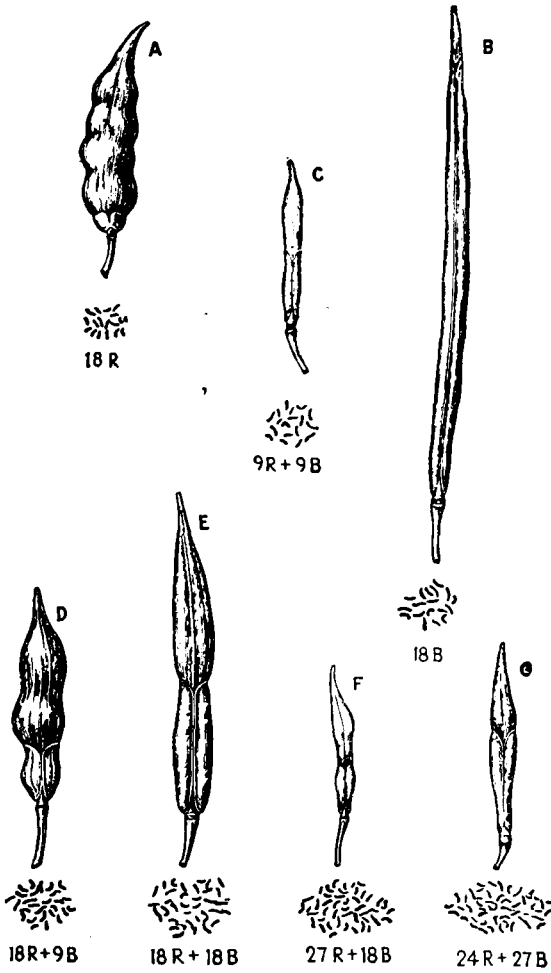


FIG. 90. Seed pods and chromosomes: (A) radish; (B) cabbage; (C) F₁ diploid hybrid between radish and cabbage; (D) triploid from a cross of A and C; (E) tetraploid *Raphanobrassica*, obtained by self-pollination of C; (F) pentaploid from a cross of A and C; (G) hexaploid, somewhat deficient in radish chromosomes. (Courtesy, SHARP: "Introduction to Cytology," McGraw-Hill Book Co., 1934; after Karpechenko.)

make up the entire cabbage set and the other nine make up the entire radish set. At fertilization therefore each fertilized egg contains two sets of radish chromosomes and two sets of cabbage chromosomes. During the development of the plant from the fertilized egg, each cell in the body receives, as a result of mitosis, the full double set of both cabbage and radish chromosomes. Thus there has been established by the process of hybridization a new tetraploid species containing in its cells all the genes of both original species. The synthetic species shows the type of sexual isolation which is expected in a distinct species: only rarely is a cross to the original parents successful, and the few offspring obtained are usually sterile.

Although in gene make-up the new synthetic species is the simple sum of the two original species this is not true as to its visible characters. Some of its characters are intermediate between the cabbage and the radish; some resemble one parent or the other; and some are peculiar to the new species. For example, the leaves resemble the radish and the root system resembles the cabbage. It is, therefore, of no value commercially. The seed pod (Fig. 90) is intermediate in structure. As illustrated in the drawings, the seed pod of the radish is spindle shaped, of one piece, and non-dehiscent, i.e., it does not burst open to release the seeds. The long seed pod of the cabbage is made up of two valves and is dehiscent. At the base of the radish pod is a small structure considered homologous to the two valves of the cabbage pod, while the tip of the cabbage pod is homologous to that of the radish. The F_1 hybrid and the F_2 tetraploid obviously combine the single structure of the radish at the tip with the double valve structure of the cabbage at the base. The triploid, pentaploid, and hexaploid show various combinations of these traits, as might be expected from their chromosome make-up.

In addition to large seed pods with many seeds, the tetraploid *Raphanobrassica* has a large and vigorous plant body characteristic of tetraploids in general. Its cells also are large. Other examples similar to the radish-cabbage case are described by Professor Dobzhansky in his recent book, previously referred to.

The importance of polyploidy following hybridization in the origin of new and improved domesticated fruits and ornamental

plants has been emphasized in an interesting book by two British authors.⁴ Many examples are listed.

The special significance of hybridization in the production of this type of chromosome change—the addition of all the chromosomes of two distinct species, known as *amphiploidy*—in the evolution of species in nature is presented in the monograph by Clausen et al, cited on p. 304. The authors point out that the phenomenon is almost an exclusive feature of the plant kingdom, and that it has been a common method of species formation in plants. The evidence is convincing that nature has frequently performed experiments similar to the man-made experiment with radish and cabbage, and that many new wild species, especially among plants, have come into existence in this way. In several instances wild species have been resynthesized experimentally from their supposed original ancestors.

There is little evidence that species formation by hybridization of the type just described in plants has occurred in the higher animals. In species with separate sexes, where sex is determined by a difference in the chromosomes, the method of hybridization and chromosome doubling would produce complications preventing normal fertility. It is in the lower hermaphroditic animals that one would expect to find it if at all. Studies of chromosome numbers by White,⁵ however, indicate that polyploidy is rare even here. In a group of flatworms (*Rhabdocoela*) he finds evidence that it occurs occasionally, in two groups of annelid worms (leeches and earthworms) rarely, and in the lung-breathing snails not at all.

ACCELERATING FACTORS IN EVOLUTION

Looked at in broad outlines, every species or variety which becomes extinct does so because of its inability to change rapidly enough to meet new conditions. As a matter of fact most species do not survive long as measured in geologic time. The rocks of the earth's crust are strewn with fossils—mute evidence that countless species have risen and thrived and have then become extinct. If

⁴ "The Genetics of Garden Plants," by M. B. CRANE AND W. J. C. LAWRENCE. Macmillan, 1938.

⁵ WHITE, M. J. D.: Evidence for polyploidy in the hermaphrodite groups of animals, *Nature*, 146: 132, 1940.

conditions remain relatively constant, as happens in the ocean for long periods of time, species may undergo little change. This is probably why so many of the primitive types of animals are found only in the sea. On the land, conditions change most rapidly, and it is here that the most remarkable evolution of plants and animals has occurred. The seed plants, the insects, the birds, and the mammals are striking examples of groups in which change has been comparatively rapid.

From the point of view of the individual or of the single generation, all evolution is slow. In Darwin's day the supposed lack of available time was given as an objection to the principle of evolution. Darwin answered the objection by citing the thickness of the sedimentary rocks and their slow rate of formation as proof of the great age of the earth. Eminent physicists of the day, however, confidently estimated the age of the earth at a few hundred million years at most, a figure regarded as inadequate for the purposes of evolution. But the difficulty has now vanished as the result of evidence from an unexpected quarter, namely, the discovery of the radioactive elements. Among these are uranium and thorium, found in the rocks of the earth's crust. Both are unstable and break down at a constant known rate; the end product of the process is the element lead. Knowing the ratio of uranium and thorium to lead in a given specimen of rock it is possible to estimate the age of the rock. Using this method the present generally accepted estimate places the age of the earth at about two thousand million (2,000,000,000) years. If life has existed on the earth for three-fourths of this time, as is estimated, it is perhaps adequate for the purposes of evolution.

In considering the specific factors which affect the *rate* of evolution, we find that some of these have to do with the organisms themselves while others relate to the external conditions.

1. THE LENGTH OF THE LIFE SPAN. The length of the life cycle is an important factor affecting the rate of evolution as measured in years. Other factors being equal, the organism with the shortest life cycle will evolve fastest. This follows naturally because the larger the number of generations produced, the greater the opportunity for selection of new variations. Species differ enormously in their life span. Among the longest-lived and slowest breeders

are the large mammals. An elephant is said to have a gestation period of about 20 months and to give birth to single offspring; sexual maturity is reached at about ten years.⁶ In the fruit fly *Drosophila*, on the other hand, a new generation may appear every two weeks or less. Hundreds of eggs may be produced by each fly. The length of the life cycle alone, however, means little, since other factors affecting the rate of evolution may override it.

2. THE RATE OF MUTATION. Obviously the rate at which favorable mutations occur affects the rate at which a species is able to adapt itself to changing conditions. Mutations are the raw material on which isolation and selection act. With respect to rate of mutation, varieties and species undoubtedly differ. Thus Demerec of the Carnegie Institution of Washington, on testing the rate of spontaneous mutation in more than a dozen geographic races of *Drosophila*, found that some local races, for example a race native to Florida, had a rate of mutation a good many times higher than that of other races.⁷

Professor Erwin Baur in Germany, who devoted years to the study of heredity in snapdragons, reports that in one species (*Antirrhinum majus*) new mutations occur in about 10 per cent of all plants. This is one of the highest rates ever found for plants or animals. On the other hand, a closely related species (*A. siculum*) produced no mutations in a period of 20 years. Most of the mutations observed in snapdragons were small changes in its various structures. In a state of nature some of these would no doubt have had adaptive value. Differences in the rate of mutation may help to explain why some groups of animals and plants have existed for ages with little change, while others give every indication of undergoing a rapid evolution.

3. SEXUAL REPRODUCTION. Sexual reproduction, involving the union of sperm and egg, is found in practically all the higher plants and animals. It has surely been a tremendous factor in accelerating evolution, because of the opportunity it affords for shuffling and recombining the genes in every possible manner, thus providing

⁶ "The Physiology of the Elephant," by FRANCIS G. BENEDICT, Carnegie Institution Publication 474, 1936.

⁷ DEMEREC, M.: A mutability stimulating factor in the Florida stock of *Drosophila melanogaster*, *Genetics*, 22: 190, 1937.

the basis for a large amount of variability upon which selection may act. This one advantage is capable of explaining the widespread adoption of sexual reproduction by organisms.

Furthermore, the great majority of plants and animals have biparental reproduction, with cross fertilization. Under this method an almost limitless number of gene combinations is possible in the zygote. The resulting variability favors a high rate of evolution. Biparental reproduction thus seems to be ideally suited to a high rate of evolution.

4. A CHANGING ENVIRONMENT. The environment of an organism includes not only the physical factors of light, temperature, moisture, pressure, air and water currents, etc., but it also includes as a very important part the other organisms that live in the same habitat. No environment is absolutely static. At times conditions change rapidly, at other times slowly. In a rapidly changing environment there is an increase in the severity of selection with wholesale elimination of the less fit, and a consequent speeding up of the rate of adaptive change. The net effect of rigorous selection is naturally to reduce the total variation within a species and thus to reduce the opportunities for subsequent divergence. On the contrary a reduction in the severity of selection favors the accumulation of mutations, with the consequent increase in variability; in this way the ground is laid for a later period of evolutionary change when conditions once more become severe.

CONCLUSION

No more concise summary of the part played by the factors in evolution as discussed in the preceding pages has been discovered than the following conclusion by Wright.⁸

I have attempted to form a judgment as to the conditions for evolution based on the statistical consequences of Mendelian heredity. The most general conclusion is that evolution depends on a certain balance among its factors. There must be gene mutation, but an excessive rate gives an array of freaks, not evolution; there must be selection, but too severe a process destroys the field of variability, and thus the basis for further advance; prevalence of local inbreeding within a species has extremely important evolutionary consequences, but too close inbreeding leads merely to extinction. A certain amount of crossbreeding is

⁸ WRIGHT, SEWALL: The roles of mutation, inbreeding, crossbreeding, and selection in evolution, *Proc. Sixth Internat. Cong. Genetics*, 1: 356-366, 1932.

favorable but not too much. In this dependence on balance the species is like a living organism. At all levels of organization life depends on the maintenance of a certain balance among its factors.

As an objection to evolution, the question is often asked, why have not all kinds of plants and animals evolved into complex higher species? The answer is that under evolution through natural selection no species is under the necessity of changing at all if it is already perfectly adapted—assuming that an organism can be perfectly adapted—to its environment. If the environment changes greatly the species must of course change, migrate, or perish.

A second reason for the persistence of simple types is that simple species are adapted to occupy particular stations in the environment, or particular niches in the web of life, that more complex ones could never occupy. Speaking figuratively, a world with all kinds of environments calls for all kinds of inhabitants.

Mutation is no doubt a universal phenomenon. As a consequence, nonadaptive changes have occurred and are still occurring in all species. Hence, no species is identical with its ancient ancestors. The environment, also, changes repeatedly; this necessitates adaptive changes in those species that are to survive. If we can judge the future by the present and the past, it seems safe to predict that as long as our planet continues to be inhabitable, change will continue to be a universal law of life.

What of the future of man? As a species, man is a newcomer on the earth. He is less specialized than most of the mammals—if we except his huge brain. It is his brain, above all, that has enabled man to become the most numerous, the most varied, and the most widely distributed of all the larger mammals. Large numbers, great variability, wide distribution, and a generalized, rather than a specialized body, all favor long life in a species. Great specialization makes a species vulnerable during periods of rapid change in the environment.

In the past, extreme specialization in animals usually has preceded extinction—as is proved by the fossils in the rocks. Does man's highly specialized brain imply the danger of his early extinction? For several reasons one may be justified in thinking that it does not. In the first place, although the human brain is

highly specialized with respect to its great size, it is generalized with respect to the uses to which it may be put. Secondly, because of his highly developed brain man is able to modify to a very great extent his own environment—a thing that no other species is able to do. But, most important of all, perhaps, man's highly developed brain enables him alone, among all living things, to look objectively at himself, to contemplate the process of evolution, and to control consciously and voluntarily the course of his own evolution. Within the limitations imposed by the world in which he lives and by his nature as he has inherited it from the past, man is therefore in a position to make of his future what he wills.

PROBLEMS

1. What was Mendel's position regarding the fact of evolution?
2. Distinguish between evolution and Darwinism.
3. State the four biological laws upon which natural selection rests.
4. What is the standing of natural selection among biologists today?
5. Does natural selection apply to modern civilized man? Illustrate.
6. Contrast Darwin's theory of the origin of the giraffe with Lamarck's theory.
7. In what groups of organisms would you expect to find sexual selection?
8. Name the principal types of isolation.
9. How does orthogenesis differ from other theories of evolution?
10. Account for the fact that tetraploid plants produced by hybridization are often fully fertile and true breeding.
11. Explain the fact that in thoroughbred race horses the color may be bay, brown, black, chestnut, or gray, with or without white spotting, while Hereford cattle are always red, with white markings and coach dogs are always white with black spots.
12. Explain how the evolutionary progress of a species is favored by the alternate isolation of groups within the species, resulting in inbreeding, and the crossbreeding among the groups.
13. How do you account for the fact that domesticated plants and animals—even those derived from a single species—are more variable than related wild species?
14. Account for the fact that the human species is much more variable than any wild species of large mammal.
15. Name two human races in which there is no overlapping with respect to some physical trait designated by you.

IMPROVEMENT OF THE HUMAN SPECIES (EUGENICS)

IT NOW SEEMS DESIRABLE to develop further the view expressed in the concluding statement of the last chapter; namely, that man has it within his power to determine to a large extent his own biological future. This conclusion implies first of all that man shall have a conscious goal or ideal for his own species. The goal of course may be a shifting one. Have we, as a matter of fact, any common biological ideals for *Homo sapiens*?

IDEALS

Practically all people will agree that mankind, in the mass, is at present far from perfect. Both physically and mentally there is much room for improvement. It may be worth our while to attempt a statement of the lines of improvement upon which most men would agree.

HEALTH. A condition of robust health, both physical and mental, surely is desired by everyone for himself, and probably would be accepted as a desirable end for all mankind. Adopting a broad definition of health, we may think of it as a state of well-being, adaptation, or fitness to the environment. Good health thus implies the possession of sufficient strength and energy for the performance of all desirable activities and the attainment of happiness. It means freedom from all hereditary defects, weaknesses, or diseases which impair efficiency, prevent happiness, or unduly shorten life. Under the term health one should include beauty, since in the truest sense beauty is a by-product of good health. Superlative physical size and strength as universal human attributes are no longer either necessary or desirable. In modern times, with

the rapid achievement of a mastery over the forces of nature, mere size and strength have yielded first place to mental ability.

INTELLIGENCE. However much we may differ in our appreciation of intelligence, few will deny that the ability to think and reason straight is one of the most adaptive qualities in man. This ability is obviously the trait of all traits that sets man above every other species. Without presuming that a high degree of intelligence is indispensable to individual happiness, we could agree perhaps that the kind of happiness of which only the intelligent are capable is most to be desired. A reasonably high level of intelligence in the average man, plus superior ability in numerous individuals, is essential for the maintenance of a high state of civilization.

VARIABILITY. No one who has given thought to the subject will contend that mankind would be more successful and happy if all individual differences were eliminated. On the contrary, many advantages can be traced to the existing variability among human beings. The striking development of civilization in recent centuries has been possible only through a remarkable multiplication of specialized occupations. As a consequence, the need for special talents is greater than ever before. If all people were cast in the same mold human culture would suffer greatly. The popular expression that it takes all kinds of people to make a world rests upon sound biological principles. That special talents have a strong hereditary basis has been indicated in the discussion of human heredity (Chapter 9). In order to promote the general welfare the State should encourage the multiplication of talented individuals.

RACIAL DIFFERENCES. So far, we have been speaking of individual differences without regard to race. On a different plane, however, the same principles apply among races. Beyond doubt there are racial differences with respect to ability to live and work in particular environments. The dark-skinned peoples, for example, are better fitted to live in the tropics than are the white-skinned. Consequently, with respect to pigmentation, there can be no common ideal for all mankind. Similar considerations apply to differences in resistance to the diseases peculiar to various parts of the world.

Many of the differences between races, however, such as skull

shape, and facial features, are of no known adaptive significance. They add variety and interest to life and no good reason is apparent for wishing them eliminated. Differences between races in such important traits as health and intelligence are probably relatively insignificant as compared with the tremendous variations in these respects within a race. Measurements of intelligence and special aptitudes have so far failed to bring out any clear-cut hereditary racial differences, although the problem of devising tests of innate ability free from the complicating effects of environmental differences has not been solved. It is therefore not scientific to state dogmatically, as some have done, that there are no such differences. Whatever differences may exist as to average and range could be established only, by careful statistical methods. Owing to the enormous variability in mental traits within each racial group there is bound to be great overlapping in the curves of variability, whatever they may turn out to be.

It seems clear that the points of likeness among races far outnumber and outweigh their points of difference. The greatest progress for mankind as a whole, therefore, would seem at present to consist in the raising of the level of health, energy, and intelligence within each race, rather than the forcible supplanting of one race by another. This is especially true in view of our ignorance regarding the gene make-up of the various racial groups. In so far as we can apply to *Homo sapiens* the principles of evolution discussed in the last chapter we may conclude that the continuation of biological progress is best served by the retention of numerous racial stocks, each race being free to develop along its own lines, with opportunities for frequent interchange of ideas and products, and for periodic intermarriages. The present partial isolation of racial groups permits the testing of various combinations of traits under a variety of conditions. Migration and intermarriages afford opportunity for the emergence of new and favorable combinations of traits.

METHODS OF IMPROVING MANKIND

Few subjects have aroused more controversy than the question of methods for improving the genetic quality of mankind. Should the center of the attack on the problem be the improvement of the

environment, trusting that the improvement of the race will naturally follow; or should our sole concern be the grading up of hereditary capacities? In the discussion that follows we shall attempt to show that both of these ideas should enter into the formation of our policy and that the greatest progress will come from a combination of the two.

Among English-speaking peoples the science dealing with the genetic improvement of mankind is known as *eugenics*, a word introduced by a famous English scientist, Francis Galton, in 1885; the term is derived from the Greek *eugenes*, meaning "well born." Galton's definition is as follows: "Eugenics is the study of agencies under social control which may improve or impair the racial qualities of future generations either physically or mentally." As defined by Galton, eugenics obviously is a science deriving its content and principles both from genetics and the social sciences.

RESTRICTIVE MEASURES (*Negative Eugenics*). The application of eugenic principles, whether going under the name of eugenics or not, follows one of two lines: first, the discouragement of matings between individuals representing types considered undesirable; and second, the encouragement of matings between desirable types. The first of these is known as negative eugenics; the second is known as positive eugenics.

1. Marriage Restrictions. Since ancient times organized society has taken an active hand in determining the genetic constitution of the population. Various tribal customs and laws tending to prevent the reproduction of specific types, or favoring reproduction among others, have been extant at one time or another. We have referred already to such laws in connection with cousin marriages (Chapter 14). Today the marriage of certain types of mental defectives, epileptics, habitual criminals, alcoholics, insane persons, and persons infected with venereal disease frequently is prohibited in our states.

2. Segregation. The common practice of segregating mental defectives and mentally diseased persons in institutions obviously has an effect similar to laws preventing their marriage. Unfortunately, large numbers of the types mentioned are allowed their unrestrained freedom, with the result that defective children are born to them. Criminal laws requiring the imprisonment or execu-

tion of individuals whose conduct is destructive, incidentally have similar selective effects, even though eugenic motives are not the primary ones in the enactment of criminal laws.

The effectiveness of isolation of undesirables as a method of improving the hereditary quality of the population depends, of course, upon the extent to which the undesirables owe their misfortune to heredity. In our consideration of the problem of heredity and environment in Chapter 12 it became clear, however, that heredity is one of the factors responsible for mental defect, mental disease, and abnormal behavior.

3. *Sterilization.* As an added means of preventing the reproduction of undesirable or dysgenic types, the majority of our states, as well as a number of foreign countries, have legalized surgical sterilization. The prescribed operation consists in tying off and severing the ducts that conduct the sperms and the eggs from the gonads. In the male the operation is a simple one, done under a local anesthetic; in the female it is a major abdominal operation. The gonads themselves are not disturbed and no part of the body except a small section of the sperm or egg tubes is removed; consequently sterilization has no effect upon secondary sexual characters or sex impulses, in these respects differing entirely from castration. In only a few states is castration legalized.¹

Sterilization laws have been criticized adversely on several grounds, and competent geneticists are not agreed as to their desirability. Aside from the objection to them on religious grounds, the point has been made that their enforcement constitutes a violation of personal liberty; that it is subject to the danger of grave abuse; and that after all the objectives sought may be accomplished just as effectively by segregation during the reproductive years. There is undoubtedly in most persons a natural and well-founded repugnance to the placing of hands upon the person of another, against the other's will, even though such action is carried out under sanction of law. From the humane point of view, the burden of proof as to the desirability of sterilization, therefore, would seem to rest upon the advocates of the measure. It should be

¹ HUGHES, JAMES E.: "Eugenic Sterilization in the United States: A Comparative Summary of Statutes and Review of Court Decisions," Supplement No. 162 to the Public Health Reports, 1940.

emphasized that in our country sterilization operations are done ordinarily only with the consent of the patient or, in case he is mentally incompetent, of his guardian. Frequently, however, the alternative is continued confinement in an institution.

Society undoubtedly has the right as a matter of self defense to prevent the increase in numbers of grossly defective types which would either become a burden on the State or a menace to others. To give the individual his choice of confinement or sterilization may, in certain cases, be more humane than to require him to remain in confinement. In the United States the legal grounds for sterilization usually are restricted to mental disease and mental deficiency, whereas in some foreign countries sterilization is prescribed in cases of gross physical defect and in cases where the probability of transmission of such mental or physical abnormality is great. In many of our states the law has become almost a dead letter. California has carried out almost as many sterilizations as all other states combined.

GENETIC VARIABLES. The effectiveness of marriage restrictions, segregation, and sterilization as eugenic measures depends upon several variables: (1) Upon the manner in which the undesirable trait is inherited; (2) upon the frequency of the gene or genes concerned in the population; (3) upon the age at which the trait makes its appearance; and (4) upon the extent to which the environment may prevent the expression of the gene. First, as to mode of inheritance, let us consider the following possibilities:

1. The trait is due to a single dominant gene.
2. The trait is due to a single gene without dominance (heterozygote intermediate).
3. The trait is due to a single recessive sex-linked gene.
4. The trait is due to an ordinary recessive gene.
5. The trait is due to two or more dominant genes, two or more recessive genes, or to some combination of these.

The easiest trait to weed out of the population is the one due to a *single dominant gene* or to a gene in which dominance is lacking. The prevention of reproduction of all affected individuals, that is, those showing the trait, and of those appearing as carriers

in a single generation will eliminate the gene from the population, provided it is a trait that always develops before sexual maturity, and provided the gene is one that always expresses itself. New mutations, of course, probably will occur. In the case of highly deleterious dominant traits, it is likely that a large proportion of affected individuals owe their misfortune to mutation rather than to heredity. The gene causing a peculiar type of tumorous growth known as Von Recklinghausen's disease (Chapter 9) fits into this category fairly well. This disease is so severe that few individuals live long enough to reproduce. In such serious defects negative eugenics can lower the percentage of genes very little.

In the case of traits which develop during or after the age of reproduction, for example, Huntington's chorea (Chapter 9), the elimination of the trait will proceed more slowly, if the prevention of reproduction is restricted to affected individuals. In a terrible and fatal disease of this type it would seem wise that the brothers and sisters, as well as the children of affected persons, who on the average have a 1:1 chance of carrying the gene, should refrain from becoming parents, even though they do not develop symptoms.

The second easiest type of trait to deplete in the population is the *sex-linked recessive*. Since males have only one X chromosome while females have two, a third of all sex-linked genes in the population are present at any one time in males and two-thirds are present in females. Furthermore, in males the effect of a sex-linked gene is always manifest, since there is lacking any normal counteracting allele. (This of course assumes that the sex-linked gene is not suppressed by the environment or other genes.) The isolation or sterilization of all affected males will, therefore, eliminate one-third of the defective genes in a single generation. If like treatment is applied to both males and females, the only remaining genes will be those carried in the heterozygous condition by females. In the succeeding generation, due to the mechanism of sex-determination, approximately half of these genes will be found in males. In this generation the prevention of mating of affected males, therefore, will reduce the supply of the gene in question by one-half. Through a continuation of the process the

percentage of persons showing the trait will be cut 50 per cent in each generation; hence, in a few generations it will be reduced to the vanishing point, except for the occurrence of mutations.

In case natural selection against a sex-linked recessive trait is severe, as in hemophilia (Chapter 11); the gene will never become very numerous in the population.

Traits due to *ordinary recessive genes* may be reduced in frequency only at a much slower rate than dominants and sex-linked recessives. This conclusion follows from the fact that males as well as females may be heterozygous for ordinary genes. The higher the frequency of an ordinary recessive trait the more rapidly it may be reduced by the restrictive measures we are discussing. If the trait is extremely rare, existing say in the order of one in 20,000, as in the case of albinism, restriction of affected individuals will have very little effect, because most affected persons are produced in marriages of two heterozygotes. In the case of albinism, if we assume that the gene is distributed at random throughout the population, about one person in seventy must be a carrier of the gene. If matings are at random the proportion of marriages capable of producing an albino is

$$\frac{1}{70} \times \frac{1}{70} = \frac{1}{4,900} \text{ (one in 4,900)}$$

The elimination of traits that depend upon the cooperation of *two or more genes* is the most difficult of all. Here even a dominant gene may go unrecognized since the trait develops only in the presence of some complementary gene. The complexity of the genetic situation in such cases has been considered in the discussion of the factor principle (Chapter 5).

With traits that are influenced strongly by environment, as well as by genes, e.g., manic-depressive psychoses and schizophrenia (Chapter 9) there is an added difficulty in applying restrictive measures. Under any system of negative eugenics likely to be adopted, genetically defective individuals who for one reason or another escape the symptoms are certain to escape detection. The most effective reduction of such traits would seem to require the use of positive measures, particularly education.

POSITIVE EUGENICS. Among the measures which may well

have the effect of increasing the frequency of desirable traits, are the following:

1. The regulation of immigration.
2. Subsidizing superior individuals.
3. Education.
4. Promotion of genetic research.
5. Improvement of environmental conditions.

Let us consider each of these briefly in the order given.

1. *Immigration.* It is customary for countries to control by law the number and quality of their immigrants. In the United States certain racial groups from the Orient are excluded entirely, and a definite quota is placed upon European immigrants, but not upon immigrants from countries in the Western Hemisphere. The purpose of the quota provision is to preserve the existing racial proportions of the population. The law prohibits the entry of persons with mental disease and the usual types of mental defect, as well as criminals, chronic alcoholics, and persons with infectious diseases. Under present laws, immigration has dropped to a small fraction of its former volume; nevertheless, the welfare of the country demands the strict enforcement of the laws, with tightening of restrictions in certain directions. Special inducements might well be offered for the attraction of superior types of immigrants.

2. *Subsidizing the Fit.* Little has been done in this country with the avowed object of encouraging the reproduction of especially well-adapted individuals. In only a few organizations are selected workers granted a bonus for the birth of children. According to Professor S. J. Holmes, of the University of California, one of the leading students of eugenics in this country, the proper distribution of allowances for the birth of children is one of the most feasible of all the methods ever advanced for the promotion of positive eugenics.² As an illustration of what might be accomplished along this line, he cites the following case:

Foreign missionaries in the Baptist and Congregational churches receive a fairly substantial allowance for each child, so that the financial burden of a large family is in many cases no greater than that of a small one. This may explain the

² "The Eugenic Predicament," by SAMUEL JACKSON HOLMES, Harcourt, Brace, 1933.

facts that the families of these missionaries are considerably larger than those of ordinary ministers, and that the missionary birth rate has shown little decline for several years.

In this country family allowances are granted to officers in the armed services and the Coast Guard, and in some cases in the Public Health Service. The Salvation Army makes family-allowance grants to its officers. The principle has been applied to teachers in a few public schools and colleges.

On the contrary, in some groups, as women school teachers, a penalty, consisting in loss of position or loss of salary, is often attached to the birth of a child. If the birth rate remains at its present relatively low level or again undergoes a decline we may expect to see a change in public opinion on the question of subsidies for the fit. When the country begins to offer added privileges and inducements to those who assume the burden of producing children, quite naturally the quality of the product will come in for increased attention. So far, the possibilities in this direction have scarcely been touched. Presumably, such provisions as the exemption clause in the Federal income tax law allowing an added exemption for each child is a step in the right direction. Competitive scholarships in colleges and universities have a similar beneficial effect, since concern over the problem of providing an education is one of the motives for voluntary limitation of family size.

3. *Education.* A knowledge of the fundamental principles of genetics, with special reference to human heredity, and an appreciation of desirable attitudes and ideals, undoubtedly affects the actions of young persons in the choice of mates. From the point of view of the happiness of the individual, as well as that of the welfare of the State, no type of learning has greater possibilities. Education in the principles of heredity need not be limited to the schools, but may be carried on through other agencies including the church, the theatre, the popular press, and the radio, provided always that persons engaged in such educational activities are thoroughly grounded in the science of genetics.

The family physician is in a strategic position to serve his patients by informing them in matters of heredity. Unfortunately, the training of physicians in this field has lagged. The condition is being remedied to some extent in progressive schools of medicine, but much still remains to be done. A good course in genetics, with

special reference to man, is highly desirable for all medical students.

The education of the people to the advantages of keeping family records and consenting to autopsies, in all cases involving doubt as to cause of death at least, will work for the best interest of the family and of the State. In this sphere as much as in any other, only knowledge of the truth can make men free.

4. *Promotion of Genetic Research.* The basic principles of heredity as concerns the distribution of the genes are now known. A good beginning has been made in the analysis of the rôles of the genes and of the environment in the development of characteristics in the organism. The mechanism of the inheritance of many specific traits in man can be clearly stated. If the knowledge we now possess could be applied intelligently to the improvement of man much progress might be made. However, genetics is still a new science, and research is yielding and will continue to yield large dividends for some time to come. The problem of the physiological action of the genes is one of those now receiving intensive study. With a more complete knowledge of the nature and action of the genes the possibilities of regulating their effects in the interests of the individual will be increased. The question of the nature of mutations and their possible control is largely one for future research.

Genetic research on plants and animals is today receiving much support from the Federal and State Governments and from privately endowed institutions. A few American institutions are making significant contributions to research designed directly to the genetic improvement of mankind, and the number is growing. Among these are the following:

The American Genetic Association, publishers of *The Journal of Heredity*, Washington, D. C.; The Genetics Society of America; The Department of Genetics of the Carnegie Institution of Washington, Cold Spring Harbor, Long Island, New York; The American Eugenics Society, Inc., New York; The Dight Institute of the University of Minnesota; Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine; and the laboratories of zoology in a number of the leading Universities.

Direct support of eugenic research by Federal and State Governments would seem to fit the part of enlightened self in-

terest, since the genetic improvement of its citizens is of the highest advantage to the State.

5. *Improvement of Environmental Conditions.* We think usually of eugenics as concerned with the improvement of the hereditary qualities of the people. It should be emphasized once again, however, that a characteristic as such is not inherited; all that we inherit is the tendency to develop certain characteristics under particular environmental conditions. Consequently, heredity has no meaning apart from the environment.

In any plan to increase the fitness of the organism, whether it be a plant, a domesticated animal, or man, due regard must be had to the environment in which the organism is to live. If one is interested, for example, in the production of beef, or in the development of speed in a race horse, he places his animals in the environment that he desires as their permanent one. The food and care is the best he is able to devise for the end in view. Selection then is made on the basis of performance under the prescribed set of conditions. It would not show good judgment to spend one's time breeding a strain of beef cattle or race horses able to survive on the poorest food or in the most polluted atmosphere or under the greatest extremes of temperature although by selection a strain could be developed that would be superior to existing breeds in enduring any one or perhaps all of these adverse conditions.

Obviously, we should look upon the improvement of man in a similar light. Unless the environment is made as nearly optimum as possible for all the people, we are not giving all of the genetically superior individuals an opportunity to express themselves. The inability to survive under extremely adverse conditions does not necessarily mean the inability to survive under modern civilization. Many of the conditions endured by our ancestors have now become artificial so far as we are concerned; we do not anticipate a return to them. In any effort designed to improve the adaptation of human beings we should be concerned primarily with the present and the future.

A study of the principles of genetics leads one to believe that neither the extreme environmentalist nor the extreme advocate of heredity has any justification for his position. Both look at one side only of the shield.

CONCLUSION

Each of the highly desirable traits—vigorous health, intelligence, and special talent—probably depends upon numerous genes. Some of these genes are dominant, some are recessive, and some show no dominance. For the full expression of these traits an optimum environment is necessary. In view of the complex nature of man, as well as his heterozygous constitution, we should expect to see many mediocre and defective children produced by superior parents. New mutations will account for some of these, but the majority are the result of segregation, independent assortment, and recombination. Conversely, and for similar reasons, we should not be surprised to see many superior individuals produced by mediocre parents. Two average parents may each contribute genes lacking in the other to obtain a child of unusual ability. The great number of persons of average ability is an important factor in explanation of the large number of superior children produced by average parents. Nevertheless, superior parents have a better chance of producing superior children than do mediocre or defective parents.

A steady increase in the number of children from the better adapted parents should result in a gradual rise in the average quality of the population. Evolution in nature is a slow process. The best we can hope for in man is that application of eugenic measures will cause a slow but steady improvement. The problem is far more complex than the development of a pure breed of domesticated animal where complete control of matings is available and where a uniform type is the goal. Many generations will probably be necessary to bring about a notable change in man. The slowness of the process, however, need not discourage us if we but recall that man most certainly is near the beginning of his history. Before him lies a future too vast for the mind to comprehend. Barring cosmic accidents, there is apparent no good reason why man may not anticipate a billion years of life on earth. Who knows indeed but that man will prove to be the one species able to avoid the extinction which in time overtakes all species.

It is inconceivable that as time passes man will fail to apply to himself more and more the proved biological principles suited to

his own improvement. As he improves himself genetically he will of course constantly seek to make the environment more and more suitable to develop the best that is in him. If the logic in the foregoing pages is sound the conclusion seems inescapable that our biological ideals for man are well within the bounds of reason, assuming that we shall have the intelligence, the will, and the perseverance to apply the knowledge which investigators have made available, and will continue to make available, in the days to come.

PROBLEMS

1. Why are the principles used in developing a pure breed of animal not directly applicable to the improvement of man?

2. List five practicable means of improving the hereditary constitution of a people.

3. List some of the laws, customs, and conditions in the United States which tend to reduce the force of natural selection by *favoring* the reproduction of individuals poorly adapted to take care of themselves and their children.

4. List some of the laws, customs, and conditions in the United States which act as selective agencies by *hindering* the reproduction of individuals poorly adapted to take care of themselves and their children.

5. Mention several advantages in late marriages with respect to the genetic improvement of mankind. Mention several disadvantages in this respect.

6. Give several specific examples of hereditary characteristics in man which are adaptive under a given set of primitive conditions but which are either useless or disadvantageous under modern conditions of civilization.

7. How do you account for the extremely great range of hereditary mental capacity *within* a race of people as compared with the relatively smaller range existing *among* the various races?

8. Give several reasons why it is very difficult to show racial differences with respect to mental traits. Does the difficulty in demonstrating such differences mean that no racial differences in mental capacity exist? Explain.

9. Discuss the possibility of the final emergence of a single human race to replace the numerous races now existing on the earth, mentioning factors and forces now favoring such a change as well as those tending to hinder it. List the advantages and the disadvantages that might result from such a change.

Glossary of Terms Most Commonly Used in Genetics

ALLELE (al ěll') (See ALLELOMORPH).

ALLELOMORPH (*allelon*, one another; *morphé*, form), one of two or more alternative hereditary units or genes, or of the characters associated therewith; for example, the gene responsible for color blindness is an allelomorph of the alternative normal gene. (Synonymous with ALLELE.)

ANAPHASES, the stages of mitosis following the metaphase, characterized by the movement of the daughter chromosomes toward the poles of the spindle.

ANTHER, a part of the stamen in seed plants consisting essentially of a spore case, in which the pollen develops. It is usually borne on a slender stalk, the filament.

ASEXUAL (*a*, without; *sex*), not involving gametes or fusion of nuclei; said of the mode of reproduction, or of an individual restricted to such mode of reproduction.

ATAVISM (See REVERSION).

AUTOSOME, any chromosome other than a sex chromosome.

BACK-CROSS, the mating of a hybrid to one of the parental varieties or species which produced the hybrid.

BIMODAL, an adjective used to describe a frequency curve possessing two high points, peaks, or modes.

CENTROMERE (KINETOCHORE), a definite region of a chromosome which takes the lead in chromosome movements during mitosis and meiosis. It is the point of spindle-fiber attachment.

CHARACTER (a contraction of CHARACTERISTIC), used to designate any structure, function, or trait of an organism. The Mendelian characters represent the end products of development, in which a particular gene or genes have a specific effect.

CHROMATID, either one of the two identical strands into which a chromosome splits in anticipation of cell division.

CHROMATIN (*chroma*, color), a substance found in chromosomes which stains readily with "nuclear" or basic dyes. Its exact relationship to the genes is unknown.

CHROMOMERES, the granules, visible especially during synapsis, arranged in definite linear order on the chromosome.

CHROMOSOMES (*chroma*, color; *soma*, body), deeply staining bodies visible under the microscope in the cells, especially at the time of cell division. The chromosomes consist essentially of genes, arranged in linear order.

CROSS-FERTILIZATION, the union of a sperm from one individual with an egg from another individual.

CROSSING-OVER, the interchange of blocks or chains of genes between two homologous chromatids; also applied to characters which show recombination as a result of such exchange.

CYTOLOGY (*kytos*, cell; *logia*, study), the study of the structure and functions of the cell.

CYTOPLASM (cell; *plasm*, form), that part of the protoplasm of the cell outside of the nucleus.

DETERMINER (GENE or FACTOR), a unit of heredity which acts as a differential factor in the development of a Mendelian character.

DIHYBRID (*di*, two; hybrid), an individual which is hybrid (heterozygous) with respect to two pairs of genes.

DIPLOID (*diploos*, double), referring to the double set of chromosomes, as found in the body cells of animals and the sporophyte generation of plants, as distinguished from the single (haploid) set, found in the mature reproductive cells.

DOMINANT, a character which appears as the result of the presence of either a single or a double dose of a particular gene, as contrasted with the recessive, which develops only when both members of a pair of genes are alike. Applied also to the genes.

EGG (OVUM), a mature female reproductive cell formed by plants and animals which reproduce sexually. In comparison with the male reproductive cell (sperm) it is very large, chiefly because of the stored food it contains.

ENDOSPERM, nutritive tissue formed within the ovule in seed plants derived from the fusion of one of the sperm nuclei carried in the pollen tube with two of the nuclei of the ovule.

EQUATORIAL PLATE, the plate formed by the chromosomes lying on the equator of the spindle at metaphase.

EUGENICS (*eugenes*, well born), the science concerned with the develop-

ment and application of methods for the genetic improvement of the human species. "The study of agencies under social control that may improve or impair the racial qualities of future generations, either physically or mentally."—Sir Francis Galton, 1885.

F₁ (čf-one), the first generation of offspring resulting from a particular mating; the first filial generation.

F₂ (čf-two), the second filial generation produced by self-fertilization of the F₁ or the mating of F₁'s.

FERTILIZATION, the fusion of a sperm with an egg, forming a single cell, the zygote. Fertilization has two effects: (1) it stimulates the egg to develop; (2) it combines two sets of genes in the embryo.

GAMETE, a mature germ cell, either an egg or a sperm.

GENE, a unit of heredity which is transmitted in the chromosome, and which, by interaction with other genes, the cytoplasm, and the environment controls the development of a character.

GENETICS, the branch of biology which deals primarily with the principles of heredity and secondarily with the rôle of environmental factors as they interact with the genes in the development of the individual.

GENOTYPE, the complete genetic make-up of an individual, in contrast to the apparent or visible type of the individual (phenotype).

GERM CELL, a cell capable of taking part in sexual reproduction as contrasted with the somatic or body cells, which are not able to do so. A germ cell may be either the mature egg or sperm or an earlier cell capable of giving rise to one of these.

GONAD, a reproductive gland, either male or female; a testis or an ovary. In hermaphroditic animals it may be a compound gland (ovotestis).

HAPLOID (*haploos*, single), referring to the reduced or single number of chromosomes, as found in the mature egg or the sperm, in contradistinction to the *diploid* or double set of chromosomes present in the body cells and early reproductive cells.

HERMAPRODITE, an organism which produces both eggs and sperms. False hermaphrodites are *intersexes*, having gonads of one sex only (see INTERSEX).

HETEROSIS (See HYBRID VIGOR).

HETEROZYGOTE (*hetero*, different; *zygote*, egg), an organism whose parents contributed to it unlike genes affecting some inherited character, or which has unlike genes as a result of mutation, and which

therefore produces gametes of two kinds with respect to such gene. (The unlike genes may be any two of an allelic series.) Such an organism is said to be *heterozygous*.

HOMOLOGOUS CHROMOSOMES, chromosomes occurring in pairs, one member of each pair being normally derived from the egg and the other from the sperm.

HOMOZYGOTE, (*homo*, same; *zygote*, egg), an organism which produces eggs or sperms of one kind only with respect to a particular series of alleles. Such an organism is said to be *homozygous*.

HYBRID, an individual resulting from the union of a sperm and an egg which differ in one or more genes, e.g., *Aa*, *AaBb*, *AaBbCc*; also used to denote the offspring of two distinct species or varieties.

HYBRID VIGOR (HETEROSIS), a phenomenon frequently noted as a result of the crossing of two distinct species, races, or varieties, the hybrid exceeding both parents in size, fecundity, or other adaptive quality. The cause of hybrid vigor is supposedly the supplying by each parent of dominant genes, for which the other parent is recessive.

IDENTICAL TWINS, two individuals developed from a single fertilized egg and therefore possessing identical sets of genes. Such twins are about as much alike as the right and left sides of the body of a single individual; also called monozygotic or one-egg twins.

INBREEDING, the mating of related individuals such as first cousins or nearer of kin. The automatic effect of inbreeding is to increase homogeneity, resulting in time in the production of a pure breed.

INDEPENDENT ASSORTMENT, PRINCIPLE OF (Mendel's second law), the random combination of characters in the offspring as the result of the random alignment of the chromosomes on the equator of the spindle at the reduction division; their random combination in eggs and sperms; and independent union at fertilization. Independent assortment occurs only when the genes affecting such characters are on separate (non-homologous) chromosomes.

INTERSEX, an individual showing characters intermediate between male and female. It may be the result of a mutation, an abnormal chromosome complex, an endocrine disturbance, or environmental factors.

LETHAL GENE, a gene that renders an individual which expresses the gene unable to live. Lethal genes are either dominant or recessive and may affect the organism at any stage of its development.

LINKAGE, a tendency of certain characters to stick together in heredity because the genes for such characters are located on the same chro-

mosome. A group of linked characters or linked genes is called a linkage group; in each species there is the same number of linkage groups as chromosome pairs.

LOCUS, the position on a chromosome occupied by a gene or any of its alleles.

MATURATION DIVISIONS (See MEIOSIS).

MEIOSIS (*meiosis*, reduction), a process consisting essentially of two successive cell divisions, resulting in cells having a single (haploid) set of chromosomes as contrasted with the double (diploid) set in the body cells. In animals, meiosis occurs in the maturation of the gametes; in most plants it occurs in the formation of the spores.

METAPHASE, the middle stage in mitosis, in which the chromosomes are arranged in the equatorial plate.

MITOSIS (*mitos*, thread), the usual type of cell division, involving the condensation of the chromatin into threads, the longitudinal splitting of the threads, their shortening into typical chromosomes, and the movement of the chromosomes to the opposite poles of the cell. Each daughter cell thus receives a full complement of chromosomes characteristic of the mother cell.

MONOHYBRID (*mono*, single; hybrid), a hybrid with respect to only one pair of genes, as *Aa* or *Bb*.

MULATTO, a hybrid resulting from the cross, Negro \times White; sometimes applied also to a person of mixed Negro-White blood of any degree, or to one of mixed Negro-Indian blood.

MULTIPLE ALLELES (MULTIPLE ALLELOMORPHS), a series of three or more alternative forms of a gene occupying a single locus on a chromosome.

MUTATION, a sudden change in a gene resulting in a new hereditary variation. Originally used to include also all kinds of sudden hereditary variations resulting from gross chromosome changes.

NUCLEUS, a minute body composed of specialized protoplasm, found within the cells of all organisms except certain one-celled forms such as bacteria and blue-green algae. The nucleus, in contrast to the cytoplasm which surrounds it, is readily stained with basic dyes.

OÖCYTE (*oön*, egg), the egg-cell prior to the completion of the process of maturation.

OÖGENESIS (*oön*, egg), formation of the egg from the oöcyte.

OÖGONIA (*oön*, egg; *gonos*, offspring), the descendants of the primordial

- reproductive cells; found in the ovary. The ultimate generation of oögonia become oöcytes.
- OVARY**, in seed plants the enlarged part of the pistil containing the ovules; in animals the female gonad which produces the eggs.
- OVULE**, a many-celled spore case within the ovary of seed plants; it produces a large spore from which the egg develops.
- OVUM** (See **EGG**).
- PARTHENOGENESIS** (*parthenos*, virgin), the development of an individual from an unfertilized egg; found normally in some invertebrates but rarely in vertebrates.
- PEDIGREE**, a record of the ancestry of an individual.
- PETAL**, one of the modified leaves of flowers, usually brightly colored, surrounding the stamens and pistil. The chief function of the petals is to attract insects.
- PHENOTYPE** (*pheno*, appear; type), the organism as analyzed into its observable characters, as contrasted with its genetic constitution or genotype.
- PISTIL**, one of the reproductive organs in seed plants which consists of the stigma or pollen receptor, the style or connecting stalk, and the ovary.
- POLAR BODY**, a minute cell containing a normal single set of chromosomes but very little cytoplasm, cast off and discarded by the maturing egg in animals.
- POLLEN**, tiny structures produced in the anthers of seed plants, usually appearing as fine yellow dust. Each pollen grain is originally a single-celled spore, with a heavy wall. The spore nucleus divides, and one of the resulting nuclei divides again to produce the sperm nuclei.
- POLLEN TUBE**, a microscopic tube which grows out from the pollen grain after the pollen lodges on the upper end of the pistil of the flower. At its tip the pollen tube carries along the two sperm nuclei, one of which fertilizes the egg in the ovule; the other unites with two other nuclei in the ovule to form the endosperm.
- POLLINATION**, the act of transferring pollen from the anther to the stigma of the flower.
- POLYPLOID**, an organism with one or more sets of homologous chromosomes in excess of the diploid number; e.g., a triploid with three sets, a tetraploid with four sets, etc.
- PROPHASES**, the stages in mitosis preceding the metaphase and characterized by the appearance of the chromosomes, the formation of the spindle, the break-up of the nuclear membrane, and the movement of the chromosomes toward the equator of the spindle.

PROTOPLASM (*protos*, first; *plasm*, a thing formed), a complex mixture of substances containing a large amount of water, proteins, other organic substances, and various salts—all together making up the "physical basis of life." The protoplasm of different organisms differ slightly in their proteins, etc. Both nucleus and cytoplasm are made up of protoplasm.

RECESSIVE, a character which appears only when both members of a pair of genes (or, in the case of polyploids, all the representatives of a locus) are alike, that is, in the homozygous condition, in contrast with the dominant which develops in the presence of even a single dose of a gene. The term recessive is applied also to the genes.

RECIPROCAL MATINGS, two matings between unlike individuals, in each mating one sex having the same characters as the opposite sex in the other mating.

RECOMBINATION, a new combination of linked characters in an individual as a result of crossing-over in one or both of the parents; also applied to the individual that shows such a new combination.

REDUCTION DIVISION, a cell division that takes place in animals in the formation of the sperms and eggs and in plants in the formation of the spores, whereby the double set of chromosomes is reduced to a single set (see **MEIOSIS**).

REVERSION (ATAVISM), the sudden appearance of an individual which differs in some respect from its parents but resembles its grandparents or more distant ancestors.

SECONDARY SEXUAL CHARACTER, a character normally dependent, either directly or indirectly, for its expression upon chromosome differences in the two sexes, but not necessarily having any direct reproductive function.

SEGREGATION, PRINCIPLE OF (Mendel's first law), the separation of a pair of genes during meiosis and the random union of these with other genes at fertilization, resulting in the typical Mendelian ratios among the progeny.

SELF-FERTILIZATION, the union of a sperm with an egg, both of which are produced by the same individual. Of necessity, such individuals are hermaphroditic.

SEX CHROMOSOMES, chromosomes concerned especially with the determination of sex. In most animals so far examined, and in some plants, the females have two X chromosomes and the male one X accompanied by its unmatched mate, the Y chromosome. In birds, and some moths and fishes the male has two X chromosomes and the female has one X

- without a Y or one X and one Y. In some invertebrates the female has two X's and the male has one X and no Y.
- SEX-LINKAGE**, an association of a Mendelian character with sex in such a way that the character in certain matings crosses from one sex to the other. The cause of this result is the location of the gene for such character in the sex chromosome.
- SOMATIC CELLS** (*soma*, body; cells), all cells in the body except the germ cell line. In animals and higher plants the somatic cells, with few exceptions, have the double number of chromosomes; they take no part in the formation of eggs or sperms, and in most species are therefore doomed to die eventually.
- SPERM** (*sperma*, seed), the *spermatozoon* or mature male germ cell.
- SPERMATID** (*sperma*, seed), one of the final generation of cells in meiosis, which, without further division transforms into a sperm.
- SPERMATOCYTE** (*sperma*, seed; *kytos*, cell), one of the cells produced by the spermatogonia which undergoes two meiotic divisions to produce four spermatids.
- SPERMATOGENESIS** (*sperma*, seed; *genesis*, origin), the process of production of the sperms; sometimes limited to the process of meiosis.
- SPERMATOGONIA** (*sperma*, seed; *gone*, generation), the descendants of the primordial male reproductive cells which give rise to the spermatocytes.
- SPINDLE**, a structure formed in the cytoplasm during mitosis and appearing to be made up of threads or fibers arranged in the form of a spindle.
- SPIREME** (*speirema*, skein), one of the early prophase of mitosis during which the chromosomes appear as coiled threads.
- SPORE**, as applied to the higher plants, a single reproductive cell, produced asexually; not found in animals except Protozoa. Spores in the higher plants contain a single set of chromosomes.
- STAMEN**, one of the reproductive organs of the flower consisting of the anther and filament; its function is the production of pollen.
- STIGMA**, the upper end of the pistil on which the pollen falls and germinates. It is usually expanded and moist.
- SYNAPSIS** (*synapto*, to fuse together), the conjugation or union in pairs of homologous chromosomes of maternal and paternal origin, respectively. It is the primary step in meiosis.
- TELOPHASES** (*telos*, end), the closing stages in mitosis during which the daughter nuclei are formed and cell division is completed.
- TESTIS**, the male reproductive gland in animals in which the sperms develop; synonymous with *testicle*.
- TETRAD**, (*tetras*, four), the group of four chromatids, the product of a pair of chromosomes, formed in the primary spermatocyte.

UNIT CHARACTER, a character which owes its difference from another character to a single gene difference. The term is falling into disuse since it is now recognized that the gene rather than the character is the unit of heredity and that every character probably depends upon more than one gene.

VARIATION, a difference, either hereditary or acquired, among individuals in a species.

VARIETY, a subgroup within a species which differs in one or more genes from the rest of the species.

X CHROMOSOME; Y CHROMOSOME (See **SEX CHROMOSOMES**).

ZYGOTE (*zygotes*, yoked), the cell formed by the union of sperm and egg; the fertilized egg.

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