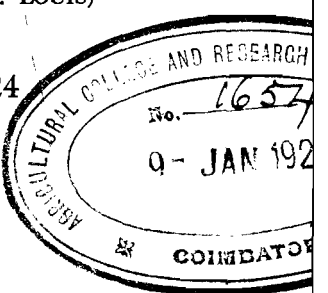
OUR PRESENT KNOWLEDGE OF

HEREDITY

A SERIES OF LECTURES GIVEN AT THE MAYO FOUNDATION AND THE UNIVERSITIES OF WISCONSIN, MINNESOTA, NEBRASKA, IOWA, AND WASHINGTON (ST. LOUIS)

1923–1924



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INTRODUCTION

THE lectures on Heredity here presented to the public were given during the year 1923–1924 under the auspices of the Mayo Foundation and the local chapter of Sigma Xi at Rochester, Minnesota, the Medical School of the University of Wisconsin at Madison, Wisconsin, the Graduate School of the University of Minnesota at Minneapolis, Minnesota, the Medical School of the University of Nebraska at Omaha, Nebraska, the Graduate School of the University of Iowa at Iowa City, Iowa, and the Medical School of Washington University at St. Louis, Missouri.

The general topic of heredity was selected because of its wide appeal to all well-educated persons. The special topics cover a large part of the recent research work in the field of heredity. The lecturers were the persons who had conducted the several researches or had been responsible for them. It is believed, therefore, that this volume includes, in language comprehensible to all, a fair conspectus of our present knowledge concerning heredity as stated by original investigators most competent to speak of the phases discussed. While it does not cover in detail the entire field of heredity, as, for example, the breeding of domesticated animals, it does cover most of the questions of general interest.

The lectures as given at each educational center were heard by large and deeply interested audiences. It is hoped that the reading public may receive them with like interest.

As this volume goes to the publishers the educational institutions mentioned are completing another series of lectures similarly planned and similarly carried out on "Nutrition." A volume containing these lectures will be shortly forthcoming.

LOUIS B. WILSON, M. D.
Director
The Mayo Foundation for
Medical Education and Research.

ROCHESTER, MINNESOTA.
November, 1925.

CONTENTS

Our Present Knowledge of Heredity

HEREDITY: THE GENERAL PROBLEM AND HISTORICAL SETTING

WILLIAM E. CASTLE

The fact of inheritance has been recognized since the days of the cave man. The son, who resembled his father in form and feature, and bore his name, received on his father's death the war club and stone hatchet, and became chief in his stead. Herein are involved what we regard as two different kinds of inheritance, and the distinction between them was at times clearly made even by the cave man. He recognized that the son resembled the father in physical and mental traits because he had sprung from the father's loins, a non-transferable birthright, but that the stone hatchet and chieftainship were things which an adopted son might receive, or a rank outsider acquire by theft or conquest.

The first mentioned, or biologic inheritance only, will be discussed here. The inheritance of property or titles is not a biologic, but a sociologic, phenomenon, although the inheritance of physical or mental traits which qualify one for leadership may well rest on biologic inheritance. This was recognized by prehistoric man, who has left us tales like those concerning Romulus and Remus, of the sons of kings who,

exposed or stolen, nursed by wolves, reared by shepherds, in ignorance of their origin, nevertheless by virtue of their inborn qualities ultimately attained the kingship.

There is a kind of inheritance often difficult to classify as biologic or non-biologic, involving characters developed after birth. Man is born the most helpless of animals. Most of the qualities which distinguish him from other animals are developed in him subsequent to birth. Does he develop these because of inborn traits like Romulus', bent for leadership (as tradition would have us believe), or does he acquire them like the child who learns the speech of the tribe at his mother's knee?

Obviously the ability to speak a particular language is an acquired character, and not a matter of biologic inheritance. Yet the capacity to develop speech, to learn a language, is a matter of inheritance, for no animals other than man, however reared, however carefully trained, can learn to talk a human language. While language itself, therefore, is acquired, its basis is inherited.

Biologic Inheritance and Acquired Characters.—It is this twofold aspect which complicates the question of the inheritance of acquired characters and leads to misunderstandings. He who enters a universal denial of the inheritance of acquired characters is usually thinking of the finished product, the end-result, for example, a knowledge of the English language. He who asserts the inheritance of acquired characters usually has in mind capacity to perform rather than actual performance, and maintains that capacity of the race, no less than of the individual, increases with exercise. Whether this

is so or not is still an open question, with which the next lecture in this course will deal.

Relation of Chromosomes to Heredity.—In modern times it was Weismann who first seriously questioned the theory of the inheritance of acquired characters, which had been assumed by Lamarck and, to some extent, by Darwin, the originators in the last century of the evolution theory. The assumption made it easier to understand how evolution might take place rapidly in useful directions. Weismann, however,

Fig. 1.—Young black guinea-pig such as furnished the transplanted ovaries.

pointed out the absence of critical evidence in its favor, the lack of any suitable mechanism for it, and asserted that the real mechanism of heredity lay in the chromosomes. That the chromosomes are the chief, if not the exclusive, agency in heredity has been established quite conclusively in the last twenty-five years. The chromosome theory constitutes one of the major biologic advances of our time. Before we discuss it further let us consider some of the facts of inheritance; then we shall see presently how the chromosome theory illuminates them.

The ground on which Weismann questioned the inheritance of acquired characters was this: Germ cells do not

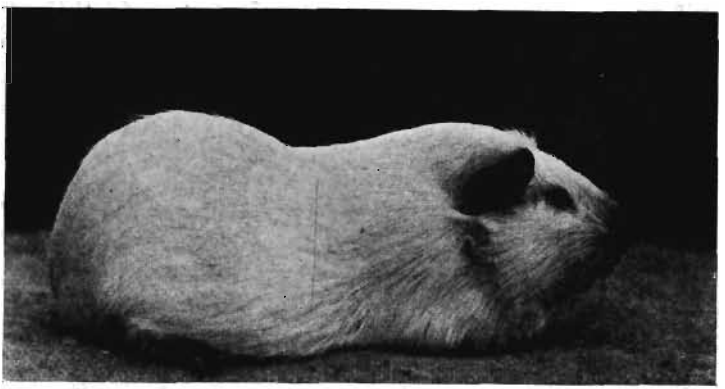

Fig. 2.—White guinea-pig, which, after being deprived of her own ovaries, received those of a black guinea-pig.

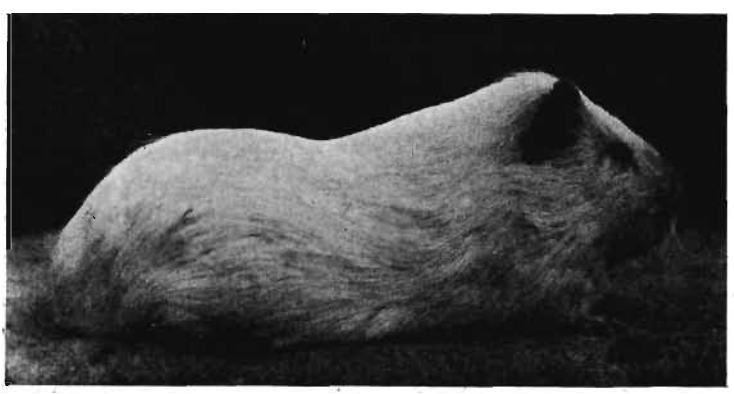

Fig. 3.—The white male which was mated with the white female shown in Fig. 2.

arise from body cells, and so changes produced in body cells cannot be handed on to the next generation unless there is some undiscovered mechanism for their transfer. Professor

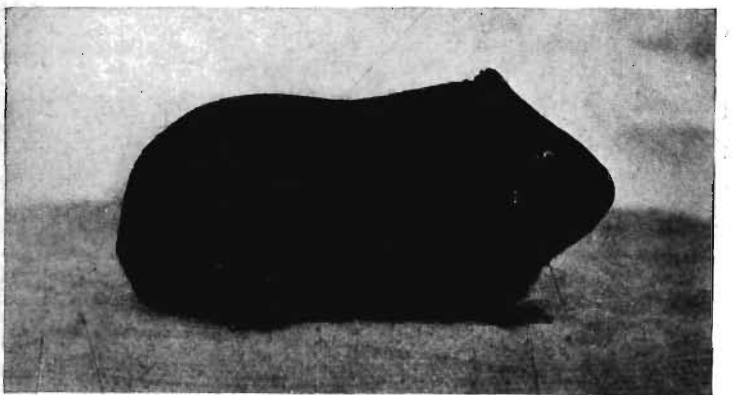

Fig. 4.

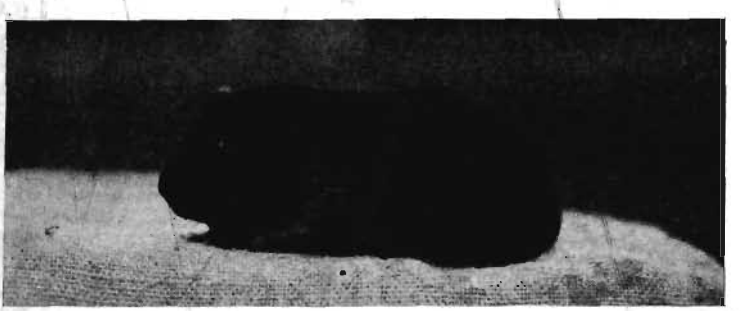

Fig. 5.

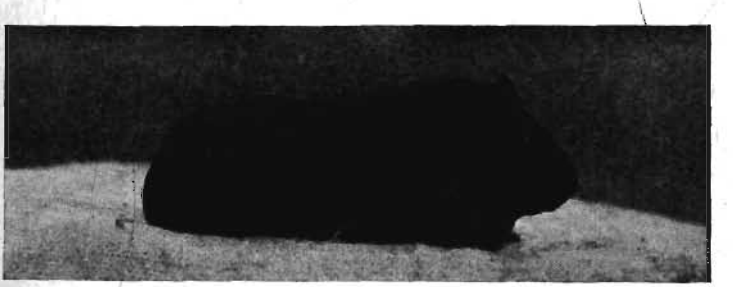

Fig. 6.

Figs. 4, 5, and 6.—Three of the six black young of the white guinea-pigs shown in Figs. 2 and 3.

Guyer and others have made interesting suggestions as to a possible mechanism for such transfer, but the possibility of transfer and its suggested mechanism are still questioned by most biologists. The indifference of germ cells to body environment is illustrated in an experiment with guinea-pigs performed by Dr. Phillips and myself (Figs. 1–6). A female albino guinea-pig was deprived of her ovaries by a surgical

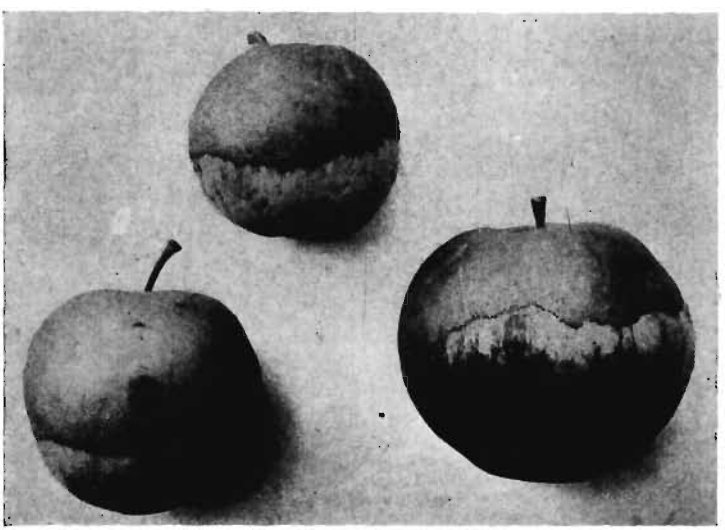

Fig. 7.—An apple "graft-hybrid" or chimera.

operation and in their stead was introduced an ovary from a black guinea-pig of pure race. The albino female was now mated to an albino male, a mating which should have produced only albino young had no operation been performed. But there resulted only black young, such as the black guinea-pig would herself have produced had the ovary remained undisturbed in her body. The environment of a

white body did not affect the genetic character of the germ cells.

The stubborn unmodifiability of living substance, so far as inherited characters are concerned, is further illustrated in animal and plant grafts. Harrison cut frog embryos of two different species in half, and united a head from one species with a tail from the other. The tadpole developed anteriorly the pigmentation of one species, and posteriorly the very

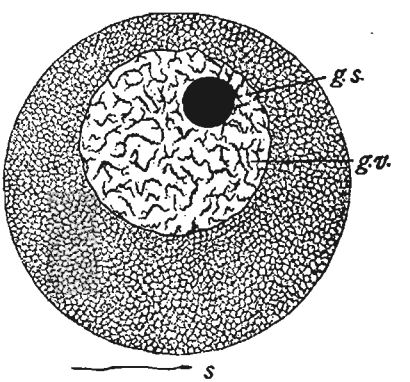

Fig. 8.—Egg and sperm (*s*) of a sea-urchin, both shown at the same magnification (after E. B. Wilson).

different pigmentation of the other, the two parts being separated by a sharp dividing line. Fruit trees produce the same kind of fruit when grafted on other varieties of the same species or even on a different species. Occasionally a graft-hybrid (chimera or mosaic plant) is formed if a stem is produced from a bud arising at the junction of scion and stock, including, side by side but unmixed, tissue derived from both sources. Mosaic fruits may thus arise as in those apples (Fig. 7) which are sour and russet in one part, sweet, smooth-

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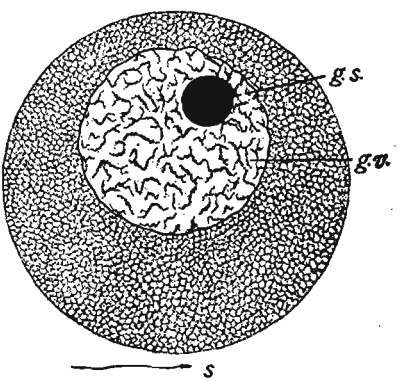

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skinned, and red-striped in another, but nowhere of mixed character.

The mechanism of heredity was correctly located by Weismann, in common with other biologists of his period, in the chromosomes of the germ cells (Fig. 8). The chromatin is in a very diffuse state in the egg, but closely compacted in the head of the sperm. Yet when the sperm has entered the egg, the chromatin which it has introduced swells up to a bulk comparable to the egg chromatin. No other germ-cell

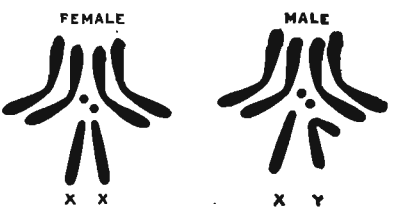

Fig. 9.—Diagram of the four pairs of chromosomes of Drosophila. In the female all pairs contain like partners, but in the male Drosophila, as in man, one pair consists of unlike mates, x and y. This pair is concerned in sex determination and sex-linked inheritance (after T. H. Morgan).

component comes in equal measure from both parents as inherited characters do, so there is strong *a priori* support for the view that inherited characters are determined by the chromosomes, a view which of late has been quite conclusively established. The number of chromosomes in each species, their relative sizes and shapes are characteristic and constant. In the fly, Drosophila (Fig. 9), there are four pairs, in the mouse, about twenty pairs, and in man, twenty-four pairs. In general, each pair of chromosomes consists of one derived from the mother and a similar one derived from the father.

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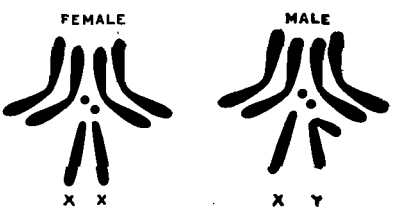

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One chromosome of each pair is thrown out of the egg, in a polar cell, before the egg is fertilized. It is a matter of chance, apparently, whether the maternal or the paternal member

Fig. 10.—Pure-bred black guinea-pig and her young.

of each pair is the one thrown out. The egg is left with only one member of each pair at fertilization. The sperm contains a similarly reduced number. By union of the two sets

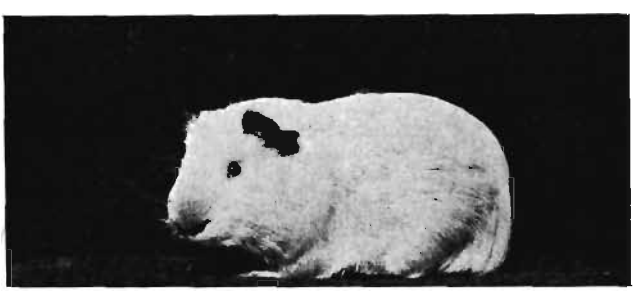

Fig. 11.—White sire of the black young of a black mother.

the duplex condition of each chromosome is restored, and a new individual is produced inheriting equally from his two parents.

A body character which is determined by some substance

located in a particular pair of chromosomes, and in no other, will be inherited in accordance with Mendel's law.

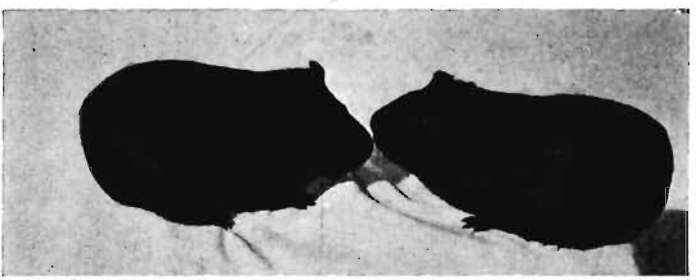

Fig. 12.—Cross-bred young (F_1) of black mother grown to maturity.

Mendel's Law.—With the rediscovery of that law in 1900 begins the modern study of heredity, for the original discovery of Mendel announced in 1866 was at that time understood in its full significance neither by Mendel himself nor

Fig. 13.—Second generation young (F_2) showing the typical result, three blacks to one white.

by anyone else, nor could it be so understood until Weismann's ideas had cleared the way for such an understanding.

Mendel's law is now so well known as scarcely to require discussion. It forms the basis of much practical work in

animal and plant breeding. Simple illustrations of its working are shown in Figs. 10–17. The inheritance of a colored

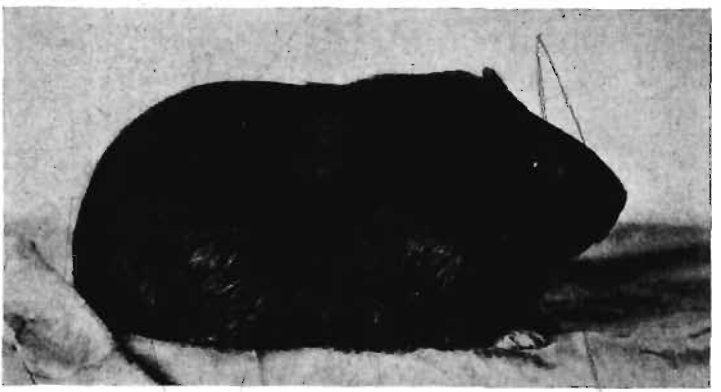

Fig. 14.—Colored smooth parent.

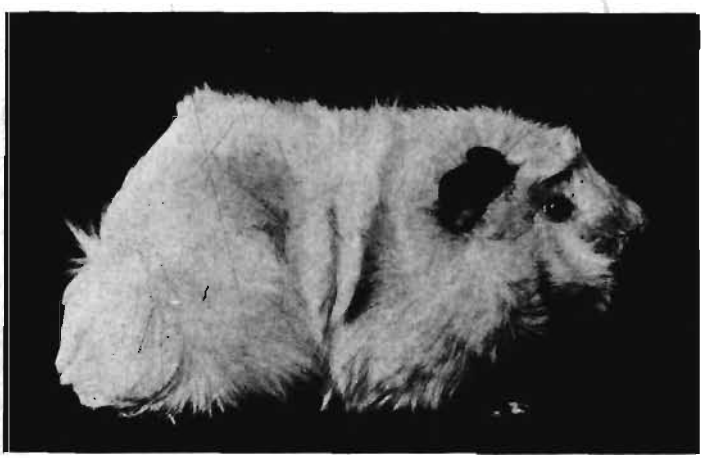

Fig. 15.—White rough parent.

coat depends on the presence of a suitable determiner of color in a particular chromosome of the colored parent. The inheritance of a rough coat depends on the presence of a rough

determiner in a different chromosome (not the color-bearing chromosome) of the rough parent.

Mendelian characters which have determiners (enzymes or what not) located in *different* chromosomes will be independent of each other in transmission. All possible combinations of them will occur in the second generation, in accordance with the laws of chance.

Fig. 16.—One of the F_1 young, both colored and rough.

When two characters located in *different* chromosomes are involved in a cross, the second generation (F_2) classes are four, numerically as 9 : 3 : 3 : 1. When three independent characters are involved, the second generation classes are 8, and their proportions are as 27 : 9 : 9 : 9 : 3 : 3 : 3 : 1.

If the genes for two characters are located in the same chromosome they will stay together in transmission so long as the chromosome remains intact. In Drosophila (Fig. 9) there are four different chromosomes, and correspondingly

there are four groups of linked mendelian characters, those having a tendency to keep together in transmission. By a process, the details of which need not be discussed, it has been possible to determine which group of characters goes with each chromosome, that is, has its genes located in that chromosome. In the male of Drosophila the chromosome always remain intact, and no changes in linkage occur. But in females changes occur which can be accounted for only

Fig. 17.—A new character combination obtained in F_2, both smooth and white. Other F_2 young are like Figs. 14–16. The numerical proportions of the classes are as 1 : 3 : 3 : 9.

by the breaking in two of a chromosome so as to allow of new groupings. Breaks occur only at a stage when each chromosome lies in close contact with its mate, and the break involves both of the pair and usually at the same level. When the break is repaired, the upper part of one chromosome may become united with the lower part of the other, and thus a regrouping of genes may result. Such changes are called crossing-over. In rabbits, rats, and mice several cases of

linked mendelian characters have been discovered, but here crossing-over occurs in both sexes. In rabbits angora coat is linked in transmission with the English type of spotting, and in rats albinism and yellow coat are linked.

Sex-linked Characters.—When a gene is located in a sex-chromosome there results a form of inheritance known as sex-linked. Sex determination will be discussed in another lecture in this course. Suffice it to note that the name sex-chromosome is given to those which are not equally represented in both sexes, as other chromosomes are. In Drosophila (Fig. 9) and in man all the chromosomes consist of like pairs in the female, including a pair of sex- or x-chromosomes. But in the male of Drosophila and man the sex-chromosomes consist of a dissimilar pair known as the x-y chromosomes. The x corresponds with the two x-chromosomes of a female, but the y is different. Suppose, now, a gene is located in an x-chromosome. It will pass from mother to daughter and son alike, but from father to daughters only. The x-chromosome in man carries, it is supposed, characters such as color-blindness and hemophilia, which are never transmitted from father to son, but only to grandsons, through daughters ordinarily unaffected. Many examples of this type of sex-linked inheritance are known in Drosophila and the characters in question are all linked with each other. There can be no doubt that their genes are located in the x-chromosomes.

The y-chromosome would furnish a mechanism for the transmission of characters directly from father to son, independently of the female line, but so far such transmission

has been demonstrated beyond question only in fishes, although in the case of man webbed toes have been reported to be thus transmitted in the Schofield family in California.

In birds the female bears the unlike pair of sex-chromosomes, x, y, the male having a similar pair of y's, but no x's. When y is the vehicle of inheritance, there results the poultry type of sex-linked inheritance. Thus is transmitted the barred plumage of Plymouth Rock fowls, reciprocal crosses giving unlike results.

Mendel demonstrated the independent inheritance of single characters, but was in doubt whether his principle of unit-characters applied to all the characters of organisms, or only to certain groups of them, and we are still in doubt on this point. A few examples will illustrate.

Inbreeding and Outbreeding.—The higher animals and plants derive added vigor from cross-breeding and frequently decline in vigor under inbreeding. This fact is an important practical consideration in animal and plant breeding and forms the basis of our customs and laws concerning consanguineous marriages. It also complicates the study of inheritance of characters, such as size and productiveness, which increase or decline with general vigor. A good illustration of cross-bred vigor is seen in a cross between common guinea-pigs and a small wild race from Peru. The F_1 offspring grow to larger size than even the tame guinea-pig, but in F_2 the adult size is intermediate between that of the uncrossed races. So far as heredity is concerned the result is blending. The extra vigor due to an out-cross can be depended on to last for a single generation only. Animal breed-

ers make good use of this principle by crossing distinct races to produce large rapid-growing offspring, but they do not, if they are wise, save the vigorous F_1 offspring for further breeding, for then the extra vigor disappears. To plant-breeders, the principle is especially important in connection with plants which can be propagated asexually. Many of our most valued varieties of orchard trees, small fruits, and vegetables, such as potatoes, probably owe their exceptional vigor and productiveness to the fact that they are first generation hybrids. A second generation raised from them by seed would probably be distinctly inferior.

Blending and Allelomorphs.—Aside from the complication of hybrid vigor, the usual result of a cross between families or strains differing in size is to produce offspring of intermediate size and proportions as in rabbit crosses. Such cases obviously do not conform with Mendel's law, as it was understood by Mendel himself. They have long been described as blending, a descriptive term we may as well retain, whatever interpretation we adopt as to the mechanism of their inheritance. By many, perhaps by a majority of investigators, blending inheritance is regarded as a form of mendelian inheritance in which many independently inherited factors or genes are concerned. This conclusion was reached through the following series of discoveries:

First: It was found that some characters, seemingly simple, depend on the inheritance of two or more independent factors, that is, factors located in different chromosomes. Thus the purple color of the flower of the wild sweet-pea is dependent on the inheritance of three independent factors,

enzymes perhaps, each located in a different chromosome. One factor, *C*, is indispensable to the production of any color in the flower, but by itself produces no color. Acting with it a second factor, *R*, produces a red color in the flower; and acting with these two, a third factor, *B*, changes the color to purple. If a white-flowered plant containing *B*, but neither *C* nor *R*, is crossed with a red containing *C* and *R*, then purple-flowered offspring are obtained, and in the next generation all possible combinations of the three factors, visibly distinguishable as purples, reds, and whites. In this case the red and blue factors are sharply dominant and no intermediates are formed, but only sharply separated classes. The principle, however, is established, that a character may depend on more than one inheritance factor, or gene.

Second: It was found by Nilsson-Ehle and by East that a genetic factor may be represented more than once in a germ cell, that what is apparently the same factor may be attached both to chromosome *A* and to chromosome *B*, members of different pairs. Consequently the character, if dominant in heredity, will occur not merely in three-fourths of the second generation offspring, but in fifteen-sixteenths of them. Or, if the character is represented in three different chromosomes, then the dominant character will in crosses occur in sixty-three out of sixty-four second-generation offspring.

Third: Increased factorial representation of a character may give the character stronger expression. Thus in maize, according to East, a factor for yellow endosperm color gives, when once represented, a faint yellow color; when twice rep-

resented, a stronger yellow; and when three or four times represented, a deeper yellow still.

If all three of these principles are combined, we obtain a satisfactory formal explanation of blending inheritance in accordance with mendelian principles. A character which blends in heredity may be assumed to have factorial representation in many or all of the chromosomes. The action of these factors may be assumed to be cumulative, the more factors present, the more strongly will the character be expressed. Applied to size inheritance, a small race will contain few factors contributing to growth, a large race will contain more factors, hybrids will contain an intermediate number.

This explanation of size inheritance, although formally adequate, is difficult to test critically, and for this reason is not very satisfactory. It may or may not be so. Personally, I am far from satisfied with the interpretation, although there is as yet nothing better to offer in its stead. It seems to me much more probable that we are dealing with graded intensities of factors than with mere numbers of factors. There is abundant evidence that the same genetic factor may assume a variety of different forms graded in the intensity of their action. Thus a single sex-linked factor for the eye color of Drosophila has been shown by Morgan and his associates to occur in a dozen or more different states producing shades of pigmentation ranging from clear white through eosin to dark red.

In rabbits, guinea-pigs, and mice occurs a similar though less extended series of allelomorphs of the so-called color fac-

tor, ranging in its very stable and strictly inherited grades from snow white to the dark gray of the wild type. In rabbits

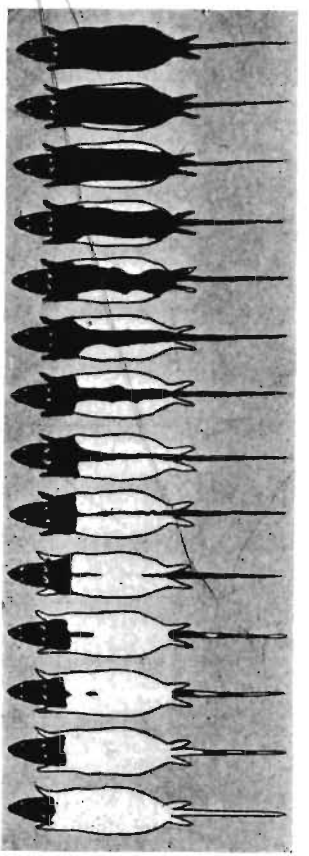

Fig. 18.—Range of variation in the hooded pattern of rats.

different types of Dutch marking behave as allelomorphs in heredity.

In rats the hooded pattern is inherited as a mendelian unit,

depending on a single gene, but it fluctuates through a wide range of grades which can be carried in plus or minus directions by selection, so that the fluctuations evidently have a genetic basis (Fig. 18). These fluctuations are not allelomorphs, that is, stable alternative grades, although two such allelomorphs, have been discovered. They are apparently

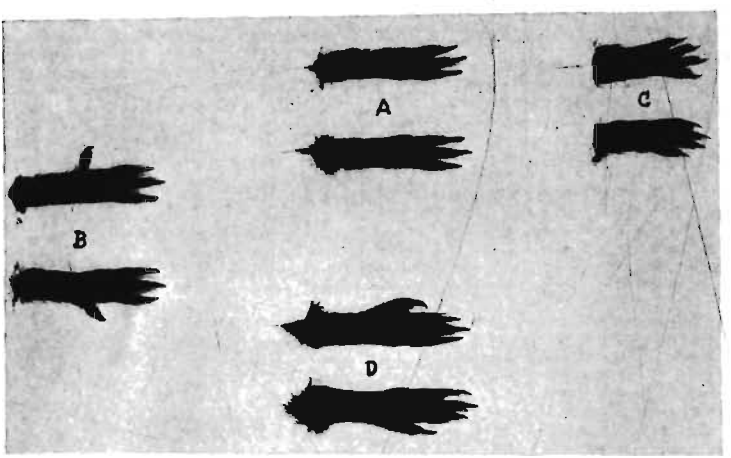

Fig. 19.—A and C, Hind and front feet of a normal guinea-pig; D, hind feet of a four-toed race developed by selection; B, usual type of hind feet produced on crossing normal with four-toed guinea-pigs, also approximating the degree of development in which the character was first observed.

due to the action of subsidiary or modifying factors located in chromosomes other than that which carries the hooded gene proper. The evidence for this view is the fact that plus and minus selected races return to a common state when crossed repeatedly with the same wild race, which presumably would introduce the same modifying genes.

Characters which scarcely reach the threshold of visibility

may by selection be intensified into well-developed characters, as was done, for example, in a race of four-toed guinea-pigs (Fig. 19). How? Either by the discovery of graded variations in one or more genes and the isolation of high-grade allelomorphs, or else through the action of modifying factors.

Imperfectly blended characters are illustrated in crosses of peppers and maize, where F_1 is intermediate and F_2 still intermediate, but with evidences of imperfect segregation.

The imperfection of the segregation is due perhaps to a variety of causes, as (1) multiple factors, (2) multiple allelomorphs or grades of the same factor, and (3) numerous modifying factors. These complex agencies render systematic selection the only means of modifying races in desired directions, the selection being preceded by crossing, if sufficient variability is not already present.

Confusion of Hereditary and Environmental Agencies.—It is not necessary to suppose that a character is hereditary simply because it has occurred in two, or even in three, successive generations. Yellow fever was not an inherited malady in Havana or Guayaquil, although it used to decimate families generation after generation. When the causative agency was discovered it was found to be a factor of the environment, not of the human organism.

Let us not ascribe to heredity familial traits which may owe their occurrence to undiscovered factors in the family environment. The student of mental traits and human behavior needs to be particularly on his guard in this respect,

since he is dealing with secondary or developed characters which may or may not have a basis in heredity. Even the supposed inheritance of a predisposition to cancer should be studied very critically.

THE HEREDITY OF SEX

CLARENCE E. MCCLUNG

Always the question of sex has been an insistent one; it is today particularly so because of the rapidly expanding activities of women in all the affairs of life. To properly determine the parts that men and women should play in order to have the best form of society, it is necessary to know more definitely than we do now the essential differential characters which distinguish them. Studies of sex have therefore very important services to render in a sociologic way. Biologically, also, sex is a problem of great significance, for an appreciation of the characteristic differences between male and female would do much to further a knowledge of the functional activities of plants and animals. A study of the heredity of sex offers one of the most promising avenues for gaining an approach to an understanding of this very difficult subject, and on this occasion I will endeavor to present the results of some modern investigations in this field.

DEFINITION OF HEREDITY

Before entering into a discussion of the subject, however, it will be well to arrive at as definite an understanding of the meaning of the terms "heredity" and "sex" as is possible. A large part of scientific controversy would be avoided if exact definitions of terms could be attained. Unfortunately

exactness in definition is dependent on completeness of knowledge, and since this can never be reached, we shall always have to labor under the disadvantage of imperfect terminology. At the same time it is very true that there is a great indefiniteness and looseness in the use of such words as "heredity," and this condition retards progress in biology and brings discredit on it in the minds of critical investigators in other fields. In the effort to clarify my understanding of the meaning of heredity, I looked up the definitions presented by different writers and was greatly astonished at the marked diversity thus exposed. Space will not permit a repetition of these definitions, but the varied conceptions entertained may be indicated by saying that heredity is conceived by different biologists to be a relation, act, fact, process, property, material, organization, rule, resemblance, or link. How many other things it might prove to be on further search for definitions I do not know, but at this point I perceived that my effort to secure clarity of understanding was not making much progress by this method, so I dropped it. Even to the uninitiated it is apparent that a thing cannot be at once a process, a material, a property, and a relation. When all these definitions were considered carefully in relation to the context from which they were dislodged, it gradually became evident that there was some community of understanding amidst the diversity. So far as I could interpret it, this appeared to be that heredity involves a condition, or state of organization, maintained in a succession of individuals by processes of reproduction. Foregoing the unattainable ideal of a perfect definition, we may therefore conclude for the purposes of

this discussion that heredity involves the elements of a form of organization, a succession of individuals, and a process of reproduction.

THEORIES OF HEREDITY

There are, of course, endless theories regarding heredity, but until recent years they have lacked any convincing support from accurate detailed observations. For our present purpose, reference may be made to two types of theories, by way of illustration. Both are characterized by accuracy of observation and treatment, but proceed in very different ways to gain the data treated.

Galton's Law.—Francis Galton, a cousin of Darwin, had much to do with establishing biometric methods and applying them to the betterment of the human race through intelligent and well-directed breeding, which he called eugenics. In getting data for his conclusions he made extensive statistical studies of human qualities like stature, color of the eye, mental ability, and so forth, and from these deduced his "law of ancestral inheritance." According to this an individual derives directly from his two parents one-half of his total inheritance, from the four grandparents one-fourth, and from all his other progenitors the remaining fourth in the same diminishing ratio for each generation. This method deals largely with groups instead of with controlled individual matings. It has not been helpful in studies on heredity of sex and will not be considered further.

Mendel's Laws.—The other type of theory to which I shall refer was developed by Gregor Mendel, and was derived from studies of individual matings carried through many genera-

tions. He conceived the organism to be a complex of a great many "unit characters," which could be independently inherited and variously combined in the offspring, even of the same two parents. To control the development of these characters he imagined a mechanism in the germ cells consisting of a definite factor for each character. In operation this mechanism worked according to exact numerical relations of a simple and predictable nature.

The material used by Mendel was principally the common garden pea, and the unit characters noted were, among others, form and color of the seed, color of the flowers, plant stature, and so forth. In studying the seeds it was found that the colors, green and yellow, might be united interchangeably with smooth or wrinkled form, and in a similar manner all the single characters could be separated and recombined according to perfectly definite rules. Such a form of hereditary processes has now been studied in a great many plants and animals with the same general results, and when combined with cytologic studies, constitutes the most definite form of analysis that has yet been made of hereditary processes.

A simple but striking example may make clearer the nature of so-called mendelian heredity. If the pollen of a white-flowered four-o-clock be used to fertilize the ovules of a red-flowered plant, and the seeds thus produced are germinated, they give rise to plants whose flowers are all pink. Both original colors seem to have disappeared in the presence of an intermediate one, but since this partakes of the character of the two which united to produce it, it would seem that whatever controls flower color is present in these hybrid

plants from both parents, as neither original color shows, but rather a combined effect of the two. A demonstration that this is the case is provided by allowing the hybrid pink flowers to fertilize their own ovules. When the seeds thus produced are planted there appear certain plants with white flowers, others with red, and still others with pink. Not only do these three colors appear in the second generation, but they always bear a definite numerical relation to each other. Of all the plants produced by the self-pollination of the hybrid pinks, one-fourth bear white flowers, one-fourth red, and two-fourths pink. Self-pollination of the whites thus derived produces only white-flowered offspring, and correspondingly the red flowers produce only seed capable of development into plants with red flowers. But the pinks, as would be expected, betray their hybrid nature by throwing the same three colors as the first hybrid generation, and in the same proportions.

UNIT CHARACTERS

For the purposes of our present consideration the following important facts emerge from these experiments: (1) Color acts as a unit, and is not altered in its nature by association with another color in a hybrid plant; (2) when the factors for two colors are simultaneously present, both are operative and produce an intermediate effect; (3) when the intermediate parent produces germ cells these are found to be unlike, for on self-fertilization, they give plants with white flowers, red flowers, and pink flowers respectively, and (4) any plant with white, or with red flowers, is homogeneous in character and produces only one kind of offspring, but the pink-flowered

plant is heterogeneous in composition, for it throws red and white as well as pink, always, however, in fixed and definite proportions.

Grouping.—Similarly other characters may be worked out and show the same type of behavior. Mendel found many of these unit characters, and in his cases they behaved independently and might show any assortment. In this way any combination might eventually be produced. Later it was found that in certain cases two or more characters act as a group and remain in the same combination; together they act as a larger unit. This has been worked out in great detail by Morgan and his collaborators, and it has been found for Drosophila that there is a fixed number of these groups and that the characters bear a definite relation to each other in the group, also that the groups vary in number of the associated characters. While there may be a limited reorganization of the elements in the aggregates, in general, the characters which entered as a group into the individual emerge in the same relation in its offspring.

Theories.—Since in sexual reproduction each individual is produced entirely by the combined action of a germ cell of the female form and one of the male form, it is necessary for these two very minute protoplasmic units to have within them some form of inner organization that, in nature and behavior, parallels the exhibition of characters in the body resulting. Theories which definitely associate specific portions of the germ cells with particular characters of the body belong to the particulate type. According to such a theory the peculiar nature and activity of each part of the germ

cell, set aside for such purposes, controls some special end-result in the development of the organism. These units are variously conceived, both in character and arrangement, but the special relation between gene or determiner always exists. In its very simplest form such a theory is far too limited to express all of the varied interrelations in the extremely complicated system of the germ cells, but in some way it is evident that there is a direct relation between discrete units of chromatin in these cells and the characters which later express themselves in certain forms and arrangements of body cells which arise by repeated divisions of the fertilized ovum. In the case of flower color, which has been used as an example of mendelian heredity, it would be necessary to assume that the white-flowered plant had in its germ cells a certain factor, which, by its operation in development, would produce the same effect in every case. Correspondingly in the red-flowered plant there must be something responsible for color development, but in this case it results in a red color. In the hybrid there are brought together in one plant both white determiners and red determiners, and the result of their antagonistic action is a compromise, an intermediate pink. It is through the disturbance of normal relations in this way that much of our knowledge of heredity has been derived. In most of the cases studied by Mendel the two contrasting characters were of such a nature that instead of an intermediate result, as in the four-o-clock, one of the characters completely suppressed or dominated the other in the first hybrid generation, but in the second the two contrasting elements reappeared in the same relations as in the color cross described.

Alternatives and Dominance.—As will be readily apparent it is this type of heredity that bears closely upon sex inheritance, for here also we have two contrasting conditions and a constant dominance of one over the other. In ordinary mendelian dominance, however, when two contrasting conditions are brought together it is always one which dominates the other, while with sex it may be either. The elements of alternatives and dominance appear in both ordinary mendelian and sex heredity, and therefore suggest a common form of mechanism in the germ cells. The early efforts to draw an exact parallel in these cases failed because of misconceptions of what really constitutes sexual differences and because the operations of mendelian inheritance had not been fully worked out. It is not necessary to go into a historical review of these early attempts, for it soon became apparent that an almost exact parallel could be drawn between a differentiation of all the members of a group into equal numbers of males and females, and a similar equivalence of classes when a hybrid was back-crossed to its recessive parent.

SEX CHARACTERS

Ordinary Characters and Sex Characters.—It now appears that there is no essential difference between the behavior of ordinary characters and those classed as sexual. It might be suggested that those differences which are related to sex are all pervasive in the organism, while mendelian characters are limited in place or time, but more detailed study has made it clear that what has been called a "unit character" is only one localized expression of a constitutional differential which

exhibits itself in many aspects throughout the body. We may then approach a study of germ-cell organization with the confident expectation that sex differentiation will be a part of the general mechanism for the control of all forms of determinism in the body.

Sex-linked Characters.—Indeed this intimate relationship is shown in a particularly striking way by a form of mendelian heredity known as "sex-linked." Several instances of this appear among human traits, and one of these will serve by way of illustration. Some persons are unable to distinguish between red and green. Both men and women are thus affected, but it is much more common in the former. A color-blind father and a normal mother have normal children, and all the progeny of the sons are free from the defect, but half of the male offspring of the daughters are defective even with normal fathers. If the mother is color-blind, all her sons are likewise, but she will not be of this character unless her father was affected and her mother came from a strain of this nature. An affected father, as it will be seen, does not have in his germ cells which produce male offspring, any determiner for this character, but the mother, even if not showing the defect, may pass it on to her sons by a normal father. To account for this peculiar condition there must be something that passes alternately from the male to the female line, and is thus bound up with sex determination in some way. If the character was associated only with males it would pass directly from father to son, but, as it is, it goes from father to grandson through the daughter. As will be seen later, this criss-cross inheritance is exactly accounted for in the move-

ments of the sex-determining chromosome, and all we have in such cases are determiners united with those for sex in the same chromosome.

GERM CELLS AND BODY CELLS

Reference has frequently been made in this discussion to distinctions between germ cells and body cells. In view of the fact that the two help make up the organism in all normal individuals, what is the basis for this distinction? Especially, since all the cells of whatever kind are derived by repeated divisions from a single cell, how can we make a division of them into two contrasted groups? Such a distinction is real, for somewhere during the course of development certain cells are withdrawn from the process of differentiation and are segregated into the gonad where they remain, in a measure, apart from the activities of the body. Such cells have been described in many forms of organisms and the time and manner of their distinction noted. The very earliest period of such splitting off of germ cells was described by Boveri in Ascaris. When the embryo is in the two-celled condition, one cell suffers the loss of the ends of each chromosome, and what remains is broken up into many small chromosomes. The descendants of this cell have been traced into the organs and systems which make up the worm's body. The other of the two original cells retains all its chromosomes entire, and certain of its descendants do likewise. These are found to appear in the gonad and to form eggs or sperm, as the case may be. In other words, there is a continuous line of cells which maintains a definite chromosome constitution, and ap-

parently does nothing except, at certain times, bud off the kind of cell which loses a part of its chromatin and then produces a progeny in the form of a worm.

In a number of insects a similar differentiation is established, but in these cases apparently the chromosome constitution is not altered, but the prospective germ cells have incorporated into them certain distinctive materials in the egg, while the cells which go to form the body lack these. The differentiation here is accomplished very early also. For vertebrates there is much difference of opinion as to when distinction is established between germ and body cells, but the distinction is admitted. If it were only a question of time it would not much matter theoretically, but it is held by some that, after the fertilized ovum has divided into a great many cells and these have become differentiated into tissue cells, certain of these lose this differentiation and become converted into germ cells. This would seem to imply that reproduction came somewhat in the way of an afterthought and that the body gave up something of its already developed structure to provide germ cells for a later generation. As a matter of observation it is difficult to decide in these cases, for the criteria for determining germ cells are few and uncertain. Logically, also, there are arguments in favor of a part of the body reproducing the whole, and there are many instances of cells losing differentiation and becoming general in type. Such cases are, however, largely confined to lower forms and are certainly not the rule in higher vertebrates. To conceive, therefore, that it is a normal occurrence for a tissue cell of any sort to lose its character, retrace its steps, and give

rise to a germ cell is against the general evidence for definiteness of organization and exactness of process in higher forms. Particularly is this true with regard to the germ cells when, in lower forms even, they are definitely set apart at an early period of development.

The Nuclear Equipment.—If, however, the cell contains a complete nuclear equipment, there is the possibility that it may function in a manner characteristic of its species, for, experimentally and otherwise, it has been proved that a normal nucleus is necessary for normal function. It has been well demonstrated that the essential part of the nucleus is the chromatin, and the inner organization of the chromatin expresses itself visibly in the form of its integration into chromosomes. Thus every species has its characteristic chromosome complex, which is marked by definiteness in number, size, form, and behavior. In most species studied, this complex is constant for all cells of the body, both germ and somatic, and we may therefore study these elements in the capacity of indexes of the inner nature of chromatin organization.

Chromosomes and Heredity.—It will be possible here only to sketch the significant facts regarding the relation between chromosome structure and behavior in relation to hereditary processes, but it is most important to know this relation, for no theory of heredity that does not conform to the known facts of cytology has any standing. First, then, it is to be noted that each chromosome has an individuality. Everything that is implied in the term "individuality" is involved in its use in this connection. We mean that it is a discrete,

distinctive unit, marked by peculiarities of structure and behavior which in some measure distinguish it from other chromosomes. Since it reappears in successive generations of cells in the organism, and in repeated generations of organisms through the usual method of individual reproduction, it has genetic continuity, of course, but, in addition, it has a nature of its own to be perpetuated. But it is not an independent unit; it is a member of a co-ordinated complex, each member of which has a part to perform in a common effort. If anything, the evidence of its peculiar and individual character is strengthened by the fact of its constant association in a group of similar but individually distinctive elements. Since the whole of present-day theories of heredity involve as an essential element the definite and persistent architecture of the chromosome, it may be well to note an outstanding instance of such organization.

The short-horned grasshoppers have been studied intensively now for more than a quarter of a century. They have been collected from Europe, Asia, North America, and South America. Many genera and a large number of species have been investigated. Wherever found they present a well-marked and highly characteristic appearance. Geologically, they are very old. In every way they present evidence of a constant and long-persistent organization. Such bodily precision and continuity might well argue for a corresponding order in the mechanism which is credited with the function of determining, in each representative of the group, its characteristic form. In this instance such correspondence between cell architecture and bodily form manifests clearly at the level

of chromosome integration. In other groups of similar inclusiveness such a degree of order may not prevail, but that in no way invalidates the evidence in this case. Cytologic studies show that in every cell of every individual in this great group there are for the males twenty-three chromosomes and for the females, twenty-four. Apparent exceptions to this rule serve only to emphasize the underlying fixity of this organization. When therefore we study the constitution and behavior of any chromosome group it is not an isolated condition that we come to understand, but something instead which has a broad significance. There is, for instance, the pertinent fact that throughout this whole group of animals one particular chromosome can always be recognized through peculiarities of behavior and function: the sex-determining chromosome whose unpaired condition in the male makes its odd number of elements.

A second general condition of greatest significance lies in the circumstance that the twenty-four chromosomes of the female grasshopper do not consist of this many different kinds of elements, but of *twelve pairs*, recognizable by differences of sizes and sometimes by form and behavior. Each grasshopper is therefore a duplex creature, and all its characters are developed under the influence of a double control. Breeding experiments with known unlike parents, in respect to chromosome forms, demonstrate that the reason for this duplex condition is that each parent contributes one member of each pair, except that in the male one pair is incomplete, having a representative from only the female parent. But what is true of the grasshoppers in these matters is true of

animals in general, so that facts derived from these studies concern, not the limited group, but organisms in general. It follows therefore that in recognizing the sex-differentiating function of the unpaired chromosome in the male grasshopper we make possible the identification of this particular element throughout a large proportion of animal and some plant species. Genetically, the demonstration of the duplex chromosome complex gives the basis for an explanation of mendelian heredity, for it explains alternative inheritance of unit characters; it accounts for limited numbers of character groups and for their relative size; it gives a basis for understanding the possible great diversity in the combinations of characters of two parents in their offspring; and, as will appear later, it shows how reorganization within the individual character group may take place.

We have now seen that each chromosome has its own distinctive character, that in the body cells it is accompanied by a mate of essentially similar nature derived from the other parent organism, and that the male differs from the female in having one of the constant specific number of chromosomes without any mate from the male parent. It is now necessary to inquire into the method by which these constant conditions are maintained, and this leads us into inquiries regarding the steps in individual development known as maturation and fertilization in the germ cells. Studies of this sort are perhaps the most difficult in cytology, but at the same time the most important. Our technical methods are highly perfected, and optical instruments are the best the world has known, almost as good as theoretically are possible, yet the

inner organization of the chromosomes transcends our analysis. Even with these handicaps great advances have been made, however, and we are now in a position to explain many things that long have been mysteries.

Maturation and Fertilization.—Germ cells, before they can unite to form a new individual, have to go through a process of preparation known as maturation. Essentially, what is accomplished at this time is to segregate into different cells the members of each chromosome pair which originally came into the germ cell from its parental organisms. In doing this it naturally follows that the total number of chromatin elements in the cell is reduced to half. The means for accomplishing this result, and others related to it, is furnished by two mitotic cell divisions which rapidly follow each other and really constitute a single operation. Besides the segregation of homologues and the numerical reduction of the chromosomes, two other important results are accomplished: First, an exceedingly intimate physical relation of each pair of homologous chromosomes, during which reactions and exchanges of the utmost delicacy may occur, is established. This provides the means by which the ultimate units of organic structure may be brought accurately together according to their own kind, with the result that the aggregate of these units, the chromosome, has suffered something in the nature of a rebirth and emerges from the intimate association with its fellow, changed and to some degree different from any other similar chromosome. This means that not only is the aggregate different, but also its ultimate units, for the chromosome is only the sum of its parts. Second, the two mitotic

divisions of the maturation period accomplish a chance segregation of the elements of the twelve pairs of chromosomes, and, in the male, a limitation of the differential, unpaired, sex chromosome to one-half of the resulting cells. There is thus provided an opportunity for internal reorganization of each chromosome, and all possible assortments of the members of the group. Whatever value there may be in providing means for variations and at the same time trying out the effects of these each time a new individual is formed, no better mechanism could be conceived for accomplishing these ends than that provided in the germ cells during maturation.

Finally, after all the reorganization, testing, and assortment of the chromosomes in the germ cells of the two parents a new combination is effected by having a sperm with its half complement of chromosomes enter an egg with a corresponding set, and thus, by the act of fertilization, restore the duplex condition commonly necessary for the development of a new individual. Fertilization then is a complementary process to maturation, and restores the conditions disrupted by it. The movements of the chromosomes in these two processes are just those required to accomplish the changes observed in character combinations in mendelian heredity; in other words, the germ-cell mechanism corresponds in nature and behavior to the observed results of its operation. This is illustrated in a particular way by the arrangement for sex determination, where equality in numbers is provided for by having a differential element so apportioned as to go into but half of the sperm. The two alternatives thus have equal opportunities for realization. Other and probably more sig-

nificant features of sexual differentiation are involved in the distinctive behavior of the sex chromosomes in the sexes, but as yet we can only surmise what they are. It is hoped that physiologic experiments now in progress may point the way to an attack on these fundamental problems of sex, problems which are one with those of organic development and differentiation, in general. Now that a background has been sketched to indicate something of our general knowledge of heredity, we may take up the more special case of sex and its heredity.

MALENESS AND FEMALENESS

Warned by my experience in attempting to find help in the solution of scientific problems by definition, in the case of heredity, I did not attempt it when the term "sex" came to be considered. Here, moreover, anyone would be prepared to point out to the investigator the obvious nature of the characters which distinguish male from female. But, like so many obvious things, the nature of these distinctions suffers in clarity and scope when investigated *in extenso*. The mighty stag and the modest doe, the gorgeous peacock and the quiet hen are certainly easily distinguished and defined, but when one examines the Amphibians, marks of distinction may be almost lacking, while in other forms there are no such things as male and female individuals, but only a combination of them into hermaphrodites. But even in the absence of visible differentiation into male and female bodies, sex is present, for there are produced the essential products of sexuality, eggs and sperm. Still lower in the scale of life we come on organisms

which unite to produce other individuals of their kind, but in which no differences can be seen in their contributions in reproduction. In all this graded scale of sex differences there is common only one element, and that is the coming together of two cells from different sources to produce a new individual. It may be that the combining cells are, so far as we can see, alike, or that egg and sperm come from the same individual, but there is some measure of difference in source, or experience, of the materials which enter into the composition of the new body. Sexual reproduction implies, therefore, this bicellular origin of new members of the group, and whether we define sex as the exhibition of visible differences in the cells or organisms involved is a purely formal matter, for we must recognize that there are differences even when we cannot distinguish them, and that they may be present as physiologic gradations when not morphologically distinct. The duality of origin in individuals is, however, an essential element of sexual reproduction.

A strict gradation from strongly marked differences in the sexes, which on occasion may be so extreme as to make it appear that male and female are of different species, down through infinitesimal differences to the state where even the conjugating germ cells are visibly indistinguishable, marks the scale of sexual differentiation. It is instructive also to note that what appear to be rigid structural peculiarities of male and female, on careful study turn out to be reciprocal modifications of a common series of characters. Maleness and femaleness are therefore not distinctions of kind, but only of degree. By appropriate treatment the quiet, domestic, egg-

laying hen may be transformed into the vociferous and belligerent sperm-producing cock. The transformation involves only the change in form and function of a persistent ensemble of parts, the passage from one extreme to the other in a bimodal series of expressions of like features. In a large measure these two contrasting states of organization are of a plus and minus character; they are reciprocal and unequal expressions of the common series of characters which often show a "lock and key" relation. It would lessen much of misunderstanding in the discussion of sex if the underlying unity, amid the apparent sexual diversity, were realized. We should not then have references to exclusively male or female characters with their misleading implications. When the matter is viewed broadly it is apparent that even the primary sexual character (the production of minute, motile sperm as contrasted with large, food-laden ova) disappears in the presence of apparent uniformity of gametes in many lower organisms. Despite, however, this approach to extinction, there is something fundamental in the difference between maleness and femaleness, and the differentiation into sexes of the individuals of a species seems to be a necessity in highly specialized groups. A thorough understanding of sex cannot fail to carry us a long way toward a comprehension of organization and differentiation, and in many ways a study of sexual differences offers the most fruitful approach to an understanding of the essential characteristics of living things.

Ovum and Sperm in Host.—If we note then the features which we associate with sex, the primary one is clearly that which involves the highly differentiated germ cells which are

so characteristic of well-marked sexes. The physiologic traits thus distinctively manifested in these sexual products have, by many, been considered as expressions of the essential qualities inhering in the two sexes. Thus the sperm, with its rapid expenditure of energy in motion, would typify the strongly catabolic nature of the male, while the inactive, food-laden ovum, by contrast, would express the preponderant anabolic character of the female. It might well be questioned whether this would be a proper *a priori* conclusion, since the egg is not in its composition female, or the sperm male; but, by reason of origin, it may be that the sexual products do partake of the physiologic differences of their hosts and thus justify the generalization. At any rate, the most characteristic thing about the female is that it produces germ cells in the form of eggs, while the male is marked by the production of sperm. Perhaps the essential relation between the body and its kind of germ cells may be summarized thus: reproduction is an inherent property of organisms; commonly it is accomplished through the medium of certain cells which are set free from the body; these cells partake of the nature of the body from which they come, because they have the same organization through descent from one single cell. If identity of cellular organization is a measure of likeness then the ovum before maturation, at least, is of the nature of the body which harbored it, while the sperm, by contrast, manifests the characteristics of maleness.

Although it is true that sex differences may grade down to extinction, commonly the members of a species are divided into the two sharply differentiated classes of male and female.

So distinctive a feature of living things is this bisexual condition that the non-biologist is apt to assume that it is a necessary attribute of life. While this turns out to be an incorrect generalization, sex is so fundamental to reproduction that, in all but the lowest forms, it has become a necessity. Often it expresses itself in wide structural and functional differences, which, in general, are characteristic wherever found. The male is marked by larger size, more vivid coloring, greater aggressiveness and wider variation of temperament. Like all biologic formulæ, however, this one is subject to complete reversal in all features under some conditions. Despite all this gradation and reversal, the reality of sex characteristics exists. Moreover, it manifests itself as an all-pervading quality of the organism. There is to start with, the primary distinction which inheres in the two types of germ cells, accompanying which are the visible modifications of all parts of the body so commonly recognized. But beyond these obvious distinctions are underlying features which mark, often in clearly recognizable form, every cell of the body. The structure, as a whole, is characteristic because the units of which it is built have their own peculiar form. It is quite as correct, and by this token also, as incorrect, to speak of male cells as it is of male organs. Correctly the reference in each case would be to the male form of cell or organ.

Embryonic Differentiation of the Sexes.—When we come to inquire into the reason for this all-pervading sex difference in individuals we soon discover that it is a part of the general inheritance, by which we mean to say that what is in the molded aggregates of the million-celled body is there because it was

present in the single cell out of which all came. The details of this we will consider elsewhere. The proof of this assertion is furnished very beautifully by the cases of identical twins and quadruplets. There are two kinds of twins: those which come from two separate eggs and those which originate from a single ovum. The embryologic development of these two varieties has been studied, and shows clear evidence of their origin. In the opossum it has been demonstrated that four embryos arise from a single fertilized egg. If the later form of the body is due to the form of organization in the single cell from which it originated, then the two or four embryos coming from a single egg should develop into organisms of almost identical character. This, indeed, is what they do, as careful and detailed examination shows. Along with this practical identity of bodily form in the individuals derived from the single egg goes identity of sex. This can mean nothing else than the determination of the form of sexual expression at the time the embryo was established. If sex were a character subject to determination or modification from without, then there would be cases where the derivatives from the single ovum were unlike, but this does not occur. It is very striking and convincing to observe sexual uniformity in twins or quadruplets, but the evidence that sex is indeed an integral part of inheritance is overwhelming when, as in polyembryonic insects, hundreds of individuals are derived from a single egg and they are all of the same sex. For all such cases it is demonstrated that the form of sex manifested is due to the nature of the single fertilized ovum from which all the many individuals came, which is merely

another way of saying that it is inherited like all the manifold other conditions of the body.

MODIFICATIONS OF NORMAL SEXUAL DIFFERENTIATION

The fact that sex is determined at the time the embryo is formed indicates that its cause lies in the mechanism which is responsible for the control of all the characters of the body. It means that sex is not something apart, or in addition to, the other features of the body, but that it is integral with them and subject to all general laws of inheritance and development. While, therefore, it is to be expected that each embryo will be definitely male or female, where sexual differentiation is strong, there is no *a priori* reason why modification, combination, or reversal may not take place if the mechanism will permit it. Such departures from the rule of fixity and constancy are therefore not to be taken as evidence against the existence of an innate sex character any more than the facts of teratology are indicative of a lacking determinism in embryonic development. We would naturally expect, on this basis, extensive and varied modifications of the normal sexual differentiation, and such variations do occur. When properly investigated they are very helpful in explaining what we regard as normal conditions, as a consideration of some of these cases may show.

Free Martin.—For many years the existence of the imperfectly developed female in cattle, the so-called "free martin," defied explanation, but recently a careful embryologic study enabled F. R. Lillie to account for this strange sexual anomaly. The free martin is always one of twins, the other of which is

a male, and does not occur when both members are females. Evidently the presence of the male exerts some influence on developing female which modifies the normal expression of its sexual characters. This was found to occur by the partial union of the placental circulations of the two embryos, whereby certain substances, or hormones, characteristic of the male, were supplied to the cells of the female and by their presence modified the course of development. It is to be noted in this instance that the sex of the unusual individual was established at the time the embryo was formed, as usual, but that a secretion characteristic of male organization was potent enough to bring about some modification of normal development. This is an instance of sex modification, and not of sex determination, brought about by foreign substances.

Sex Reversal.—In recent years several authentic cases of sex reversal have been described in birds, where the individual, at first a functional female, becomes changed into an active male. This might be taken to signify that sex is not an innate character, but that it is a chance condition determined by external circumstances. If it is shown that an individual may at one time be a female and at another a male, it is clear evidence, in this case, that sex is not a fixed state of organization. Sex persists but its form is altered: the animal produces germ cells but they are sperm instead of ova, and the bodily features correspondingly change, for sex is a coordinated state of each cell in the body, primarily determined by the form of germ cell actively functioning. Of course this is not the only instance where a change in one part of the body

affects all the other organs. All the glands of internal secretion have this general influence. Disturbances in the thyroid may have marked effects upon the entire body. Disease of the pituitary may result in producing a giant out of an otherwise normal individual, and so on. It is, therefore, not strange that an alteration in the gonad should result in profound and appropriate changes in every part of the body. What is remarkable is that the type of germ cell should be reversed. In the case described by Crew a disease condition of the ovary resulted in its change to a sperm-producing organ. In the absence of any information regarding the changes brought about in the cells it is quite impossible to offer an explanation of such cases. In the light of what is known of other instances it must be assumed that an effect upon the nuclear mechanism is brought about by the neoplasm in the gonad, but what it is or how produced is unknown. This is only one of many cases where conditions external to the germ cells are known to produce alterations in the form of sex expression. Another case where a pathologic condition of the gonad affects sex characters, is the one reported by Smith, in which a parasite growing into the body of a crab causes the male to assume much of the appearance of the female.

Intersexes.—In organisms with glands of internal secretion a modification of the gonads may profoundly affect the whole organization of the body, so that the essential cellular nature of sex becomes obscured. In the insects such a system of internal modification is lacking and each cell of the body is in a measure independent. Whatever form of sex expression is thus imparted to the fertilized egg is carried unchanged

into all its descendants. In every part of the body the cells, after organ development is complete, take on the characteristic form which marks the sexual nature inhering in them. If the gonads of the opposite sex are transplanted into the body, the constituent cells remain unchanged. Sex in such cases is an unalterable characteristic established at the very beginning of the organism. Commonly, this is of the strictly alternative nature of male or female, but Goldschmidt and others have found that, in the gipsy moth, if the parents are of different races or species the normal alternative of extremes of sexual expression into male and female may be abridged or even reversed. The individuals thus produced are termed "intersexes," because they show a complete gradation of characters throughout the whole organism. It is important to note here that the degree of intergradation is a racial function, and is constant for any particular cross. Even in these cases, however, the sexual level set up at fertilization is maintained throughout the organism and is unalterable either by internal or external agencies.

Gynandromorphs.—Intersexes, although abnormal sexually, are homogenous in the degree of abnormality. As contrasted with these, the gynandromorphs present an individual heterogeneity. One part of the body may be purely male in nature while other portions may be female. Sometimes one-half of the entire body may be male, while the opposite is female. Almost any conceivable combination of the two sexes, consistent with developmental processes, may be found. Here again it is apparent that the inner organization of each cell is the determining factor in sexual expression, so

that of two cells lying side by side, one may show male features and the other female.

Lability of Sex.—As contrasted with instances of fixed and unchangeable sex levels instances of lability quite as striking appear. One of these is the marine worm, Bonellia, in which the female has a body an inch or more in length to which is attached a proboscis a yard long. The male, on the contrary, is a fraction of this size and lives parasitically in the uterus of the female. Dimorphism is striking enough here to suggest fixity, yet in the larval condition it appears that there is generally an indifferent stage at which time an individual may become either male or female. The history is curious and interesting. If the larvæ are kept separate they generally develop slowly into females, but if allowed to attach themselves to the proboscis of a mature female they become males. By removing these differentiating males at various periods Baltzer was able to get intersexes ranging from the female to male type, according to the length of attachment. It is of interest to note here that once a grade of sex differentiation has been reached, it becomes fixed and cannot be reversed. Thus, although apparently a very different condition from that of the insects, Bonellia shows a fixity of sex, but this is established later than the time of fertilization.

A very curious case is that of *Crepidula plana*, reported by Gould. In this mollusk all individuals are first males and later become differentiated into females. If, however, these early males, or even animals in the intermediate stage of sexual development, are kept near large individuals of either sex, completion of transformation is not carried out to the female

stage. A reversal from the definitive female state to that of maleness is not possible. Here, even in the presence of a high degree of lability, a final determination is reached which cannot be altered.

In all these cases, as indeed in all organisms, there are definite evidences of sex in some degree of differentiation. That is to say, sex is an inherent property of the organism, just as is irritability, contractility, or any of the other properties of protoplasm. Occasionally, though, there occur anomalous sexless individuals. These, of course, are unable to perpetuate themselves and are, in fact, mere accidents in nature. Such sexless individuals sometimes occur in polyembryonic insects like Litomastix.

GENETIC VIEW OF SEX

Extensive statistical studies on many forms of animals show that the normal proportion of males to females is 1 : 1. There are exceptions and modifications to this rule, but it is apparent that equality in numbers between the sexes is in some way maintained in reproduction. When a genetic parallel is sought it is found in the behavior of a character which is homozygous in one parent and heterozygous in the other. From this standpoint it would be expected that the hereditary mechanism of the germ cells should present a corresponding dimorphism. Before this genetic interpretation was conceived, the cytologic basis for sex determination and the equality of the sexes in numbers had been determined. In 1891 Henking had observed that in the spermatogenesis of a bug, Pyrrhocoris, the sperms are of two kinds, distinguished

by the presence or absence of a certain chromatin element, which is sometimes uncertainly referred to as a chromosome. The dimorphic nature of the sperm is merely described by Henking and no particular significance is attached to it. Except that it relates to a nuclear difference which presumably divides the sperm into two equal groups, the account of Henking does not differ from several other reported cases of sperm dimorphism.

In 1899 I described in the Orthoptera a similar case to that of Henking, but definitely identified the differential element as a chromosome, while Henking and others had considered it a nucleolus. The clear recognition of the differential element as a chromosome made it necessary to find an explanation which would be consistent with the part which the chromosomes were regarded as playing in inheritance. Briefly, the argument ran as follows: The chromosomes are the bearers of the hereditary determiners; there are two classes of sperms in equal numbers, with one chromosome as a differential; the only quality which divides the members of a species into two equal groups is that of sex; if both classes of sperm are functional, as they seem to be, the differential chromosome is the sex-determining element. This conclusion, which was published in 1901, was a purely logical one called forth by the circumstances of the case, and not brought forward as a theory of sex determination developed from a study of sex. It was a by-product in a cytologic study and resulted as a logical necessity in cell activities. In a few years it was found, in an extensive series of studies, mostly in this country, that a great many animals, both vertebrate and invertebrate, showed

the same phenomena in their germ cells. Stevens and Wilson demonstrated a modification of the Orthopteran conditions in which the differential chromosome has a mate, usually smaller, so that the question of difference in the two sperms is not that of presence and absence, but of one or another chromosome.

MODIFICATIONS OF BISEXUAL REPRODUCTION

Parthenogenesis.—In some groups of organisms the strictly bisexual method of reproduction is interrupted and the female takes over the whole task of perpetuating the species. This parthenogenesis is not an asexual form of reproduction, but only a modification wherein the male is suppressed in its operation, at least for a time. Among other objections to the chromosome explanation of sex determination, the cases of parthenogenesis were early instances, but, upon investigation, they have proved one of its strongest supports, for the chromosome behavior is strictly in consonance with the requirements of the unusual circumstances. When parthenogenesis alternates with the ordinary bisexual form of reproduction fertilized eggs produce females. It was asked, "If the two kinds of sperms are produced and thus determine sex, how is it that parthenogenetic females always result from fertilized eggs in such instances?" In aphids and other insects investigated it was found that the two classes of sperm are formed as usual, but that only the female-producing variety is functional. Fertilization therefore must result only in female production. But if the female has the full complement of chromosomes, how can it produce males, which have one less chromosome? Investigation of these cases

reveals that at the time of maturation, the egg, which is to produce a male, casts one entire chromosome into the polar body, thus bringing the number down to that characteristic of the male. The theoretic requirements are thus accurately met in these aberrant forms of sexual reproduction. A case of hermaphroditism alternating with separate sexes in the nematode, Angiostomum, receives a similar explanation. The parasitic hermaphrodite is female in its constitution, and results from the fertilization of an egg by a sperm from a separate male. In the production of sperm two sorts are formed as usual, but the male-producing variety is non-functional, so that again fertilization always results in a hermaphrodite.

Cytologically, the gynandromorphs are extremely interesting. Here, in one individual, are both male and female parts, even cells, sharply separated. If the chromosome hypothesis of sex is correct, then in these differentiated parts of the individual there should appear the correspondingly distinguishable chromosome groupings. This indeed is the case, and Morgan and Bridges in Drosophila were able to trace out these sexually different parts by studying gynandromorphs with sex-linked characters where it was possible to know the sex mechanism because of the existence of body characters associated with the sex-determining chromosome. There are several ways in which it is possible for an individual to have cells in its body which are of different chromosome constitution, but, so far as the result is concerned, it is a matter of indifference how this comes about.

In all these instances of unusual sex conditions it now ap-

pears that the chromosome mechanism is strictly correlated in its form and behavior, so that the relation between a certain chromosome and the characters that distinguish the sexes is now well established. Since this particular element has a distinctly differential effect, it would be reasonable to expect that its reaction would also be characteristic in relation to other cell parts and to outside agencies. It is most interesting to find through the work of Mavor with roentgen rays that this difference can be experimentally demonstrated. By subjecting Drosophila individuals with known sex-linked characters to the action of Roentgen rays and then breeding them, it is found that the x-chromosome is particularly susceptible. The determination is readily made by noting the associated body characters.

EFFICACY OF SEXUAL AND ASEXUAL REPRODUCTION

Sex undoubtedly is a biologic problem of the very greatest interest, but as yet it remains without a convincing solution. There is always the temptation to reduce it to one simple formula, but the chances are that it is very complex in its nature. Progress is made only by exploring all possibilities, and so here we must hope to come to a comprehensive understanding by building up from partial conceptions. Viewing the matter broadly, it is at once apparent that there are distinct advantages in the conditions of sexual over asexual reproduction. In the latter, definite limitations on continuity are imposed by the environment. Only the conditions which permit fairly continuous active functioning are adapted to direct reproductive processes. The existence of germ cells

which may be separated from the organism and survive periods of stress provides a means of perpetuating the species in adverse conditions. No two organisms react in precisely the same way to a common environment; therefore, their germ cells are not exactly alike. In the immense numbers of germ cells produced there are accordingly many slight differences developed, and, besides, cells from two different individuals must combine in order to produce a new individual. Thus there are set up many combinations which are tried out against the environment. Added to this is the fact that, in the production of germ cells, the parental contributions represented by the chromosomes are tested out against each other and then sorted out by kinds, so that all the possible combinations are made. In this step, internal reorganization of the cell mechanism occurs, and the result is later tested by the conditions under which the resulting organism must live. These various combinations of mechanism and experience provide both for a great number of variants of the common type of organization, and for the elimination of excessive variation in the type. Since in the nature of individuality there inheres this differential response to life conditions, sexual reproduction offers vastly greater possibilities of testing for varied adaptation than does direct reproduction.

Influence of Sex on Evolution.—All these are clearly evident conclusions and are true if both parents are of the same general nature, but in sexual reproduction there is added one more factor making for differential experience. Every function of the body is differently performed by male and female. As was pointed out in detail by Geddes and Thompson in regard to

metabolism, the male is strongly catabolic while the female is, *per contra*, anabolic, and these are characters which mark their germ cells correspondingly. In every other way the sexes differ, even down to most minute details of behavior. This is just what would be expected, for cytologic evidence shows that every cell of the body is characteristically different, and must function accordingly in the sex composites. In some way this bimodal reaction is bound up with the existence of a high degree of differentiation and specialization within the organism. The forms reproducing asexually have but one type of response to environment; sexual reproduction provides two, and these are tested, compared, and combined in each act of reproduction. In some way a higher degree of complexity and accuracy of function results. One might compare these circumstances with the speed and accuracy of movement shown by an organism with one leg compared with another having two. The results would be all out of proportion to the numerical difference. Possibly something more refined in the way of a parallel might be conceived in these terms. Let it be supposed that the members of a species are divided into two classes, one of which is colored red, the other blue, and that in a common series of light reactions the reds profit in one direction while the blues gain advantage in a complementary way. If in producing new individuals these different gains can be combined so that the next generation starts with even a slight advantage, in time a much more perfect light response would result.

But in all nature there is nothing like sex, and so no parallel will do more than suggest the part it plays in the infinitely

complex matter of developing an instrument of such delicacy and precision, for example, as the human mind through the manifold steps of decreasing fineness of mental processes that stretch down to mere reactions of lower organisms. Sex certainly is bound up in some way with this perfection of organization, and one of the most enticing problems of biology is the determination of this relation.

THE INHERITANCE OF ACQUIRED CHARACTERS

JOHN A. DETLEFSEN

Perhaps few debated questions of biologic science have been more fully discussed than the question of the inheritance of acquired characters, or, as it should be stated, the inheritance of acquired somatic modifications. For many years biologists felt free to assume such inheritance since the assumption was so simple and direct, and withal it seemed reasonable. The whole question has been intimately associated with the development of evolutionary theory. As early as 1875 Sir Francis Galton stated that the assumption was based on questionable evidence usually difficult of verification. About ten years later August Weismann denied all transmission of bodily modifications, in part because the evidence was of a flimsy, anecdotal sort, and in part because he could neither conceive nor find a mechanism whereby such transmission was possible. While the subject is still a matter of controversy, the question has more than a purely academic interest; for the relatively permanent effects of continued effort and training by ascendants on descendants, the possibility of transmitting an acquired immunity, and the like engage the interest of educators, sociologists, and physicians.

The inheritance of acquired somatic modifications is usually connected with Lamarck's explanation of evolution. Lamarck concluded that the effects of environmental agencies and the

effects of use and disuse of anatomic parts or physiologic functions were not only seen in the individual as immediate adaptive responses, but that such effects were transmitted, at least in part, to the progeny. While Darwin resorted in the main to a different type of explanation for evolution we also find Darwin sometimes approving some parts of the lamarckian hypothesis. After Weismann's critical and incisive examination of the lamarckian hypothesis, the theory was rejected by many as unsatisfactory, and the inheritance of acquired bodily modifications was usually thought to be impossible.

The cardinal features of Weismann's theoretic considerations which have persisted relate to the continuity and independence of the germ-plasm. The germ-plasm is continuous in the sense that it is supposed to be derived intact from similar germ-plasm of the preceding generation without elaborate differentiation and specialization. In other words, the germ cells are set apart in the earliest divisions of the embryo to give rise to similar germinal materials which are passed on again to succeeding generations. The somatic cells undergo differentiation and serve as a temporary vehicle for housing the immortal germ-plasm. The germ-plasm is independent in the sense that it is isolated and not in general contact with the somatic tissues; nor is it likely to be influenced by the stimuli which play on the body cells. Any circumstance which alters the body does not of itself modify the germ cells in a corresponding way simply because it modifies the body. Removing, mutilating, or changing cells or parts of the body does not produce correlated changes in the germ-plasm. The

inherited body characters are determined by the physical and chemical structure of the egg and spermatozoön from which that body arises, but the body does not in turn determine the structure of the germ cells which it will house. Thus there has been a tendency to regard the somatic cells and the germ cells as two separate entities. Therefore the Weismannian or neo-Darwinian regards all permanent racial changes as due to changes within the germ-plasm itself, but these changes are fortuitous and perhaps just as likely to take place in one direction as another. In any event, the changes in the germ-plasm are not determined by sheer modification of the body cells. As a formal helpful hypothesis Weismann's views have aided us in orienting ourselves, but his theories are not necessarily to be accepted as final.

Lamarck's theory has passed through vicissitudes. Its earliest reception was luke-warm, but an interest was stimulated by Spencer, Cope, Packard, and others. The resulting debates led to a general rejection of Lamarck's view and Weismann and the neo-Darwinians held the field almost undisputed. It must be admitted that the great majority of observations and experiments have rather favored Weismann's position. The question has always been one of unfailing interest, and recent observations and experiments have led to a reawakening of interest. There is also a feeling that natural selection alone acting on fortuitous germinal changes offers a formal but not a completely acceptable explanation of evolution, with its numerous manifestations of hereditary adaptations and high specialization.

The evidence bearing on the subject is drawn from (1)

the observations in the fields of embryology, paleontology, cytology, ecology and the like, and (2) the direct examination of experimental results. The inferences drawn from the former sources are based on circumstantial or indirect evidence; but those based on the latter are thought to be more direct and therefore more conclusive.

Observation and experiment have given ample evidence that organisms respond to their environment and that such responses are sometimes of an adaptive type. Thus increased friction or pressure leads to skin thickening, epidermal pads, and callosities. Some biologists have thought the repeated acquisition of callosities in many successive generations has led to racial or hereditary callosities. Darwin, for example, pointed out that the thickened epidermis on the soles of the feet in the human embryo might represent the inheritance of a repeatedly acquired callosity; for said Darwin (1883) "in infants long before birth the skin on the soles of the feet is thicker than on any other part of the body; and it can hardly be doubted that this is due to the inherited effects of pressure during a long series of generations." A similar case in the wart-hog was recorded by Leche (1902). This animal kneels on its fore-limbs and pushes itself with its hind-limbs as it digs with its tusks in the ground in search of food. Horny callosities protect the surface on which it kneels. Strangely enough, these are seen even in the embryo. Thomson (1910) commenting on this case says, "This seems to some naturalists to be satisfactory proof of the inheritance of an acquired character. It is to others simply an instance of an adaptive peculiarity of germinal origin wrought out by natural selec-

tion." Duerden (1920) in a recent lucid and suggestive paper showed that the unhatched ostrich embryo possesses sternal, pubic, alar, and median mesotarsal callosities. The first three of these occur in exactly those regions where they are useful to the daily habits of the ostrich as it rests on its sternum, and where they would probably develop in any event as individual adaptive responses, since a new lateral mesotarsal callosity which is not present in the embryo develops through daily habit when the chicks are a month or two old. Since the responsiveness of the skin to pressure appears adequate in developing the lateral mesotarsal callosity and thus meets the immediate individual needs, one may legitimately marvel why these anticipatory hereditary callosities appear in the embryo before any demand is made in the organism.

In investigating the evidence bearing on our question, we frequently find ourselves confronted by a disconcerting choice of explanations. One might argue that the habit had lead to the racial character, or that the character had first appeared and made the habit possible. From the neo-darwinian viewpoint, the ostrich might acquire somatic callosities during any number of generations, but these would hardly induce a germinal change leading to racial callosities; for a racial callosity would be due to a germinal variation in the "right" direction. Indeed there may have been several or many germinal changes inducing callosities; but in that event natural selection would be invoked to explain the persistence of the useful callosity. This is, however, a purely formal explanation, since the lateral mesotarsal callosity would seem to imply that no racial callosities are an absolute necessity for sur-

vival, and that individual adaptation would supply the ostrich with ample callosities when needed. What advantage in natural selection would an inherited callosity as a racial character have over an equally effective ontogenetic one? The shortcomings of natural selection do not make the neolamarckian explanation more acceptable; for the latter has not yet explained how the appropriate determiners for an ontogenetic character acquired by habit could become incorporated in the germ-plasm, and thus give rise to a phylogenetic character.

Other similar cases lead to the same sort of dilemma from which there is at present no completely satisfactory escape. In the human races, exposure to strong light leads to increased skin pigmentation or tanning as an adaptation to prevent injury to the living cells beneath. In general, the darker races inhabit the tropics; but we do not know whether they have become dark skinned because they inhabit the tropics, or whether as variations arose the dark skinned alone could successfully migrate to the tropics and survive. While we are reasonably sure that the individual becomes adapted to strong light by tanning, we are not inclined to admit that racial adaptation is dependent on this individual somatic adaptation—if we assume the weismannian viewpoint.

In studying the circumstantial or suggestive evidence, we soon learn that these alternative explanations are disconcerting and confusing. Whether we speak of the blind fishes of dark caves or modified appendages of aquatic mammals, or even of the instinctive habits and behavior of insects, birds, or mammals, we are usually left in a state of doubt.

The neo-lamarckian theory does not make clear how the appropriate determiners for a purely somatic character acquired by changes of habit, function, or environment can become incorporated in the germ cells. The neo-darwinian views do not explain the cause of any germinal variation; much less the occurrence of several, perhaps many, correlated germinal changes in the right direction, at the right time, and of sufficient magnitude to have survival value in natural selection.

Hereditary adaptations are not always simple matters and they do not necessarily arise in one way. It is reasonably clear that in some cases the structural changes appear first and their special use is a later acquisition, perhaps quite accidental and entirely unrelated to the original cause of the structural peculiarity. For example, the ground parrot of New Zealand, originally living on fruits and insects, became a predatory carnivorous pest with the introduction of sheep. It was really fitted for the latter mode of life, before its new food appeared. In other words it was "preadapted." However the evidence is not clear and cogent that "preadaptation" is always the rule. As in the case of pigmentation in the human races, we may state in a purely formal way and for the sake of simplicity of argument, that the germinal change preceded the situation we call adaptation. We may admit the usefulness and prevalence of ontogenetic adaptations, but point out that when the appropriate germinal change took place (fortuitously) the descendants were selectively endowed in that they did not depend on ontogenetic adaptation. However, we are still far from having proved the case.

The suggestive evidence from cytologic studies is often cited as bearing on our question. In *Ascaris megalocephala*, it has been shown that the two cells of the second cleavage mitosis are demonstrably different, for the discrete chromosomes of one blastomere stand out in contrast to the diminution of chromatin in the other blastomere. In each succeeding cleavage mitosis up to the fifth, one "undiminished" blastomere persists. After this the undiminished cell gives rise to the future germ cells. A few similar cases in some other Ascarids, and in the fly Miastor, are seized as fully sufficient evidence of the continuity of the germ-plasm. However, the distinction between body cells and germ cells is less sharply drawn at present. Indeed, it seems that there is some question as to a continuous unbroken stream of germ-plasm as such, and in any significant sense, from generation to generation. Certainly in plants, and in some lower animals, the sharp distinction between germ cells and body cells does not hold. Ordinarily we considered peritoneal epithelium as distinct somatic tissue; but Hargitt (1923) showed in *Diemyctylus viridescens* (amphibian) that germ cells may perhaps be derived from peritoneal cells. Janda (1912) found gonads regenerating from the peritoneal septa when the anterior segments of Criodrilus (oligochæte) were removed.* The production of germ cells may after all be a problem of differentiation and dedifferention. In any event the continuity of germ cells or germ-plasm has no imperative con-

* C. B. Davenport (1925) recently described the regeneration of ovaries in mice, and states, "There is, it may be concluded, no doubt that the ovary under favorable conditions may regenerate *de novo* from the old stalk or even from the peritoneum of the adult mouse."

nection with the independence of the germ-plasm, which is our present question.

After we have reviewed the suggestive or circumstantial evidence, we must frankly acknowledge it is more or less indirect, and does not constitute proof, as we ordinarily understand the word. In some cases the presumptive evidence for the inheritance of an acquired somatic modification may be strong, but we are still confronted by disconcerting alternative explanations. Obviously, disuse of an organ must accompany its phylogenetic or racial degeneration, while increased development makes increased use or new use possible; but which is cause and which is effect is exactly the crux of the argument. Hence, attempts have been made to solve the problem by direct experimental methods.

Perhaps most influences to which individuals are subjected under experimental conditions affect the somatic cells alone, but exert no demonstrable influence on the germ cells. It is usually conceded that docking dogs and sheep, dehorning cattle, circumcision and similar mutilations are pure somatic modifications which involve only body cells, and in no way modify inheritance, which is a matter of germ cells. Removing the tails of newborn mice for nineteen generations (Weismann, 1893) or removing the eye of 200 newborn rabbits over a period of six years (Mulder, 1897, quoted from Szily, 1924) were without hereditary effects. Roberts (1918) exposed fruit-flies with vestigial wings to high temperatures and found greatly enlarged wings which at times were fully developed and functional; but a restoration of normal temperatures led to the original vestigial winged condition immediately.

All such cases of somatic response without germinal effects constitute only a negative sort of evidence. The number of such individual cases may be high, and the obvious inductive inference may follow the premises; but in the inductive sciences the premises may be strictly true and yet the general sweeping conclusion may be false. All such direct somatic changes without visible germinal effects do not exclude the possibility that some kinds of somatic changes may have important germinal effects.

That the germ cells can be reached through the body was shown by Sitowski (1905, 1909). He fed the larvæ of the moth (*Tineola biselliela*) the fat-soluble dye, Sudan-red, and the coloring effects were visible in the adults, the eggs, and the larvæ of the next generation. Obviously this represents the mere mechanical transmission of a foreign substance, in which the fat was the vehicle, but it is not a true inheritance. However, it does show that the germ cells may be reached through the body.

We have seen that the somatic cells may be modified without germinal effects. The germ cells may also be effected directly without first modifying the soma, for experiments with various physical and chemical agents, such as temperature changes, *x*-rays, alcohol, and the like, give ample evidence of such possibilities. Tower (1906) claimed that temperature and humidity changes applied to the adult during the so-called sensitive period of germ-cell maturation gave rise to modified progeny without first inducing similar modifications in the subjects. Cole and Bachhuber (1914) used the ingenious method of mating to a female rabbit (at one and the same

œstrus) both a normal male and a male fed with lead acetate. The genetic characters of the parents were so chosen that the young from the treated and the normal control male could be identified. A similar type of experiment was performed with fowl. The retarded development of progeny from treated males suggested a definite effect of lead acetate on the germ cells. Stockard and Papanicolau (1916, 1918) subjected guinea-pigs of both sexes to alcohol fumes with little or no permanent effects on the adult; but the offspring and later untreated generations showed marked defects (less fertility, greater mortality, arrested development, defects of the central nervous system and eyes, and other anomalies). Recently Little and Bagg (1924) reported on the appearance of very striking defects in the F_2 and later descendants of mice exposed to light doses of *x*-rays. Brachycephaly, club-feet, eye defects, and other unexpected characters appeared. All such cases represent direct germinal response, but not the inheritance of any acquired somatic modification.

A few experiments have been recorded which are sometimes interpreted as cases of "parallel induction." This simply means that both soma and germ cells are independently modified by the same environmental stimulus, but always in such a specific manner that the new inherited character determined by the modified germ-plasm resembles the original somatic modification, although both somatic and germinal responses are quite independent of each other.

Standfuss (1898), for example, subjected the pupæ of *Vanessa urticæ* (a butterfly closely related to our common mourning-cloak) to freezing temperatures and found melanic

variations in the adults. Under normal conditions seven pairs of these melanic adults gave normal offspring, but four of the male offspring of an eighth pair were again abnormally dark. Fischer (1901) performed similar experiments on *Arctia caja*, the tiger-moth. Schröder (1903) subjected the pupæ of the currant-moth to high temperatures, with results similar to those of Standfuss and Fischer. A number of suggestions have been made to explain these results; but of all these, the studies of von Schuckmann seem to me to offer the most reasonable argument. Von Schuckmann (1909) found the normal untreated chrysalis to be more heavily pigmented than the adult, and this suggested that Standfuss', Schröder's, and Fischer's experimental treatment merely arrested development and perhaps caused some general germinal disturbance which again arrested development. Tower (1906), working with the potato beetle, reported that it was possible to dissociate the somatic from the germinal effect. He had found that (1) variations of temperature and humidity gave somatic effects alone, when applied to the pupæ; but (2) when the adults were exposed to the same experimental conditions only the germ cells were modified; (3) if the stimuli were applied to both stages, both the somatic and the germinal effects were visible and the results appeared like the inheritance of an acquired somatic modification. The first two types of experiment readily suggest that the results of the third admit of explanation on the basis of parallel induction. (Tower's experiments have been rather severely criticized and objections to his conclusions have not yet been reconciled.)

While this total number of experiments which might be adduced as evidence of parallel induction is very small and the correctness of the interpretation itself is still open to question, it is significant that Weismann hastened to invoke parallel induction, a clever device to save the original premise, the independence of the germ-plasm. This hypothesis has attracted a number of biologists, but the very meagerness of experimental data should prevent hasty generalization. Other biologists look on parallel induction as a fatal admission that germinal change may be guided by environment, even if it is independent of somatic change—which is for them the essential feature of lamarckism.

The usual concept of a true inheritance of acquired somatic modifications implies that the soma is first modified by the environment and that these effects are then passed on to the germ cells, modifying the germ cells in such a specific way as to produce a new inherited character resembling the original somatic modification. This hypothetic process has been labelled "somatic induction" to distinguish it from parallel induction. A number of experiments have been cited from time to time as proving the possibility of such somatic induction. For many years Brown-Séquard's experiments were cited in almost every discussion on the subject. The neo-lamarckian hailed them as decisive, while the weismannian explained them away by several different routes. This has been a common experience with experiments bearing on our question and perhaps means that the real facts and causes are imperfectly understood in many cases. Brown-Séquard had found that complete or partial section of or injury to the

spinal cord, sciatic nerve, or central nervous system was followed by epileptoid symptoms, various morbid states of the nervous system, and so forth; and that the offspring in some cases showed similar abnormalities. It has been pointed out that the guinea-pig is in any event predisposed to epileptoid attacks brought on by simple stimuli such as scratching an epileptogenic area; and moreover, that toxins from infection are not excluded. Occasionally some elements of the experiments are either ignored or attributed to "pure coincidence"—on the whole, unsatisfactory methods of explaining biological phenomena.

In recent years Kammerer (1911, 1924) has been more active and more frequently quoted than all other exponents of neo-lamarckism. His experiments are numerous. In a number of them he made use of the facility with which adaptive color changes or changes in habits of reproduction take place in amphibians and reptiles. For example, the European salamander (*Salamandra maculosa*) has an irregular and variable color pattern of yellow spots on a black background. By keeping it on a yellow background, a marked extension of the yellow pattern took place—a well-known adaptation for concealment. Now Kammerer reared part of the offspring of such individuals on a yellow background and part on a black background. In the former group he found an inordinate extension of yellow and in the latter group much yellow, and rather more than one might expect on a black background. These results might imply perhaps the ostensible persistence of a parental modification. Šećerov (1912) suggested parallel induction, on the ground that his experi-

ments showed that light penetrated through the body walls to the gonads. Castle (1923) attributed Kammerer's results to selection, for those animals which responded to the initial treatment were the very ones which had the genetic constitution to elaborate more yellow. Breeding from such would give yellower offspring. The environmental conditions in the experimental treatment merely revealed those individuals whose genetic potentialities would permit the greatest production of yellow pigment.

In all experiments dealing with the possibility of transmitting acquired somatic modifications, it is a common experience to find one generation of biologists explaining away the findings of the previous generation, especially when the apparent results fail to agree with certain general principles or theories which we have come to regard as firmly established (sometimes forgetting that they still remain theories). Some, who have regarded the prime question as settled, pay but little attention to Kammerer's numerous experiments. Others treat the results more seriously, but explain them as due to direct germinal response *with or without coincident somatic* modification, or due to the inadvertent selection of materials during the course of the experiment. And still others dismiss them because the records are too meager or corroborative experiments are lacking. One and the same experiment may be regarded as pertinent by one critic and irrelevant by another. We cannot solve our problem by comparing the predilections of the critics. We must, I think, frankly confess we do not know the real and complete explanation back of many of Kammerer's results. Much more detailed knowl-

edge is necessary before we shall be in a position to pass final judgment on this perplexing question.

A recent group of experiments by Guyer and Smith (1918, 1920) and continued by Guyer (1921, 1922, 1923) has attracted much attention to the question under consideration. After injecting fowl serum immunized to rabbit lens into female rabbits at about the tenth to fourteenth day of pregnancy, several young were born with unmistakable eye-defects, although there were no visible effects on the dam's eyes. The evidence suggested the possibility of breaking down the embryonic lens substance by the action of specific lens antibodies. The adult lens was uninjured because it was already cut off from the general circulation, but the embryonic lens could be attacked since it was surrounded by abundant vascular tissue at the tenth to fourteenth day of pregnancy. The defects consisted of lens opacity, cleft iris, persistent hyaloid artery, microphthalmia, anophthalmia, and the like. Similar defects also followed active immunization with rabbit lens substance directly injected into a pregnant doe (the 84 line). The most remarkable feature of these series of observations is the fact that the defects were certainly transmitted by inheritance, even through nine generations in some cases. When defective males were mated to normal females of unrelated strains the offspring were normal, but the defects reappeared in the second filial generation. In general, the defects acted like simple mendelian recessives, although they were neither simple nor regular, but rather variable in their expression.

It is still an open question whether Guyer's results repre-

sent parallel induction, or somatic induction, or neither. If the lens antibodies actually attacked the embryonic lenses and their germinal correlatives simultaneously, then we would have parallel induction; but if the disintegrating lens could produce its own auto-antibodies, which then attack the germinal correlatives, we might have somatic induction. Guyer reported that the serum of rabbits with hereditary defective eyes showed lens antibodies.* While it is true that Guyer regarded normal rabbits as stabile forms wholly unlikely to develop eye-defects unless deliberately produced as in his experiments, and while his normal controls failed to show eye-defects and such defects were also absent in the large colonies of other investigators and breeders with whom he was in contact, nevertheless a number of students have ventured to wonder whether the three lines (the 3A1 line, the 16A line, and the 84 line) from which the majority of hereditary defects took origin could not have been due to germinal changes quite unrelated to the experimental treatment—since after all the number of lines was not numerically great.†

* Guyer (1923) recently reported that lens antibodies were produced when rabbit lens was needled *in situ*. Furthermore defective-eyed offspring were obtained from such subjects, although Guyer conservatively stated in his recent presidential address before the American Society of Zoölogists (1924) that these particular cases of defects had not yet been demonstrated to be hereditary.

† In order to bring the discussion of Guyer's experiments up to date, mention of von Szily's criticisms should be made. von Szily (1924) pointed out that similar hereditary eye-defects in rabbits were recorded by von Hippel, von Szily, Hochstetter, and Koyanagi, and that these defects were not related to any experimental treatment. (I have likewise found such eye-defects in the white rat.) Szily also implied that perhaps all of Guyer's eye-defects were traceable to his ♂ 2, a normal buck used extensively in the experiments, but who was probably a heterozy-

The reappearance of a modification in several consecutive generations is sometimes confused with true inheritance, but the two are not necessarily identical because the reappearance may be due to the persistence of an unusual condition or an obscure environmental stimulus extending over a series of generations. Thus, an acquired modification due to an obscure infection may reappear in the progeny simply because they are reinfected rather than because the acquired modification has been inherited. The cases of persistent vestibular defects reported by Griffith (1922) now appear to me to be explicable in part on this basis. Griffith subjected albino rats to long periods of continuous rotation (up to one and a half years) by keeping them in circular pens turning at sixty and ninety revolutions a minute, some in a clockwise and others in a counterclockwise direction. Several weeks after removal from the rotating pens, a number of subjects developed a specific type of disequilibration, showing among other effects a peculiar twist or tilt of the head and permanent modifications in ocular after-nystagmus. Now

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gous carrier of eye-defects. Szily laid stress on the fact that Silfvost, and Findlay have attempted similar experiments with negative results. Since we now know that such hereditary eye-defects occur as mutations, the significance of eye-defects in Guyer's experiments becomes a question of probabilities, and instead of regarding such defects as "wholly unlikely" to occur without experimental treatment, we must solve the problem of what is the probability that eye-defects would be present as germinal characters in at least three or four unrelated individuals chosen among experimental subjects. To this question we have as yet no satisfactory answer. Szily's gratuitous supposition that all or most all Guyer's eye-defects might be traced back to ♂ 2 is merely convenient for his argument; but a genetic relationship between ♂ 2 (the male progenitor of the 3AI line) and the remaining lines of eye-defects has not been demonstrated.

in the normal rat, the ocular oscillations which follow a unit stimulus of twenty turns in ten seconds on the cyclostat (in either a clockwise or counterclockwise direction) last about ten seconds for animals over six months old. It varies inversely with age as I have since found, the greatest change occurring within the earlier months of life. (At thirty days it lasts about thirteen seconds.) The disequilibration which Griffith reported was specific inasmuch as long-continued clockwise rotation was followed by a left twist of the head and a very much reduced ocular after-nystagmus when the unit cyclostat stimulus was also in a clockwise direction; but after-nystagmus was normal when tested by a counterclockwise unit stimulus. Long-continued counterclockwise rotation gave the exact reverse picture. Putting these observations in tabular form in order to visualize and compare them easily, we have approximately the following:

Direction of unit cyclostat stimulus.	Character of ocular after-nystagmus.	
	With left head twist following long clockwise rotation.	With right head twist following long counterclockwise rotation.
Clockwise.....	Reduced to about one-half normal.	Normal.
Counterclockwise	Normal.	Reduced to about one-half normal.

The permanently reduced clockwise after-nystagmus following long-continued clockwise rotation and the analogus results from long-continued counterclockwise rotation thus gave the appearance of a permanent habituation. Furthermore,

Griffith claimed the progeny frequently showed similar cases of disequilibration, always specific and "regularly dependent on the direction in which the ancestors were rotated." No such subjects appeared in Griffith's large related control stock. Similar disequilibrated rats do occur, however, without any previous rotational history as shown by Casamajor (1914) and Detlefsen (1923). The obscure point in Griffith's findings that may have bearing on the question of inheritance of acquired somatic characters is the specific nature of the disequilibration. I was able to secure and test for after-nystagmus seventy-two cases of middle-ear infection in a colony of some 6,000 rats. Of these seventy-two, thirty-seven showed a right twist of the head, and thirty-five a left twist of the head. As far as external appearances (posture, head twist, position of eyes, and so forth) or modifications of normal after-nystagmus were concerned, all of those with the occiput turned to either the left or the right, as the case might be, were indistinguishable from Griffith's animals with a left head twist following clockwise rotation, or a right head twist following counterclockwise rotation, respectively. On the basis of 986 cyclostat tests in these seventy-two cases, the table on page 95 was prepared, giving the means and standard deviations for the length of ocular after-nystagmus in seconds following a unit cyclostat stimulus.

The essential similarity between Griffith's rotated specimens and my cases of labyrinthitis is apparent.

Any circumstance which violates the integrity of the left labyrinth gives a reduced clockwise after-nystagmus, and similarly for the right labyrinth a reduced counterclockwise

Direction of unit stimulus.	Average length of ocular after-nystagmus in seconds.	
	Occiput to left (left labyrinth violated, right labyrinth intact).	Occiput to right (right labyrinth violated, left labyrinth intact).
Clockwise.....	M = 5.36 σ = 1.32	M = 9.61 σ = 2.16
Counterclockwise.....	M = 9.56 σ = 2.21	M = 5.35 σ = 1.11

after-nystagmus. I have inactivated a single labyrinth by intense heat or by burring with a dental burr, and have found results qualitatively and quantitatively similar to these cases of a suppurative labyrinthitis. It is, therefore, reasonably clear that the specific individual habituation of Griffith's disequilibrated specimens is purely illusory and does not represent habituation in any real sense, but is dependent on the function of the individual labyrinth. Perhaps the cyclostat tests in these pathologic cases suggest the real reason back of any specificity (positive and complete association between direction of rotation and type of disequilibration) such as Griffith reported in his cases of immediate disequilibration following rotational treatment; for, if the right labyrinth is more sensitive to counterclockwise rotation in any plane (both with acceleration and retardation), then such long-continued counterclockwise stimulus should first break down the right labyrinth, and leaving the left labyrinth more or less intact would give the illusory appearance of permanent habituation since the left labyrinth is less sensitive to counterclockwise rotation. The cyclostat records would then show a marked reduction in length of

ocular after-nystagmus, exactly as they do in my cases of labyrinthitis. In my own rotation experiments using continuous intermittent rotation in a given direction (rotating one minute and resting one minute) over long periods of time and covering four generations, several such disequilibrated specimens have appeared. Five cases showed an association such as Griffith found between the type of rotation and the nature of the disequilibration, and one did not. While these numbers do not constitute proof in a statistical sense, they are not inconsistent with the foregoing suggestion.

If the permanently disequilibrated cases in Griffith's experiments owe their illusory appearance of permanent habituation to the residual effect left after the inactivation of a single labyrinth accompanied by infection, and if they do not represent true individual habituation, it is difficult to see how true racial habituation could arise from such antecedents. Griffith reported the continued appearance of specific disequilibration in the non-rotated descendants of rotated ancestors. We may legitimately suspect the transmission of infection by parents to offspring, but it should be stated emphatically that sheer reinfection does not explain the specific nature of disequilibration in the non-rotated progeny ("regularly dependent upon the direction in which the ancestors were rotated"). In this respect Griffith's observations stand unique and uncorroborated. My own records on the incidence of ear infection show that in a random group about 1 to 2 per cent. of our albino rats become disequilibrated and that the chances are even for infection on either side.

Many albino rats show pus in the bulla, without having the infection attack the inner ear.

No attempt has been made at an exhaustive list of all reputed cases of somatic induction. In many cases the available data are too meager to justify an estimate of their value, and discussion is futile.

SUMMARY

The evidence bearing on the inheritance of somatic modifications may be divided into two groups, according to the source. The circumstantial or suggestive evidence, taken from the fields of paleontology, embryology, ecology, and geographic distribution, still remains suggestive; for at present we can only offer fortuitous germinal changes followed by natural selection as a formal but not necessarily final and completely acceptable explanation of many hereditary adaptations and cases of high specialization. Where racial or hereditary differences, which distinguish two distinct groups living under different environmental conditions, are of the same order as the somatic differences readily produced within a given race by these distinct environmental conditions, the apparently logical conclusions suggest the inheritance of a somatic modification. However, when we put the matter to an experimental test, the evidence is not so clear. No group of experiments has been carried far enough to convince many impartial and conservative biologists that somatic induction is possible. It is perhaps conceivable that our experiments do not duplicate the exact and necessary conditions which may have been effective over many genera-

tions during the course of evolution. While we are quite justified in being unusually skeptical and in demanding rigid proof because so many reputed cases have been either disproved to be "somatic induction" or have been more acceptably interpreted in other ways, we should nevertheless keep an open mind on the question. While no student of evolution doubts the occurrence of germinal variations, and while natural selection is a self-evident condition of living organisms, much remains to be discovered and elucidated by intensive biologic study on the *modus operandi* of evolution.

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HEREDITY IN RELATION TO CANCER

MAUD SLYE

The problem of definitely establishing the inheritability or non-inheritability of any disease or pathologic condition is a difficult one, because it is very difficult to isolate completely the single condition under study.

Perhaps nowhere else in the entire medical field, and certainly nowhere else in the field of heredity, has there been such readiness to form and express a judgment on so slight a scientific basis, as in the question of the relation of heredity to pathologic conditions. For example, hundreds of cancer patients in the hospitals, perhaps most of them, can give no history of cancer in the family; we therefore conclude that cancer is not hereditary. Hundreds of tuberculous patients may give a family history of tuberculosis, and we conclude that tuberculosis is hereditary. Neither conclusion has any scientific justification on such a basis.

We are only on the threshold of the study of relationships between heredity and pathologic conditions. Indeed it is not many years since practically all students of heredity concerned themselves with such externals as those of color, spotting, size, shape. Very few adequate studies have as yet been made of the relation of heredity to disease, or to health, but these are problems which are susceptible of isolation and intensive study in the laboratory, and of definite

proof. Exact facts regarding the relation of heredity to each disease should be the basis for both prevention and treatment, since such facts will necessarily establish certain fundamentals of etiology.

It is with the effort to establish the fundamentals of the nature and behavior of cancer that these studies of the relation of heredity to cancer have been pursued for thirteen years, since the inheritance behavior of any living tissue is its biologic fundamental.

TECHNIC

The materials used for these studies consist of a pedigreed stock of mice in my hands for many years. To this stock, built up in every ramification in this laboratory, no outside material has ever been added, except occasional new strains of Peromyscus, wild house mice, and Japanese waltzing mice. These new stocks were fully analyzed and pedigreed before their use in these studies.

The routine of the laboratory maintains the most perfect hygienic conditions; all utensils and food are as nearly as possible sterile. All infections, vermin, and parasites are excluded so far as can be done, and it is a notable fact that the more perfectly the infections and parasites are excluded, the higher is the tumor rate in the laboratory, since the parasites bring in many fatal infections which kill off the mice before they reach cancer age.

The tumors under study are not grafted nor in any way experimentally produced. They are spontaneous neoplasms, arising in the natural life of the animals exactly as man's

spontaneous tumors arise, without experimental procedure of any sort, except that of selective breeding.

THE LAW OF HEREDITY

One of the facts consistently demonstrated in these studies is the inheritability of resistance to cancer, and of susceptibility to cancer.

The more profound and biologic aspect of the demonstration has not been fully grasped, and in the opinion of certain medical authorities, the demonstration of the inheritability of susceptibility to cancer in mice (which is now quite generally conceded in the scientific world) has no bearing on the question of the inheritability of susceptibility to cancer in man. It has, therefore, seemed advisable to re-emphasize the more fundamental aspect of the matter at this time.

Underlying all behavior in the organic world there is biologic law. Of many of these laws and their ramifications we have, in all probability, no knowledge whatever. But there is one whose fundamental principle is clear, and that is the law of heredity. Having the facts of this most fundamental and most potent of all biologic laws, next to the laws underlying life itself, we continue very largely to ignore it.

The dictionary gives some such definition of heredity as this: "The law according to which plants and animals inherit and transmit from generation to generation certain characteristics or tendencies." But if we give it its full biologic definition, we must say: Heredity is the force which makes and holds together the genus and species. It determines that birds shall have wings and a special chest capacity

for flight; that they shall have a bill, wide vision on all sides; and for the specific bird, it determines a certain plumage and a certain song, as of the robin, or the blue bird, or the thrush. It determines that the frog shall have a special breathing apparatus to function on land or in the water; and for the specific frog, as the bull-frog, that he shall have a certain coat color and pattern, a given size, a given call. It goes even deeper than this, and determines that the human embryo, beginning with a single cell, like any unicellular animal or plant, divides in the same way, and in its complex cell division and differentiation recapitulates in hurried fashion the history of organic evolution.

Let me here state what I conceive to be the biologic law of heredity, the law common to all life: *that which goes into the germ-plasm must come out in the offspring.*

I must ask you to conceive of this simple law as being as ironclad and as immutable as any elementary law of physics, or any elementary law of chemistry. If acid is added to metal, a fixed reaction occurs inevitably. What is put into the germ-plasm will come out in the offspring just as inevitably.

Now the most striking characteristic of natural law is that we cannot break it. We can study it, learn to understand it and work with it, or we can ignore it and combat it and be broken by it; but we cannot break it or change it. It is this very immutability that holds the organic world together.

The law of heredity is a general law; not one law for a mouse and one for a man, but one common law of heredity, applicable equally to the seed of a geranium, to the ovum of a guinea-pig, or of man.

The progress of evolution reveals the constant and unbroken control maintained by the law of heredity, in that man, the latest product of evolution, starts with a single cell, recapitulates in his embryonal development the history of organic evolution, and in his turn sets off the single cell (the germ-plasm) made of the stuff he received from his ancestors and no other; and he puts into it the identical material, which in its turn again divides, and in its embryonal growth briefly recapitulates organic history, until in time it becomes the finished example of the species. Each individual is made of the material received from his ancestors: in his general build, in his length of leg, in the shape of his nose, in the color of his hair, in the kind of kidney, the kind of liver, the kind of epithelium, the kind of connective tissue, and the kind of endothelium.

He starts with a vague nose shape, but it will grow into the nose shape of his ancestry; he starts with tiny legs, but they will grow to the inherited length. He inherits a liver, which will in time react, like the livers of his ancestors, to the same causes. He inherits also a type of epithelium and of connective tissue, which will in time react, like the epithelium and connective tissue of this ancestors, to the same causes.

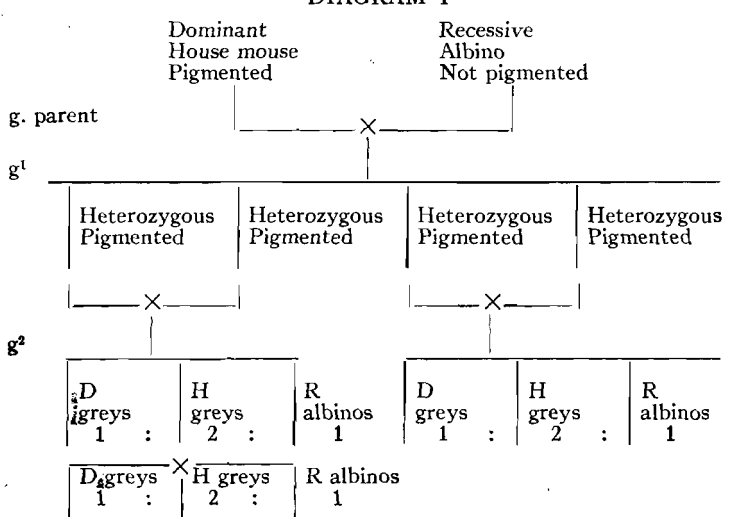
In 1865 Mendel worked out with garden peas, the best study of the method of heredity that we have ever had. Later, and following him, Cuénot and others worked it out with mice, and it worked with mice exactly as it worked with peas.

Now it is vastly farther in the scheme of evolution from peas to mice than it is from mice to man. Mice are mammals like man; their structure is similar to that of man. Their organs are like man's, arranged in the same relation to each

other, made out of the same types of materials, functioning in the same way for the maintenance of the organism. If I cut a mouse's arm, it bleeds like man's, and then regeneration sets in, as it does in man; the edges draw together, the epithelium proliferates, scar tissue is formed, which eventually either in part or wholly is absorbed. The process is identical with that of man's tissues, functioning like those of a man, just as the geranium stock does if you cut it. The law of heredity transmits a type of protoplasmic behavior down the full line of evolution, so that similar tissues function in the same way because they were derived from a common ancestry. If we do not accept this, we must discard the theory of evolution, for this is the heart of the theory of evolution.

Mendel's Law.—The method of heredity as worked out by Cuénot, following Mendel, is this:

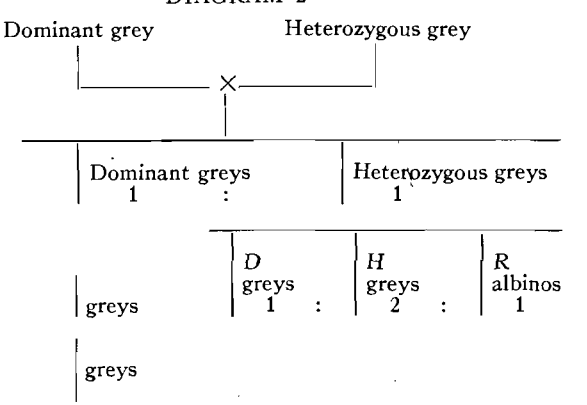
DIAGRAM 1



If a pure-bred house-mouse (grey) is mated with a pure-bred albino, the first hybrid generation will all be grey; that is, pigmentation is dominant over albinism.

If now any two of these heterozygous greys are mated (that is, carrying potentially both greyness and albinism), the second hybrid generation will show three types of offspring: dominant greys, heterozygous greys, and recessive albinos. The dominant greys, if bred together, will breed true, producing only dominant greys. The recessive albinos will breed true, producing only albinos; while the heterozygous greys, which carry potentially both albinism and greyness, will, if bred together, behave just as did the first hybrid generation heterozygotes in heredity, and yield three types of offspring: dominant greys, heterozygous greys, and recessive albinos.

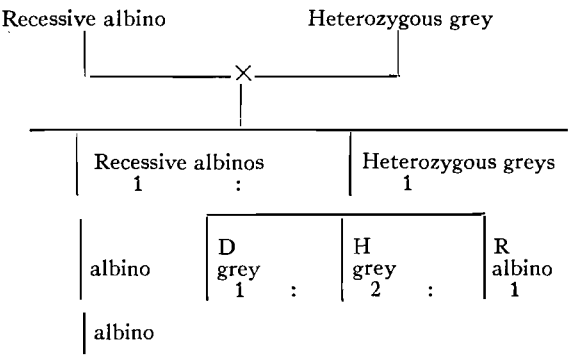
DIAGRAM 2



If a dominant grey is mated with a heterozygous grey, the first hybrid generation will yield two types, dominant greys and heterozygous greys in the proportion of 1 : 1. The

dominant greys, if bred together, will breed true, but the heterozygous greys, if bred together, will behave just as the first generation hybrid heterozygotes did in heredity, that is, they will yield three types of offspring: dominant greys, heterozygous greys, and recessive albinos in the proportion of 1 : 2 : 1.

DIAGRAM 3



If a heterozygous grey is mated with a recessive albino, the first hybrid generation will yield heterozygous greys and recessive albinos in the proportion of 1 : 1. The albinos, if bred together, will breed true. The heterozygous greys, if bred together, will again give three types of offspring: dominant greys, heterozygous greys, and recessive albinos in the proportion of 1 : 2 : 1.

If two pure-bred albinos are mated, the offspring will all be albinos (whether the mating is inbreeding or hybridization), that is, there will be a complete lack of the pigment-making mechanism. Pigment is an absent character in these individuals. It did not go into their germ-plasm and they cannot transmit it to their offspring. If only albino mice are

allowed to breed, the pigment-making mechanism will be lost for mice, and cannot be recovered, and there will thereafter be only albino mice. Albinism is a recessive. Pure-bred albinos cannot transmit the dominant.

Now if the same pure-bred albino, into whose germ-plasm no pigment-making mechanism entered, is mated with a grey house-mouse, into whose germ-plasm the pigment-making mechanism did enter, we shall get in the first hybrid generation heterozygous greys; that is, pigment-making is dominant over the lack of pigment-making, therefore, the mice are grey. But while the pigment-making mechanism entered the germ-plasm from one parent, from the other side there entered the absence of the pigment-making mechanism. Since both of these unit characters went into their germ-plasm, both of these characters will come out somewhere in the offspring.

The Unit Character.—A unit character is to heredity what an electron is to chemistry; incapable of analysis, it segregates out and is transmitted as such.

When we are dealing with a complex organism like a man or a mouse, there is a multiplicity of these unit characters which have gone into his germ-plasm from his ancestors, and which get into all possible combinations. For example, there is a tendency to a heavy and a tall skeleton; a tendency to a particular length in the limbs; a tendency to blackness in the hair with a tendency to curliness of hair; a tendency to a certain kind of liver, which will tend to a certain type of epithelium with a tendency to a certain type of behavior. These are all unit characters.

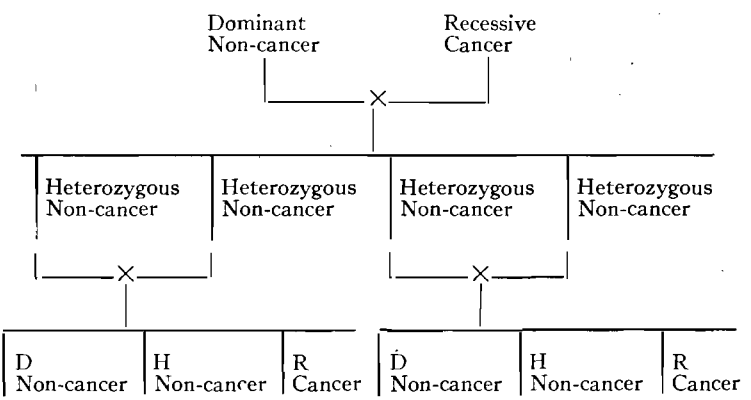
Every organism, then, is a synthesis of unit characters which cannot be correctly interpreted or manipulated in experimental work with accurate results, until it has been analyzed into these component unit characters. Until the truth of this fact has come home to the experimental biologist, pathologist, bacteriologist, physiologist, and student of therapy our results are certain to be invalidated by artifacts.

If animals bought in the market are used for the study of even a simple problem, they may be worthless until they are analyzed, because some of them may be pure bred while others will certainly be heterozygotes in every character in which they can be tested, and they will not behave alike in any given experiment, since they have not the same unit characters and the same tendencies. There is no biologic control in the experiment until each animal to be used has been analyzed.

Application of Law of Heredity to Cancer in Mice.—I proceeded then to study the inheritability of cancer in this way, making a biologic analysis of stock by hybridization and by inbreeding, and I found, equally by the method of hybridization and by inbreeding, that if two mice with carcinoma of the lung (primary or secondary) are mated, a strain of 100 per cent lung-tumor mice can be extracted from them. Or, by mating two mammary gland carcinomatous mice a strain of 100 per cent mammary gland carcinomatous mice can be extracted. That is, both in inbreeding and in hybridization, susceptibility and non-susceptibility to cancer behave like unit characters: they segregate out and are transmitted as such.

I tried also the test of hybridizations of cancer mice with absolutely non-cancerous mice. By a cancer mouse we mean a mouse whose ancestors had spontaneous cancer, into whose germ-plasm a tendency to spontaneous cancer entered, and who himself has cancer. By a non-cancer mouse we mean one which came from wholly non-cancerous parentage, into whose germ-plasm there went resistance to cancer.

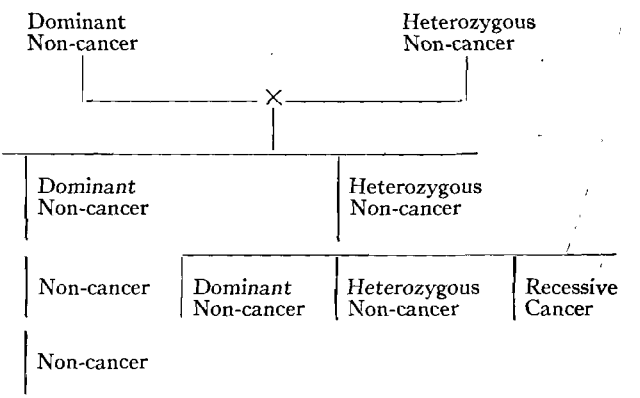
DIAGRAM 4



If a pure-bred, non-cancerous mouse is mated with a cancerous mouse, the first hybrid generation will all be non-cancerous. If now any two of these heterozygous non-cancerous mice (that is, carrying potentially both non-cancer and cancer tendencies) are mated, they will yield in the second hybrid generation three types of offspring: dominant non-cancer mice, heterozygous non-cancer, and recessive cancer mice. The dominant non-cancer mice, if bred together, will breed true; the recessive cancer mice will breed true, but the heterozygous non-cancer mice, if bred together, will yield three

types of mice just as the first hybrid generation heterozygotes did, namely: dominant non-cancer, heterozygous non-cancer, and recessive cancer mice.

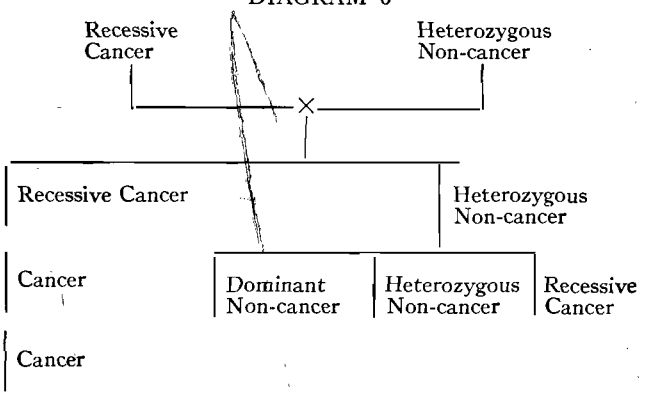
DIAGRAM 5



Again, if a dominant non-cancer mouse is mated with a heterozygous non-cancer mouse, the result will be, in the first hybrid generation, dominant non-cancer mice and heterozygous non-cancer mice about in the proportion of 1 : 1. The dominant non-cancer mice will breed true, but the heterozygous non-cancer mice will, if bred together, behave in heredity just as the first hybrid generation heterozygotes did and yield three types of offspring: dominant non-cancer, heterozygous non-cancer, and recessive cancer.

Again, if a recessive cancer mouse is mated with a heterozygous non-cancer mouse, the result will be, in the first hybrid generation, recessive cancer and heterozygous non-cancer. The recessive cancer mice, if bred together, will breed true, but the heterozygous non-cancer mice, if bred together, will

DIAGRAM 6



again yield three types of offspring: dominant non-cancer, heterozygous non-cancer, and recessive cancer.

The mice used in these experiments are all analyzed individuals, whose tendencies and heredity behavior can be predicted. If a pure-bred cancer mouse is mated with an analyzed pure-bred, non-cancer mouse, into the common progeny of these two there go: a tendency to cancer, and a tendency to the absence of cancer; and the first hybrid generation can, and infallibly does, transmit both tendencies. But susceptibility to spontaneous cancer is recessive to resistance, and so the first generation shows none of it, and in all my experience never has shown it. But the tendency to cancer segregates out, and in the second hybrid generation it appears again, in the same organs and in the same tissues of those organs which showed the ancestral tumors.

GENEOLOGIC TABLES

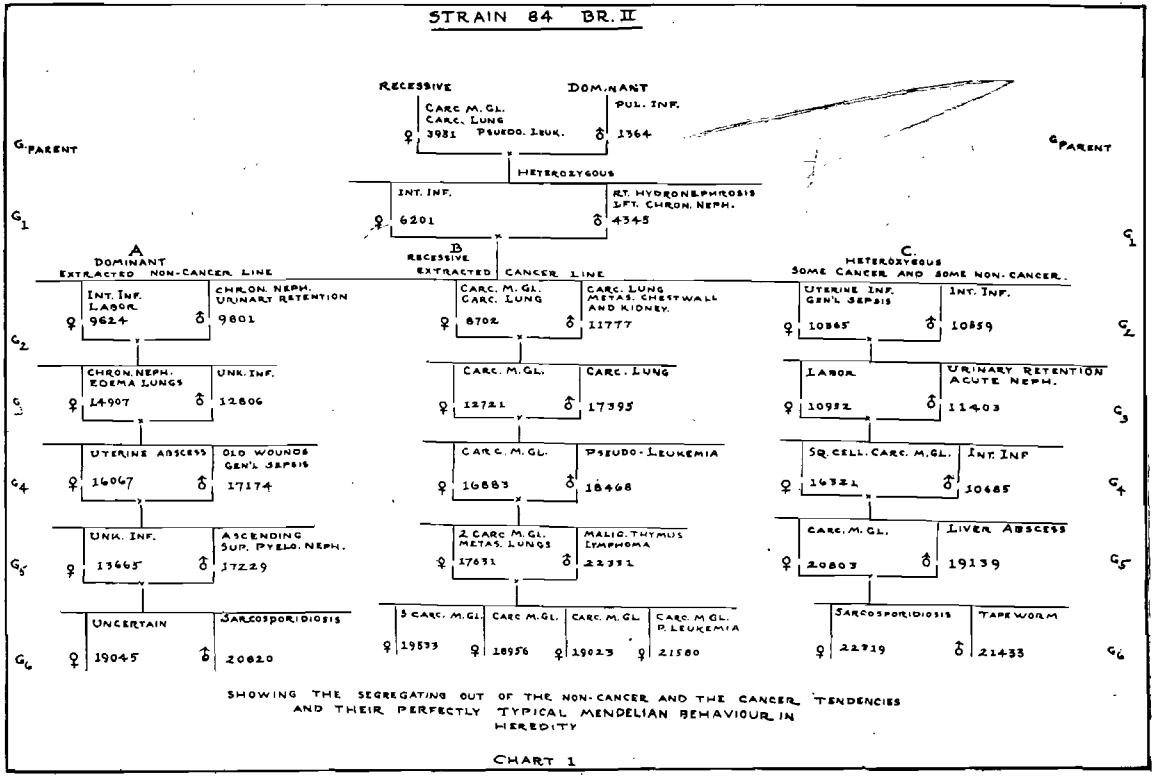
Chart 1, showing three lines derived from strain 84, branch 2, is perfectly typical. The parent female 3931 died of car-

cinoma of the mammary gland, carcinoma of the lung, and pseudoleukemia. She was *hybridized* with the absolutely non-cancerous male 1364, who died of pulmonary infection. In accordance with the mendelian expectation from such a cross, no cancer appears in the first hybrid generation (cancer is recessive to non-cancer). For the parents of this branch of the family, female 6201 and male 4345, both heterozygotes, were selected.

There was extracted from this hybrid-cross three lines of mice: the dominant A, which, neither in direct descent nor in any accessory fraternities, ever showed one case of neoplasm, malignant or benign; the recessive line B, 100 per cent malignant disease, and the heterozygous line C showing both cancerous and non-cancerous individuals. The chart shows how the same types and locations of neoplasms as were bred into the strain with parent female 3931 segregate out and are transmitted as such wherever tumor occurs, both in the recessive, 100 per cent cancer line B, and the heterozygous line C; namely, carcinoma of the mammary gland, carcinoma of the lung, pseudoleukemia, and its closely related tumor type, thymus lymphoma.

It is interesting to note that in the animals of this stock, chronic leukemia and pseudoleukemia (alymphatic leukemia, not lymphogranulomatosis) have occurred only in the cancer strains and have behaved as if they were true neoplastic diseases.

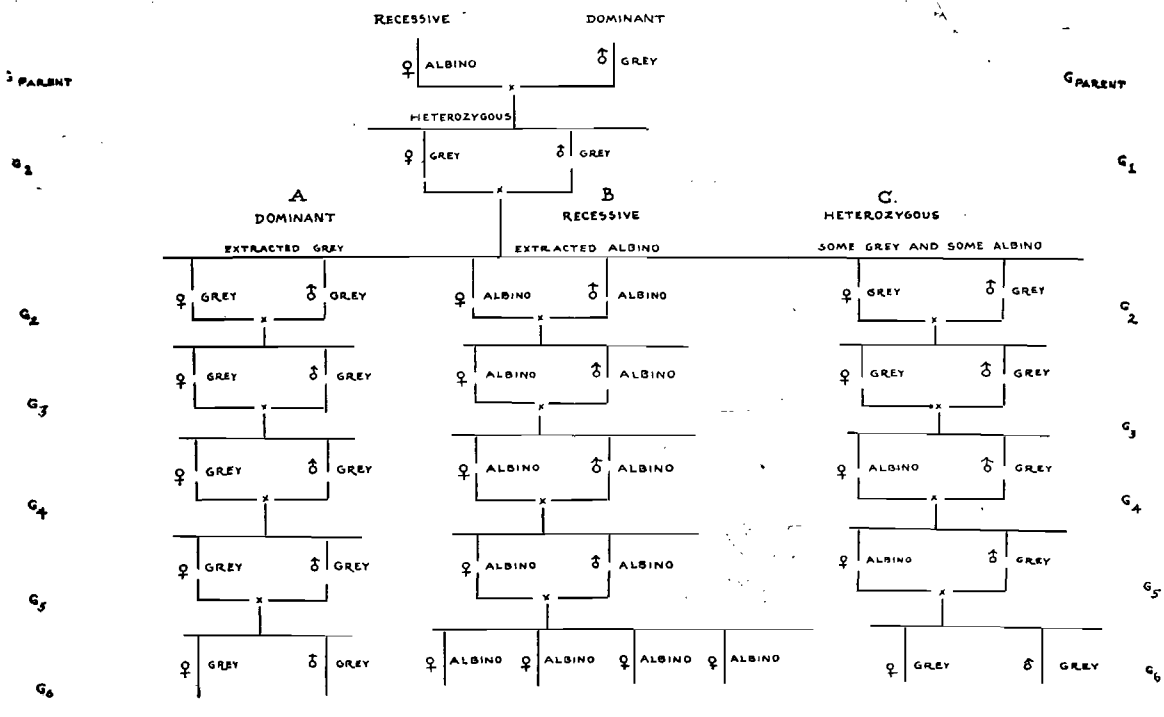
Chart 1, then, shows the segregating out and the transmission, as such, of the non-cancer and the cancer tendencies, as well as the tendency to a specificity of tissue type (which



SHOWING THE SEGREGATING OUT OF THE NON-CANCER AND THE CANCER TENDENCIES AND THEIR PERFECTLY TYPICAL MENDELIAN BEHAVIOUR IN HEREDITY

CHART 1

MENDELIAN EXPLANATION CHART



SHOWING THE SEGREGATING OUT OF THE PIGMENTATION AND THE NON-PIGMENTATION TENDENCIES AND THEIR PERFECTLY TYPICAL MENDELIAN BEHAVIOUR IN HEREDITY

locates the neoplasm in a certain organ), and their perfectly typical mendelian behavior in heredity as unit characters.

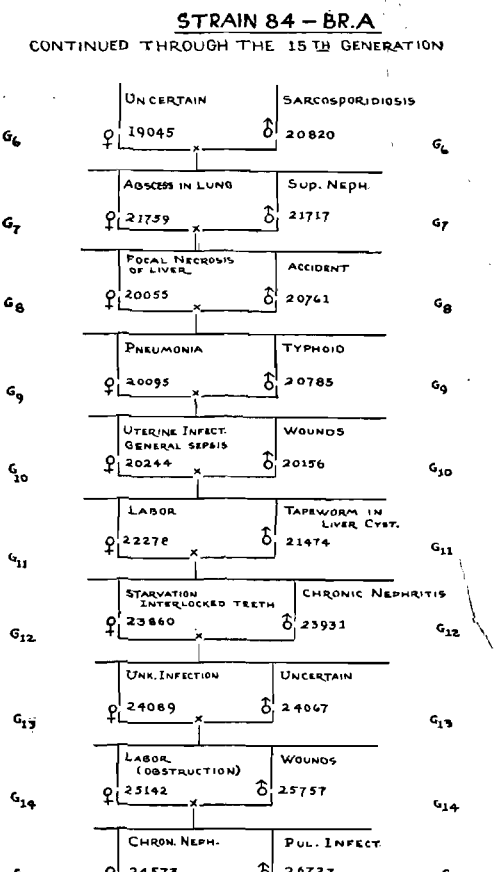


CHART 3

How exactly this follows the mendelian expectation is shown in *Chart 2*, which gives the classic behavior when a

hybrid-cross is made between the recessive albinism and the dominant pigmentation. Here also three lines are extracted, individual for individual, parallel with those shown in Chart 1, namely: first, a dominant line A, in which albinos never occurred either in the direct descent or in the accessory fra-

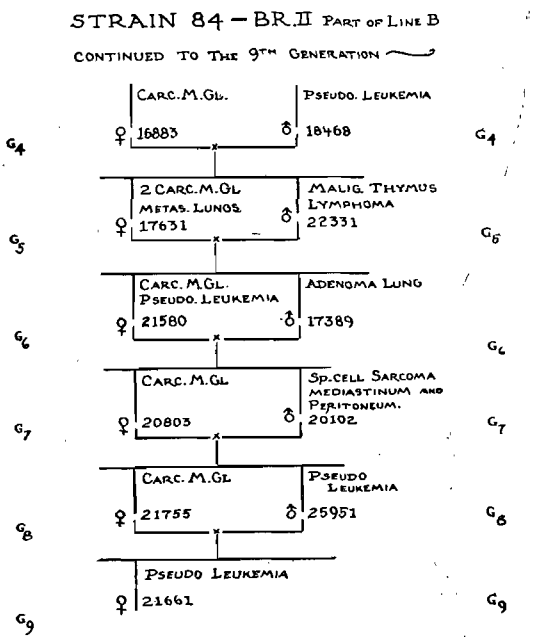


CHART 4

ternities; second, a recessive line B, 100 per cent albinos, in which no pigmented individual ever appeared; and third, a heterozygous line C, showing some albinos and some pigmented mice.

Chart 2, then, shows the segregating out and the transmis-

sion, as such, of the pigment-making tendency and the lack of the pigment-making tendency, and their perfectly typical mendelian behavior in heredity as unit characters. That is, the pigment-making tendency and the non-pigment-making tendency behave in the matter of heredity just as did the cancer and the non-cancerous tendencies shown in Chart 1.

Chart 3 continues part of line A extracted from strain 84, branch 2, *through the fifteenth generation without the occurrence of a neoplasm of any sort.* This shows the absolute segregating out and transmission as such of the non-cancerous tendency. When a non-cancer line has once been extracted, spontaneous neoplasms have never occurred in such a strain again throughout my entire observation, unless cancer has again been hybridized in from an outside source.

Chart 4 continues strain 84, branch 2, line B, through the ninth generation. This is the 100 per cent cancer line extracted from this same cross. It shows how the types and locations of the neoplasms occurring in this line of the strain are the same as those bred into it in the original cross from female 3931, namely, carcinoma of the mammary gland, carcinoma of the lung, and pseudoleukemia, with its closely related tumor type, thymus lymphoma. Female 21580 (generation 6) shows the carcinoma of the mammary gland of her grandmother and the pseudoleukemia of her grandfather. It is interesting to note also the sequence here of pseudoleukemia and thymus tumors through six consecutive generations, following the selection of male 18468 as the parent male in generation 4. The original parent female 3931 (Chart 1) had pseudoleukemia along with carcinoma of the mammary

gland and primary carcinoma of the lung. Male 20102, in generation 6, had a spindle-cell sarcoma of the entire mediastinum and of the peritoneum. This single case of sarcoma

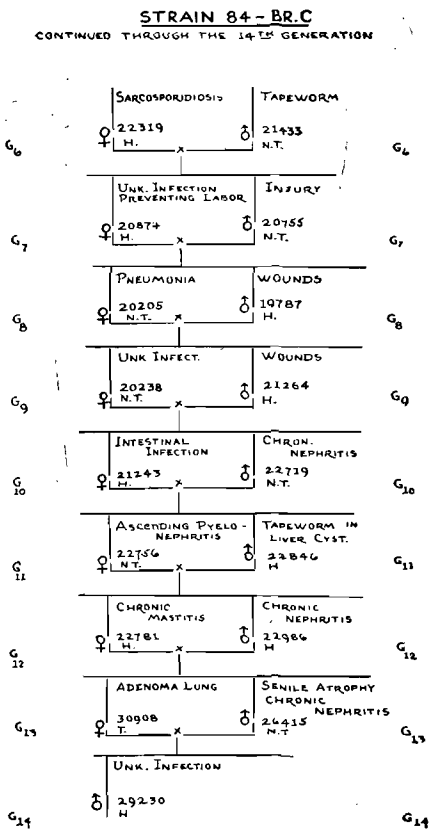


CHART 5

was derived from an ancestor several generations antecedent to female 3931, the parent of strain 84.

Chart 5 continues line C of this same strain through the fourteenth generation. This is the heterozygous line. By

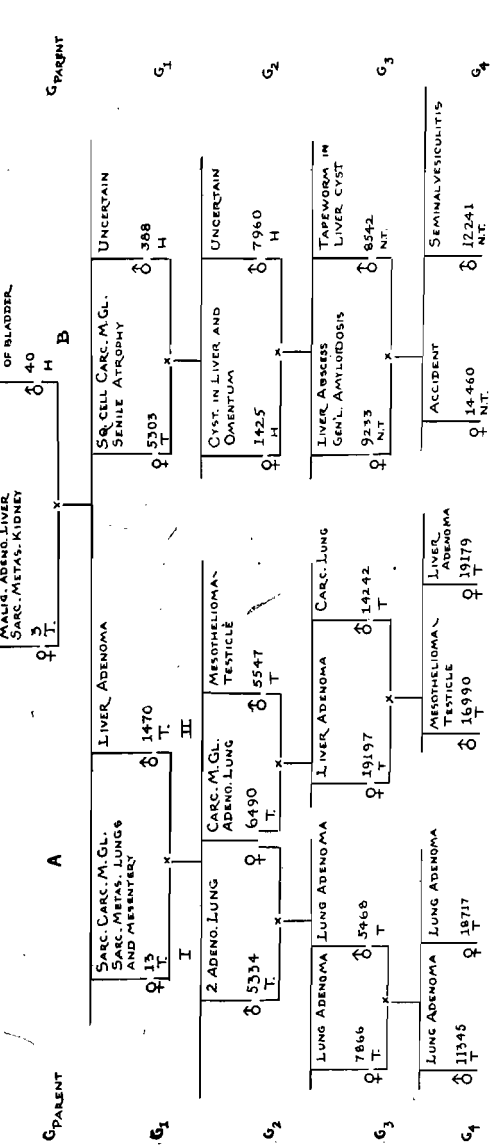

PART OF STRAIN 53
G PARENT
A
B
G PARENT
G1
G2
G3
G4
I
II
SARC. CARC. M. GL. SARC. METAS. LUNGS AND MESENTERY
♀ 13 T.
LIVER ADENOMA
♂ 1470 T.
SARC. CARC. M. GL. MALIG. ADENO. LIVER. SARC. METAS. KIDNEY
♀ 3 T.
CYST IN VICINITY OF BLADDER
♂ 40 H
SQ. CELL CARC. M. GL. SENILE ATROPHY
♀ 5303 T.
UNCERTAIN
♂ 388 H
2 ADENO. LUNG
♂ 5334 T.
CARC. M. GL. ADENO. LUNG
♀ 6490 T.
MESOTHELIOMA TESTICLE
♂ 5547 T.
CYST. IN LIVER AND OMENTUM
♀ 1425 H
UNCERTAIN
♂ 7960 H
LUNG ADENOMA
♀ 7866 T.
LUNG ADENOMA
♂ 5468 T.
LIVER ADENOMA
♀ 19197 T.
CARC. LUNG
♂ 14242 T.
LIVER ABSCESS GEN'L. AMYLOIDOSIS
♀ 9233 N.T.
TAPEWORM IN LIVER CYST
♂ 8542 N.T.
LUNG ADENOMA
♂ 11345 T.
LUNG ADENOMA
♀ 18717 T.
MESOTHELIOMA TESTICLE
♂ 16990 T.
LIVER ADENOMA
♀ 19179 T.
ACCIDENT
♀ 14460 N.T.
SEMINAL VESICULITIS
♂ 12241 N.T.

CHART 6

the continued selective breeding of a heterozygous individual with a non-cancerous mate (as indicated by H and N. T. in the chart) all occurrence of neoplasms was held off until the thirteenth generation. Here, by the mating of two mice heterozygous to lung tumor, lung tumor occurred in the thirteenth generation, the parents concerned being female 22781 and male 22986. By the right selective breeding in any heterozygous line, neoplasms can be made to occur or can be held off at will.

Chart 6 shows part of strain 53, line A branching into two extracted 100 per cent cancer families, and line B, from the same parents, developing into a 100 per cent non-cancerous family. The heterozygous line is not shown in this chart, for lack of space. In line A, family 1, a 100 per cent lung adenoma family is being extracted, by the selection as parents of the family, of two mice with lung adenoma, namely, male 5334 and female 6490; while in family 2 of the same line, adenomas of the liver and mesotheliomas of the testicle are the prevailing tumors, there being four adenomas of the liver in the ten individuals forming the direct descent of these five generations.

In line B after the first hybrid generation (female 5303 with a squamous-cell carcinoma of the mammary gland), there was no further appearance of tumor. By the continued selection of analyzed non-tumorous individuals after the second filial generation, all neoplasms were completely ruled out of this branch of the strain.

Female 13 of filial generation 1, line A, had a sarcoma-carcinoma of the mammary gland like her mother, female 3,

with secondary sarcomas in the lungs and mesentery. With her secondary lung tumor she was able to start a 100 per cent lung tumor line, the secondary lung tumor being as efficient

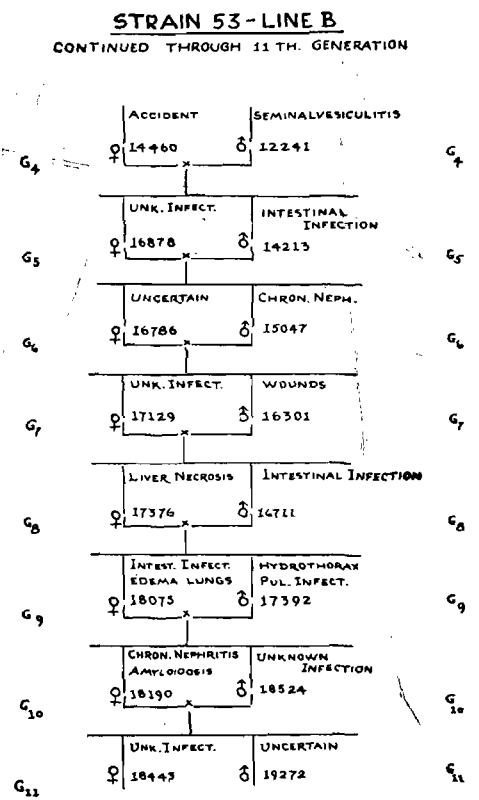


CHART 7

as a primary lung tumor in transmitting lung tumor potentiality.

Cyst and abscess formation are prevalent in line B of strain 53, although in no case do these cysts or abscesses lead

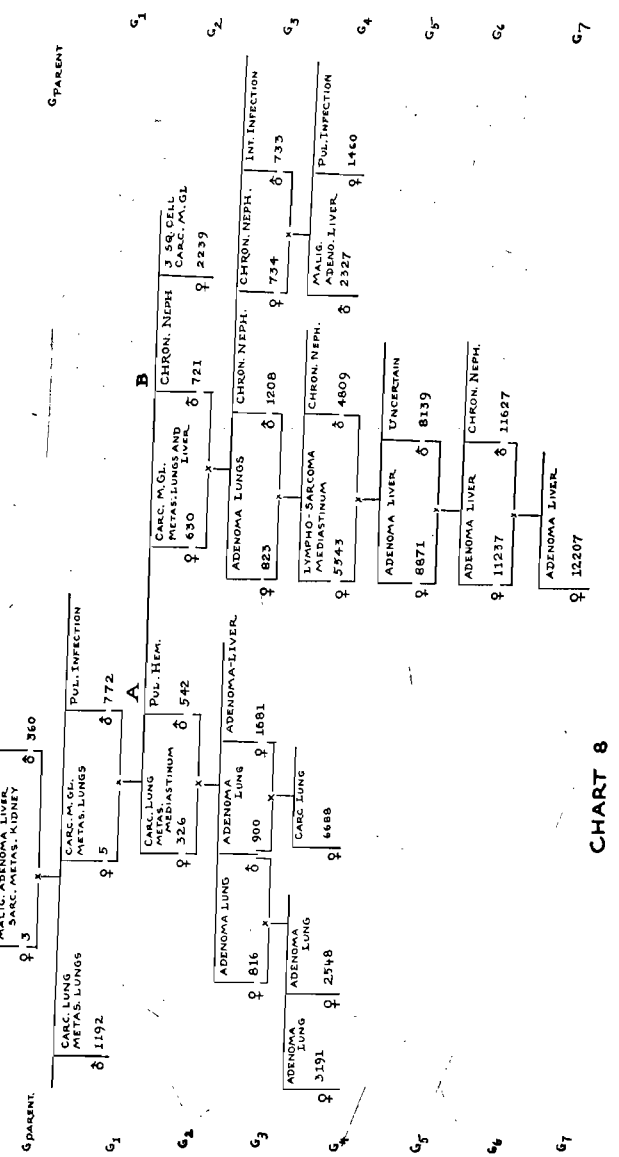

PART OF STRAIN 215 AND SOME DERIVATIVES.
G PARENT
SARC. CARC. M.GL. MALIG. ADENOMA LIVER. SARC. METAS. KIDNEY
♀ 3
UNCERTAIN
♂ 360
CARC. LUNG METAS. LUNGS
♂ 1192
CARC. M.GL. METAS. LUNGS
♀ 5
PUL. INFECTION
♂ 772
A
CARC. LUNG MEDIASTINUM
♀ 326
PUL. HEM.
♂ 542
ADENOMA LUNG
♀ 816
ADENOMA LUNG
♂ 900
ADENOMA-LIVER.
♀ 1681
ADENOMA LUNG
♀ 3191
ADENOMA LUNG
♀ 2548
CARC. LUNG
♀ 6688
CARC. M.GL. METAS. LUNGS AND LIVER.
♀ 630
CHRON. NEPH.
♂ 721
B
3 SQ. CELL CARC. M.GL.
♀ 2239
ADENOMA LUNGS
♀ 823
CHRON. NEPH.
♂ 1208
CHRON. NEPH. INT. INFECTION
♀ 734
♂ 735
LYMPHO-SARCOMA MEDIASTINUM
♀ 5543
CHRON. NEPH.
♂ 4809
MALIG. ADENO. LIVER.
♂ 2327
PUL. INFECTION
♀ 1460
ADENOMA LIVER.
♀ 8871
UNCERTAIN
♂ 8139
ADENOMA LIVER.
♀ 11237
CHRON. NEPH.
♂ 11627
ADENOMA LIVER.
♀ 12207
G1
G2
G3
G4
G5
G6
G7

CHART 8

PART OF STRAIN 338 — BR. II A — WITH PART OF ANCESTRY

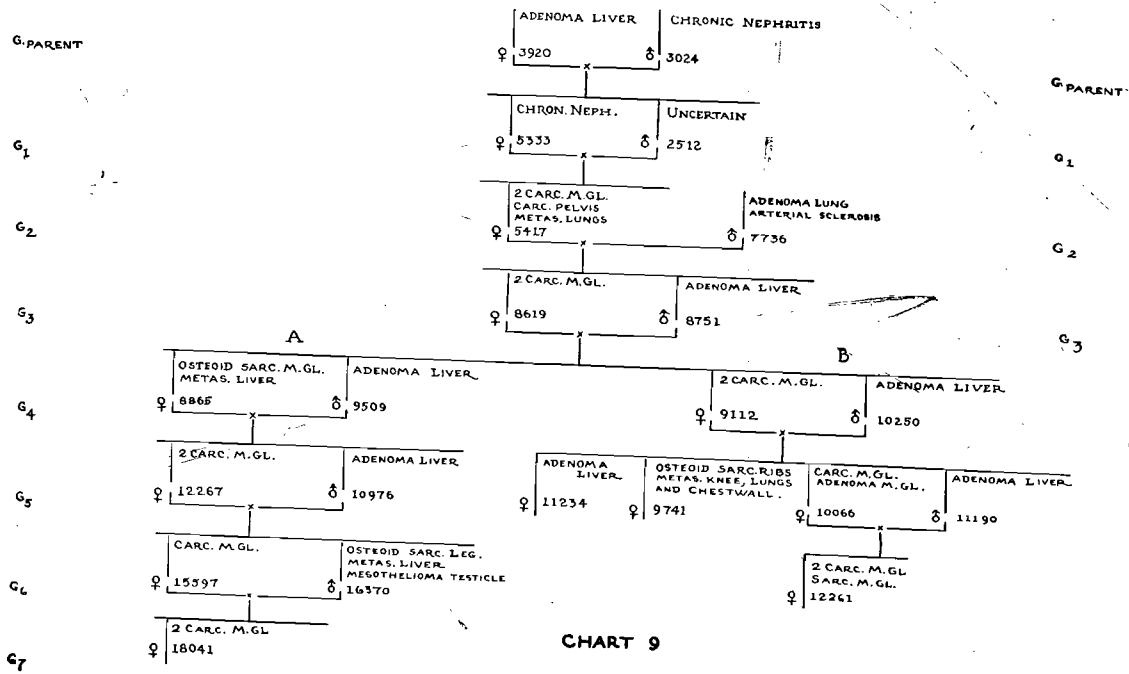


CHART 9

to tumor formation in this family. The offspring is made of the identical material of the germ-plasm of its ancestry, and its tissues behave in the same way.

Chart 7 shows line B of this strain continued through the eleventh generation without the occurrence of neoplasms. Never, either in the direct descent or in any accessory fraternity, did a neoplasm of any kind occur in this branch of strain 53 after the neoplastic tendency had once been bred out from the second filial generation.

Chart 8 shows part of strain 215 and some derivatives. A 100 per cent lung tumor strain is extracted in line A from female 5 with secondary carcinoma of the lung. A 50 per cent liver adenoma strain is extracted in line B. Strain 215 was made by the mating of female 3, who had a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver, and sarcoma metastasis in the kidney, with male 360, who was proved heterozygous to lung and mediastinal tumors. The chart shows how the different types and locations of neoplasms introduced by these two parents segregate out and are transmitted as such in the succeeding strain.

Charts 9 and *10* show part of strain 338, branch 5, with partial ancestry, and its offspring carried through the ninth generation. The original ancestor of this strain also was female 3, already referred to in Chart 8. She had a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver, and metastatic sarcomas of the kidney. There is a striking outcropping of liver tumors in this strain. The different unit characters, sarcoma, carcinoma, and specificity of liver tissue get into all possible combinations in the strain,

so that even in the small number of individuals represented in these two charts, carcinoma of the liver, sarcoma of the liver, both primary and secondary, and adenoma of the liver are found. That is, the carcinoma tendency segregates

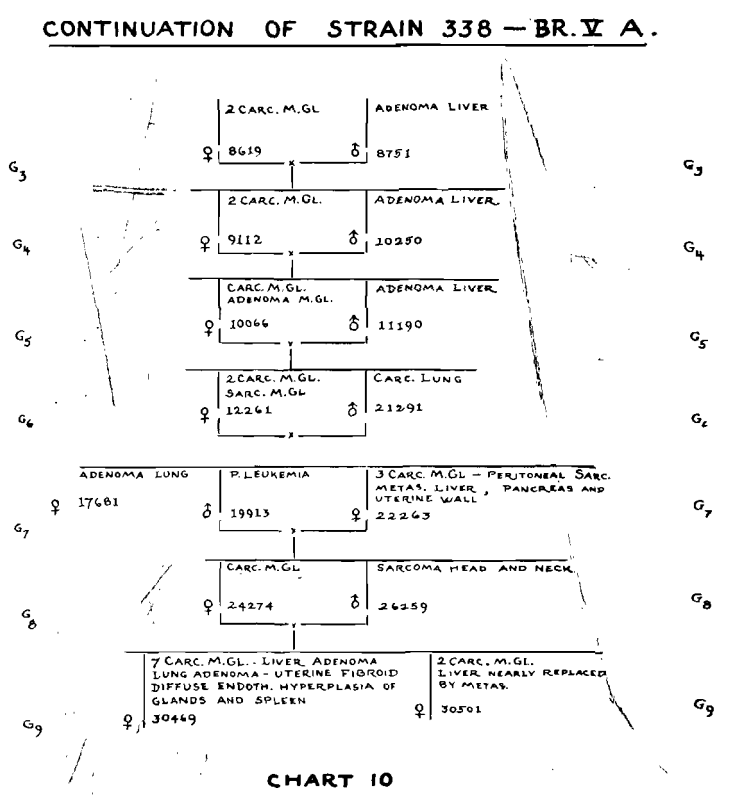


CHART 10

out and is transmitted as such. The sarcoma and adenoma tendencies act similarly. A specificity of liver tissue which will insure its yielding to neoplasms, segregates out and is transmitted as such, and is therefore a unit character.

PARTS OF STRAIN 48 AND 292

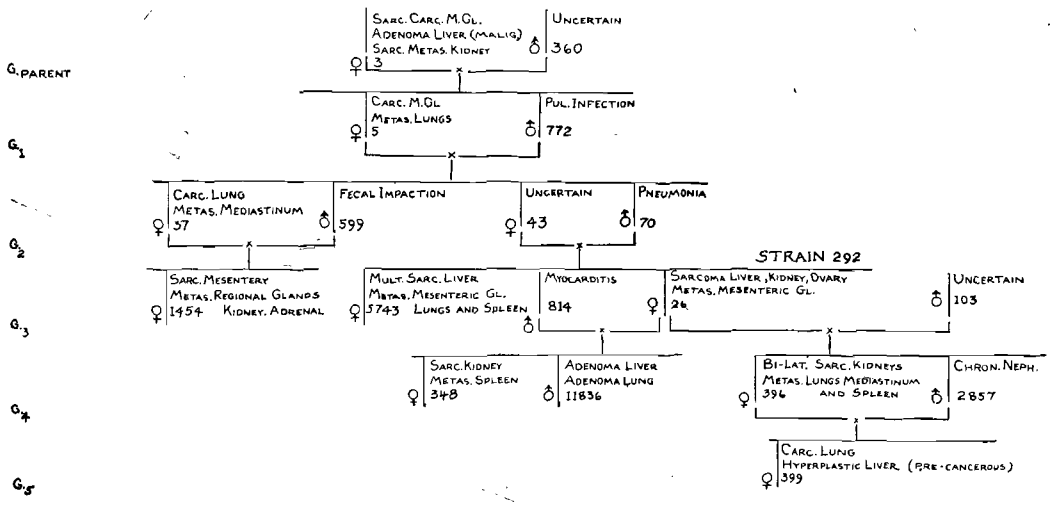


CHART 11

Chart 11 shows parts of strains 48 and 292. These are two strains derived from the same original mating as was strain 215 (Chart 8), that is, female 3 (with a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver, and a metastatic sarcoma of the kidney) and male 360, who introduced carcinoma of the lung and mediastinum. Here again the particular types and locations of tumors introduced by the parents have segregated out and been transmitted to the resulting strains, both as primary and as secondary neoplasms.

In the third and fourth hybrid generations, the outcropping of sarcoma, both primary and secondary, is shown in females 1454, 26, 348, and 396. Liver tumors derived from female 3 also occur in these strains, as shown in females 5743 and 26 and in male 11836. There is also a "precancerous" liver in female 399. Here also lung tumors, derived from male 360, occur: primary in female 37 and 399 and in male 11836, and secondary in females 5, 5743, and 396.

Secondary carcinoma of the mediastinum is seen in female 37, and secondary sarcoma of the mediastinum in female 396; secondary carcinoma of the lung in female 5, and secondary saroma of the lung in females 5743 and 396. There are three cases of secondary sarcoma in the spleen in females 5743, 348, and 396. Rarely in this stock, except in strains derived from female 3, have there been any tumors of the spleen either primary or secondary.

Here, again, after the first hybrid generation, mammary gland tumors disappear, another indication of how these unit characters segregate out. The mammary gland tumors

preponderated in other strains derived from the same mating. The dominating tumors, both primary and secondary, in these strains are in the liver, kidney, spleen, mesentery, lungs, and mediastinum. These were the neoplasms deliberately bred for in these strains.

In these strains, then, female 3 introduced:

1. Primary carcinoma of the mammary gland, in female 5.
2. Primary adenoma of the liver, in female 399 and in male 11836.
3. Primary sarcoma of the liver, in females 5743 and 26.
4. Primary sarcoma of the kidneys, in females 26, 348, and 396.
5. Secondary sarcoma of the kidneys, in female 1454.
6. Secondary sarcoma of the spleen, in females 5743, 348, and 396.
7. Primary sarcoma of the mesentery, in female 1454.
8. Secondary sarcoma of the mesentery, in females 1454, 5743, and 26. Parent male 360 introduced:

1. Primary lung tumors, malignant and not yet malignant, in females 37 and 399, and in male 11836.
2. Secondary lung tumors, in females 5, 5743, and 396.
3. Secondary carcinoma of the mediastinum, in female 37.
4. Secondary sarcoma of the mediastinum, in female 396.

Here again, the secondary tumors, although they are much fewer, arise in the same organs as do the primary.

Female 3 is listed in these charts as having a sarcoma-carcinoma of the mammary gland. This tumor was unquestionable carcinoma in some parts and apparently sarcoma in other parts. There has been considerable difference of

opinion concerning these mixed tumors. Slye, Holmes and Wells, Loeb, Lewin, Bashford, Woglam, and some others diagnose them as such, while LeCount, Ewing, and others consider them to be entirely carcinomatous, with pressure distortion of the cells simulating sarcoma in some areas.

The biologic evidence of the work in this laboratory unquestionably supports the opinion that there are these mixed tumors. Female 3, with such a tumor, has unquestionably transmitted carcinoma in every strain into which she has been hybridized; and she has equally certainly transmitted sarcoma in some branch of every strain into which she has been crossed—Charts 1, 2, 4, 5 (female 3 shown in ancestry charts 6 and 7), 8 (same parentage as Charts 6 and 7), and Chart 9.

I have preferred the term "sarcoma-carcinoma" to represent this type of tumor because, according to the biologic evidence, it is not a sarcomatous carcinoma nor a carcinomatous sarcoma, but rather a sarcoma plus a carcinoma, each type of tumor being transmitted separately as such. Biologic evidence, as manifested in heredity behavior, is too fundamental to be ignored.

Chart 12 shows part of strain 73, which was derived from the same female 3, mated this time with male 30. Male 30 came from a strain carrying tumors of the lung, mediastinum, and diaphragm, and was proved heterozygous to tumors of these organs, having been tested in various crosses.

The son of this mating, Jap W. F., died before necropsies were made, and consequently the cause of his death is not known. He was crossed with a Lathrop silver-fawn female, who also died before necropsies were made. Their offspring, however, are shown in two branches, A and B.

PART OF STRAIN 73

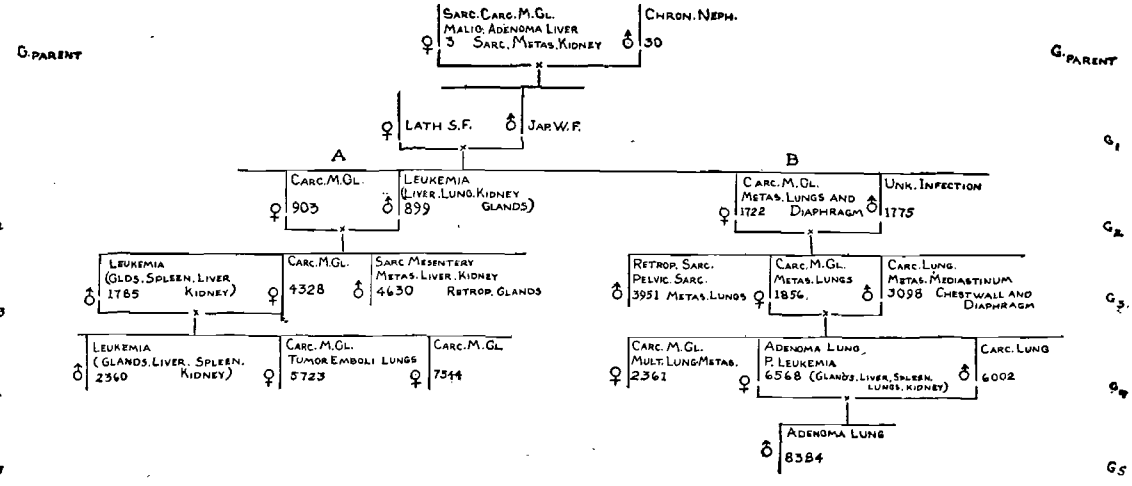


CHART 12

The chart shows how in branch B, every mammary gland carcinoma metastasized in the lungs; even the retroperitoneal and pelvic sarcomas (male 3951) did so. With the exception of male 1775 this branch shows 100 per cent of lung tumors, primary and secondary. Two generations showed metastasis to the diaphragm, female 1722 and male 3098.

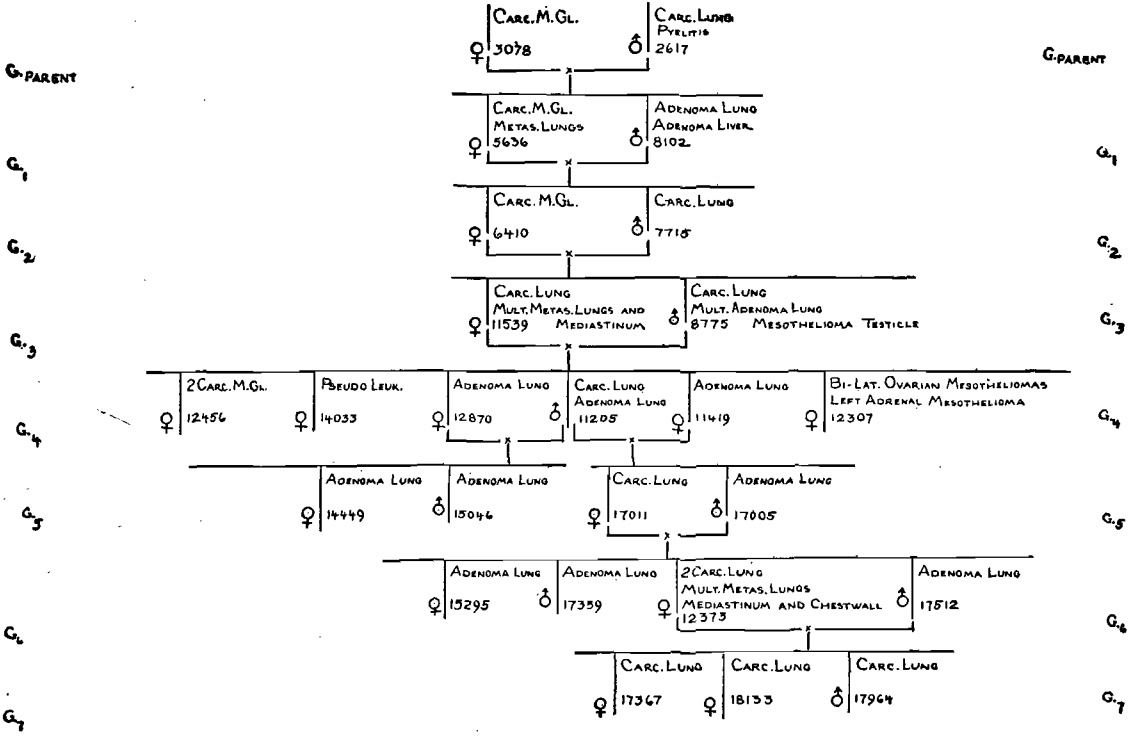
On the other hand, in branch A, carcinomas of the same type and of older and larger growth failed to metastasize in the lungs (females 903, 4328, 5723, and 7544). In female 5732, although the mechanical basis for lung secondaries was present in multiple tumor emboli throughout the lungs, no lung tumor developed. The sarcoma of the mesentery in male 4630 metastasized in the liver, kidneys, and retroperitoneal glands, but not in the lungs.

There were three consecutive generations of leukemia in this strain, in males 899, 1785, and 2360. Although the lung is one of the principal organs for leukemic infiltration, in males 1785 and 2360 there was no filtration in the lungs, while in male 899 the lung infiltration was very slight. On the other hand, the marked leukemic infiltration in this family was in the same organs in which the tumors of the parent female occurred, that is, the liver and kidney. The metastatic tumors, also, in this family were in these same organs.

In branch B, however, the 100 per cent lung tumor strain, female 6568, who had pseudoleukemia along with an adenoma of the lung, showed marked infiltration of pseudoleukemia throughout the lungs.

In branch B all tumors metastasize in the lungs, and pseudoleukemia picks out the lungs predominantly; while in branch

PART OF STRAIN 522 WITH PARTIAL ANCESTRY



A, the tumors of the same type in the same organ and of older and larger growth fail, in every case, to metastasize in the lungs. Even the leukemic infiltration fails to invade the lungs in this branch.

Chart 13 shows strain 522, female 5636 with a secondary lung tumor (g^2), mated with male 8102 with a primary lung tumor, producing a 100 per cent primary lung tumor strain (center of the chart). The pseudoleukemia in this 100 per cent lung tumor strain, female 14033, showed marked infiltration in the lungs.

From these charts, which are perfectly typical, it is evident that individuals with secondary tumors in any given organ seem to be as potent as individuals with primary tumors in that organ, to transmit by heredity primary tumors in that organ.

Chart 14 shows female 9137 of the fifth generation, who had the malignant adenoma of the liver of her maternal grandmother five generations back, the adenoma of the ovary of her paternal grandmother, and the papillary carcinoma of the lung of her paternal grandmother five generations back.

Susceptibility to cancer and resistance to cancer have behaved consistently, just as true albinism and pigmentation do in heredity. That is, just as true albinism is the total absence of the pigment-making mechanism present in the pigmented mouse, so susceptibility to cancer consistently behaves like the absence of a mechanism fitted to control proliferation and differentiation in regenerative processes. At any rate, whether or not it is exactly this, it seems to be the absence of some controlling mechanism, and an animal either has it or has not, whether he is a mouse or a man.

STRAIN 201 WITH PARTIAL ANCESTRY

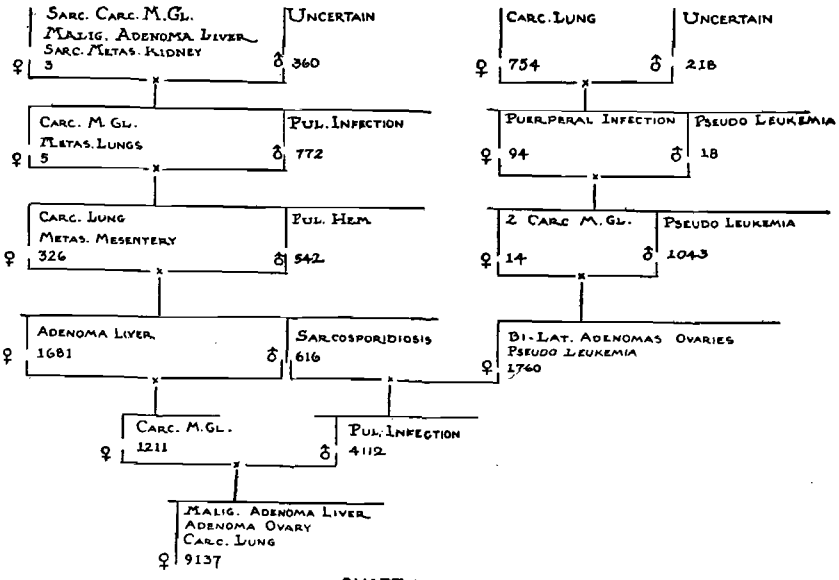


CHART 14

In my experience whenever spontaneous cancer comes out in a strain, it is because it has been bred in, in some degree, and however remote the cancer ancestry, it is to be found if analysis is carried far enough, and not only the neoplastic ancestor, but the ancestors which carried the same types and locations of tumors as those shown in the later generations.

The unit characters concerned in the heredity of spontaneous tumors, whether we are dealing with mice, rats, or man, are these: (1) A specificity of organ tissue type from ancestor to offspring, which determines that some certain tissue, as the liver or kidney, shall be like the tissue of its ancestral organ and react in the same way to the same cause; for example, liver tumor begets liver tumor; (2) a specificity of epithelium from ancestor to offspring, which will cause it to proliferate without differentiation and without control under a given provocation; that is, carcinoma begets carcinoma, and (3) a specificity of connective tissue from ancestor to offspring, which will cause it to proliferate without differentiation and without control under a given provocation; that is, sarcoma begets sarcoma.

Like all other unit characters, the unit characters here enumerated may get into all possible combinations, and we therefore, when dealing with fundamentally analyzed stocks, have such a result as I have shown from female 3 (Charts). This female with a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver, and metastatic sarcoma in the kidney, is able to transmit to her posterity, and has so transmitted, all possible combinations of these unit characters; namely, carcinoma of the liver, sarcoma of the liver,

adenoma of the liver; carcinoma of the mammary gland, sarcoma of the mammary gland, adenoma of the mammary gland; carcinoma of the kidney, sarcoma of the kidney, and adenoma of the kidney.

There are only two possible methods of studying the inheritability of any character, including cancer. These are (1) the long, painstaking, difficult analysis of stock in the laboratory, so that analyzed individuals are obtained whose hereditary potentialities are known and can be dealt with as such, and (2) the so-called statistical method. The former method has been pursued for fifteen years in this laboratory; the latter has been used in the study of the inheritability of cancer in man.

All such statistics are based on the memory of the patient and the diagnoses concerning his ancestors. Both may lead to incorrect conclusions. Rarely are any but recent facts recorded, or the diagnoses based on necropsy. There is, then, no certain scientific material to form a basis for these statistics. But where these statistics are right, as they frequently must be, even by chance, a biologic reading of them would show that they also demonstrate the inheritability of spontaneous cancer in man.

Chart 15 shows line A of branch 3, strain 164, continued through eight generations, and how by the right selective matings of heterozygous and non-tumorous mice, the occurrence of malignant disease is held off until the sixth generation. If, now, female 12876 with a lymphosarcoma of the mesentery, left kidney, and right ovary, had had her statistics taken in the hospital without error, even for three genera-

tions, no statistics of tumor would have appeared; nevertheless the inheritance of her tumor type is direct from her grandfather four generations back. By the mating of two heterozygous offspring of this tumor mother, namely, female

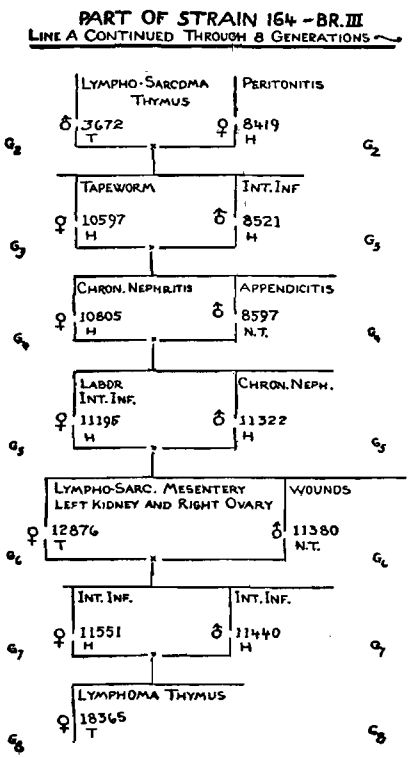


CHART 15

11551 and male 11440, again in the next generation a malignant thymus lymphosarcoma occurs in female 18365. At the same time all other types and locations of tumors are ruled out from this strain by the right selective matings.

If human cancer statistics, when correctly compiled, were biologically read, they would show as certainly as do mouse statistics the inheritability of cancer. They would show that the human heterozygote carries and transmits neoplastic tendencies exactly as do mouse heterozygotes, although they themselves do not develop the disease. This follows exactly the classic mendelian pattern from the mating of pigment-bearing with non-pigment-bearing mice.

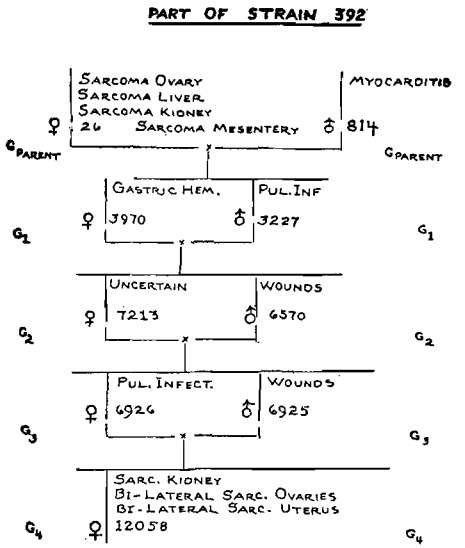


CHART 16

Chart 16 shows part of strain *392*. The parent female *26* had a sarcoma of the ovary, sarcoma of the liver, sarcoma of the kidney and perirenal tissues, and a sarcoma of the mesentery. She was mated with male 814, who died of myocarditis. By the right selective mating the occurrence of sarcoma (and

all other types of neoplasms) was held off through the three succeeding generations. In the third hybrid generation, by the selection of two individuals heterozygous to sarcoma, sarcoma appeared in the immediate offspring, generation 4, female 12058, repeating the sarcoma of the kidney and of the ovaries of her grandmother four generations back, adding also bilateral sarcoma of the uterus. No present-day hospital statistics could have shown the correct causes of death through four generations. If, therefore, this had been a human case, there would have been no record of tumorous ancestors; yet there is here the most evident and perfect persistence and final emergence of the exact type and locations of neoplasms, through the right selective breeding to bring it out.

Chart 17 shows strain 465 with partial ancestry. Studied somewhat in detail, it will afford perfect evidence of, first, the segregating out and consequent inheritability of tumor types, and, second, the segregating out and consequent inheritability of a specificity of organ tissue type, transmitted through generation after generation, both where inbreeding and where hybridization was employed.

Female 3 and male 30 were the ancestors of the paternal side of this strain. Female 3 had a sarcoma-carcinoma of the mammary gland, a malignant adenoma of the liver, and metastatic sarcoma of the kidney. Male 30 was proved heterozygous to tumor. This is a case, then, of mating a tumorous individual (recessive) with a heterozygote. In accordance with the mendelian expectation from such a cross, tumor comes out in the first hybrid generation; namely, female 883 with an adenoma of the liver.

In the first filial generation this female 883, with an adenoma of the liver, was mated with male 842, who died of uncertain

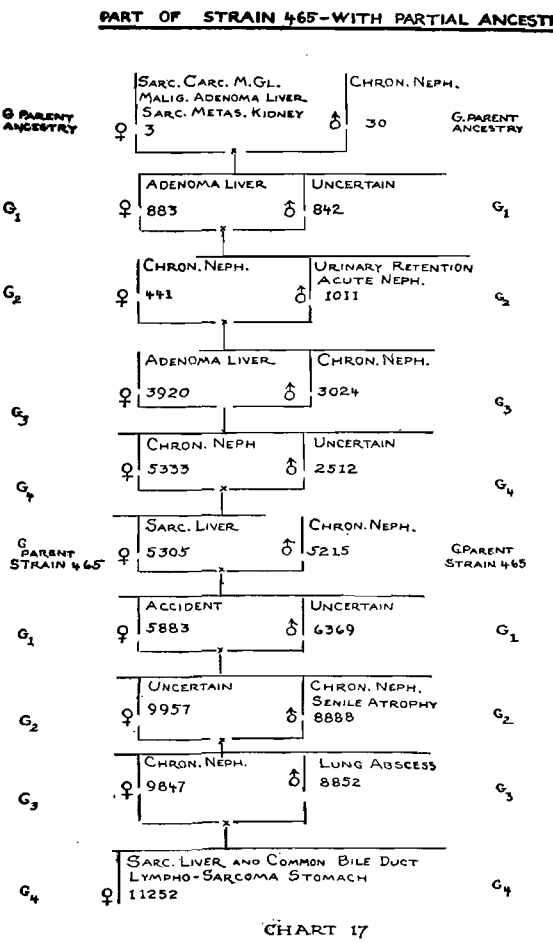


CHART 17

causes, but who was proved heterozygous to tumor. Their son, male 1011, who ultimately died from acute nephritis, was heterozygous to liver tumor. He was hybridized with

female 441, entirely unrelated, who was also heterozygous to tumor. Their son, male 3024, was hybridized with female 3920, who came from liver tumor ancestry and who herself had an adenoma of the liver. There was an outcropping of liver tumor in the second hybrid generation, female 5305, with a sarcoma of the liver. Note here how there segregated out, on the one hand, the unit character sarcoma introduced by female 3, five generations back, and, on the other hand, the specificity of liver tissue type locating tumors in the liver, which also was originally introduced by female 3, transmitted through and reinforced by female 883 and female 3920. In this generation the unit character sarcoma got into combination with liver tissue of a type to yield to neoplastic growth (another unit character), so that female 5305 reveals a sarcoma of the liver.

Female 5305 was hybridized with male 5215, who died of chronic nephritis. Through three succeeding generations, by the right selective matings, all occurrence of neoplasms was prevented. But the certainty of its transmission by heredity is indisputably demonstrated, for, by the use of analyzed individuals, two mice heterozygous to liver tumor were selected in the third filial generation; namely, female 9847, who died of chronic nephritis, and male 8852, who died of a lung abscess; and liver tumor appeared in the next generation. The liver tumor occurred as the result of the same combination of unit characters, namely, the combination of sarcoma and the neoplastic tendency in the liver.

To summarize the facts demonstrated in Chart 17:

1. Sarcoma segregated out and was transmitted as such.

2. Adenoma segregated out and was transmitted as such.

3. Other types of neoplasms segregated out and were not transmitted at all in this line of succession.

4. A specific type of liver tissue (that is, not possessing the non-cancer mechanism) segregated out and was transmitted as such, so that five liver tumors occurred in this small family alone.

5. A specific type of tissue in all other organs (that is, possessing the non-cancer mechanism) segregated out and was transmitted as such, so that all other organs refused neoplastic growth, with the single exception observed in female 11252, whose liver sarcoma spread by extension into the common bile duct, and who had also a lymphosarcoma of the stomach; but it is notable that this is the family in which nearly all of the few stomach tumors in this stock have occurred.

DISCUSSION

In the light of such perfect evidence as this, it is not logically justifiable to question the segregating out as unit characters of the sarcoma tendency, the carcinoma tendency, adenoma tendency, and the tendency to a specific type of organ tissue determining the location of neoplasms, and their transmission by heredity. Moreover, when we have such analyzed human individuals and such exact data concerning their neoplasms (if such a time ever comes), we shall find that exactly the same laws govern the transmission and occurrence of human neoplasms, since there would otherwise be no such thing as biologic or organic law.

Charts 11 to 17 inclusive show how the tendency to neo-

plasms of specific types and of specific organs is carried along by heterozygotes, and how by the right selective matings alone, both in inbreeding and in hybridization, neoplasms of these types and of these organs can be held off or brought out at will in the resulting strains by the use of analyzed individuals. Such neoplastic tendencies can be carried along by heterozygous individuals through as many generations as are desired, just as the tendency to albinism can be similarly carried along by heterozygotes. By right selective breeding, however, both the neoplastic tendency and the albinic tendency can be made to emerge at will.

The heterozygote, then, the product of hybridization in any species or any variety, may be a very puzzling factor in heredity, hiding as he does the recessive potentiality behind the dominant appearance. For he contains in his germ-plasm and therefore can transmit to his offspring unit characters different and frequently opposite in nature, as, for example, a pair of heterozygous black mice transmit albinism to their immediate offspring; or a heterozygous individual without cancer may transmit cancer to his immediate offspring, because potential cancer went into the germ-plasm from which the heterozygote developed. The heterozygotes in the human cancer problem have been the individuals who have blinded the readers of human statistics to the fact of its inheritability.

There is a somewhat wide-spread objection in the medical profession today to the conception that cancer is inheritable, and by some, a very ready and categoric denial of its inheritability, on the basis of these misread human statistics. As

the opinion of many physicians in this matter is based on the statements made by the Society for the Control of Cancer, I quote from last year's annual leaflet, issued by the Society, item No. 6, "Cancer is not inherited. It is not certain even that a tendency to the disease is inherited." Let us examine this statement:

I have remarked how man repeats in his embryonal development the history of organic evolution, beginning as a single cell. In this cell there are no nose, no legs, no vertebræ arranged in a perfect and beautiful spinal column, no liver, no epithelium, and no cancer. What resides in this single cell is the tendency to these things. That is the basis of all heredity. All inherited characters are inherited tendencies of the cell. There is no other form of inheritance.

I have discussed the evolutionary basis of the law of heredity, a common law of protoplasmic behavior; what goes into the germ-plasm comes out in the offspring; the fundamental necessity of similar tissues behaving in similar fashion, if there is to be such a thing as species or race. The mouse tumors under study in this laboratory arise in the same tissues and in the same organs as the tumors of man; they follow the same clinical course; they cause death in the same ways. Under the microscope they present the same fundamental neoplastic characters as similar tumors in similar organs in man. They are the same biologic entity as analogous tumors in man. And, consequently, if we do not discard the entire theory of evolution, we must admit that they behave in the same way in the matter of heredity as in all other matters.

When we have found, as we have found in this laboratory

for thirteen years, that tendencies to carcinoma and non-carcinoma, to sarcoma and non-sarcoma, and to a specificity of tissue type in specific organs segregate out and are transmitted as such, so that the result of analysis of individuals and the manipulation of their unit characters can be accurately foretold, then we must either discard the entire biologic science of today, or admit that these same characters segregate out and are transmitted as such in man.

Moreover, the accurate human statistical evidence, accepted by the most vigorous opponents of cancer heredity, itself demonstrates the inheritability of cancer in man, when it is correctly and biologically read.

Recent results obtained in experimental tumor production also demonstrate that heredity is the certain fundamental basis for success in such tumor production. It is interesting to note the increasing harmony between these results and the studies in spontaneous cancer, as the field of experimental tumor production is more completely developed.

Tumor Cells Growing in Vitro.—When living tumor cells are placed in a test tube or other mechanical container and are given the right conditions of attachment and food, they perform the common inherited function of all nourished living cells; that is, they divide and the mass grows. Here the neoplasm is reduced to its lowest terms, and manifests the only inherited behavior types possible in its restricted location, namely, the absorption of food and the undifferentiated mass growth by cell division, sarcoma cells producing undifferentiated sarcoma only, and carcinoma producing undifferentiated carcinoma.

Grafted Tumors.—When living tumor cells are grafted into a living host, and are given the right conditions of attachment and food, they also perform the common inherited function of all nourished living cells, that is, they divide and the mass grows. Here the problem of inheritance behavior is more complex than that furnished by the tumor cells growing *in vitro*. The behavior problem is now twofold: the inheritance behavior of the piece of tumor and that of the living container into which it has been grafted.

The tumor tissue, grafted into the living host, manifests exactly the same fundamental types of inherited behavior shown by the tumor cells growing *in vitro*. Its cell division and mass growth, and its death if nutriment is withdrawn, mean nothing with reference to the inheritance possibilities of the living host into which the tumor has been grafted. Its inheritance potentialities are those of the tissues of the animal of which it was a spontaneous tumor, not those of the tissues of its host. Here, also, as in the case of the tumor cells growing in the test tube, the cell mass, when given proper conditions of attachment and food, grows without differentiation and without control up to the limits set by its environment.

The evironment of the grafted tumor, however, instead of being a mechanical container, is a living organism with inheritance potentialities of its own, which must determine the limits of the growth of the parasitic tumor, but not the fact or the type of the growth itself. If the host normally regenerates its own cells, assaulted by the inoculation, and builds up an accessory circulatory system for the graft so that nutri-

ment is supplied, the cells of the parasitic tumor continue their division and mass growth. If the adjacent tissues of the host do not regenerate and do not build up an accessory circulatory system, no nutriment is furnished the parasitic cells, and consequent cell death occurs with the sloughing out of the graft. "A take" of grafted tumor, fundamentally then, depends on the normal regeneration of the assaulted tissues, and not on the abnormal growth of the host cells.

The Relation of Heredity to Experimental Cancer.—Let us apply here the criterion of inheritance behavior in these grafted tumors and spontaneous animal tumors. Little and Tyzzer found that heredity controls the susceptibility to these tumors in various strains of mice, but that susceptibility and non-susceptibility do not behave as unit characters, but rather as a complex of unit characters, probably many in number. Susceptibility to these grafted tumors uniformly appeared in the first hybrid generation in 100 per cent of the cases, and in steadily decreasing frequency in later generations.

The appearance of susceptibility to grafted tumors in the first hybrid generation between pure stocks, would show that one of the most important factors concerned in the transmission of susceptibility to grafted tumors must be a dominant. The logic of the situation confirms this conclusion, for obviously the first and most important factor in determining the acceptance of a graft, whether of tumor, of bone, of skin, or of any other organic tissue, is the ability of the assaulted tissues to regenerate normally, and thus to give proper conditions of attachment and food. If the tendency to regenerate

abnormally, as in cancer, were dominant over the tendency to regenerate normally, very few would remain in the organic world but cancerous individuals.

The fundamental basis of susceptibility to grafts, then, is the exact opposite of the fundamental basis of susceptibility to spontaneous cancer, which is the tendency of the assaulted tissues to regenerate abnormally in the uncontrolled and undifferentiated method of the neoplasm. There is, therefore, the most perfect harmony between the heredity studies in grafted tumors and those in this laboratory with spontaneous cancer; in both cases heredity has been found to determine the occurrence of cancer, and in both cases resistance to cancer has been found to be dominant over cancer susceptibility in 100 per cent of the cases.

The production of experimental liver tumors in rats by workers in the Crocker Fund Laboratory in New York shows definitely that an underlying hereditary predisposition determines the success of this experiment. At the last two meetings of the American Association for Cancer Research, Wood has reported that, when rats that developed experimental liver sarcoma were bred together, much higher rates were obtained in the offspring, such families sometimes giving 100 per cent of positive results. This shows a most striking hereditary basis underlying the success of this experiment.

It is of great interest also to note that Tyzzer of Harvard, Bashford of the Imperial Cancer Research Fund of England, and other workers have reported that spontaneous tumors later developed in mice immune to grafted tumors. In an

article concerning a transplanted myosarcoma of the rat, Bullock and Curtis of Columbia report a spontaneous tumor of this type occurring in the tail of a rat which had been infested with tapeworm larvæ, without developing a liver sarcoma, thus showing that this rat developed the type of tumor to which it was predisposed by heredity rather than the type of tumor experimentally attempted.

Fibiger also, in his experimental production of gastric tumor by injecting nematode larvæ into the stomachs of rats, found an underlying hereditary basis for the success or failure of the test.

For example, although he reports squamous-cell carcinoma in the stomachs of certain laboratory rats fed with these larvæ, he failed entirely to secure any proliferation in the stomachs of many other strains of rats tested. Among a very large number of mice in which he tried to produce such tumors he found only three, nor did he have any success with wild house mice, wild rats, and other strains of laboratory rats and mice. He was forced to admit from these negative results that there must be a predisposition to such tumors determining the success of this experiment.

Such an explanation of his results places them in perfect harmony with the fundamental influence of heredity in cancer susceptibility shown in the studies carried on with spontaneous cancer.

Fibiger further states that spontaneous mammary gland carcinoma has arisen in two mice, and mammary gland sarcoma in one mouse, all of whose stomachs he had infested with spiroptera without securing stomach neoplasms, that is,

the presence of artificially introduced larvæ in the liver or stomach and intestines of rats and mice of spontaneous cancer strains, does not produce neoplasms in the liver or in the stomach or the intestines necessarily, but spontaneous neoplasms arise in those organs which by inheritance lack the cancer-resistant mechanism, just as they do in mice in this laboratory.

Even should it eventually be possible to find some experimental method by which cancer can be produced in all subjects, this would not disprove the inheritability of cancer, as a study of the biologic facts will show.

Overthrow of Normal Generative and Regenerative Powers.— There resides in every living organism the power to regenerate within certain limits. These limits are set by the normal metabolism of the organism. For example, under normal conditions a beheaded planarian can regenerate a head. But if this beheaded worm is put into a solution of alcohol, not lethal in strength, it is no longer able to regenerate a head, but will perform partial regeneration in proportion to the strength of the alcohol solution. If the solution is sufficiently strong, all power of regeneration is lost.

If sea-urchin eggs are centrifuged, they will not generate normally. If the centrifuging is sufficient, they will not generate at all. A less degree of centrifuging will produce abnormalities of generation, proportionate to the degree of centrifuging used.

These facts demonstrate that it is possible to overthrow partially and even completely, not only the normal inherited regenerative powers in the tissues of an organism, but even

the normal inherited generative powers. There is no organic mechanism which cannot be overthrown, wholly or in part, by a sufficiently strong assault. For example, it is possible by a sufficiently strong assault, to destroy the pigment-making mechanism in a young mouse with inherited black hair. It is thus possible, by destroying the pigment-making mechanism, to cause local albinism at the point of assault. But this fact has nothing to do with the inherited pigment-making function in the mouse, or its potentialities under normal conditions.

A parallelism to these facts of normal regeneration and generation, and the possibility of their destruction, partial or complete, undoubtedly exists in the facts of abnormal regeneration operating in the production of neoplasms. Resistance to neoplasms has consistently behaved like the presence of a mechanism fitted to control proliferation and differentiation in regenerative processes. This mechanism, like the pigment-making mechanism, it is undoubtedly possible to kill, so that by an efficient assault, it might be possible to produce a local lack of this mechanism, just as we can produce local albinism by an assault on the local and inherited pigment-making mechanism.

The pigment-making mechanism exists in different degrees among different individuals, so that among mice, for example, some individuals form red pigment (most highly oxidized melanin); some form grey pigment (a less degree of oxidation of melanin); some form black pigment (a still less highly oxidized melanin); and so on, down to those whose pigment-making mechanism is of the type which produces

only the palest blue or cream color, the latter being barely distinguishable from albinic white.

In just this way individuals may vary greatly in the completeness of their mechanism for controlling growth and differentiation in regenerative processes, that is, the cancer-resistant mechanism. Individuals of the first class, who have the highest degree of non-cancer mechanism, would then rarely produce cancer under any provocation. But individuals with the lowest degree of cancer-resistant mechanism might relatively easily succumb to artificial conditions for cancer production. Whereas under the normal life of the organism, no set of circumstances would arise that could produce cancer, under the continued and artificially excessive provocation they might succumb; just as an individual with enormous muscular power, capable of resisting any normal impact against his musculature, would succumb under the impact of 100 tons. His mechanism, efficient under normal conditions, would have no opportunity to function. Many of the experimental procedures using artificial means of producing tumors, may easily be of this shattering type. So that, in those individuals that have only a low degree of cancer-resistant mechanism, this controlling mechanism may have no opportunity to function.

However, the stocks used for the experimental production of cancer, so far reported, never have been analyzed as to their natural cancer potentiality, and therefore we have no scientific basis for decision as to what part of the results of such experiments are due to natural cancer potentiality and what portion remains the unquestioned experimental result.

It might then be possible, by an irritation sufficient to destroy the cancer-resistant mechanism, to cause cancer in every organism, the readiness with which this could be done being dependent on the degree of cancer-resistant mechanism possessed by each individual.

It may therefore be possible to discover a type or types of irritation sufficient to cause neoplasms in every living organism; and tapeworm larvæ, nematodes, coal-tar painting and *x*-ray burns, along with other types of irritation, may, individually or collectively, prove efficient cause for the overthrow of any inherited cancer-resistant mechanism, just as all heads can be turned grey or even cut off, no matter what the inherited potentialities might be; for one inherited potentiality of every organic mechanism is that it can be destroyed by some form of assault. The inherited mechanism for cancer resistance, therefore, does not differ in this respect from every other inherited potentiality.

It is extremely interesting and gratifying to find this striking harmony between the experimental spiroptera cancer and liver sarcoma, and spontaneous neoplasms in mice, whereby the demonstration of the inheritability of spontaneous cancer is corroborated by a line of research which seemed at first (to many) likely to show that experimental cancer could be produced in all animals, and which was taken by many commentators to indicate that the tendency to cancer might not, after all, be inheritable. These results suggest that when the field of experimental cancer production has been more completely investigated, the most perfect harmony will be found to exist in every detail between those lines of work which ex-

perimentally produce true neoplasms, and the work with spontaneous cancer.

Thus far this harmony has been maintained in that all researches have demonstrated that inherited predisposition is the basic essential in determining the appearance of cancer.

THE INFLUENCE OF HEREDITY ON THE OCCURRENCE OF CANCER

H. GIDEON WELLS

Until recently it has not been possible to speak with assurance concerning the influence of heredity on the occurrence of cancer; the evidence at hand has been of such an unsatisfactory character that the validity of whatever conclusions were drawn was always open to question. Numerous attempts to secure information by studying general mortality statistics, hospital populations, or isolated clinical observations have led to contradictory results, as they were bound to do from the inherent errors in the data obtained from such sources. Furthermore, until within a comparatively short time, we had no definite knowledge of the principles of heredity itself, and this ignorance foredoomed to futility any speculations on the subject.

It so happens that the year 1900 saw the rebirth of two unrelated discoveries which, together, have led to an entirely new outlook on the problem, for they placed for the first time on an experimental basis the investigation of both heredity and cancer. In this year, independently, three botanists (de Vries, Correns, and Tschermak) reported the rediscovery of the fundamental principles of heredity which the Austrian monk Gregor Mendel had worked out so accurately and described in 1866.

The same year witnessed the work by Loeb in Chicago and by Jensen in Copenhagen, demonstrating that sarcomas in rats and carcinomas in mice can be inoculated into other animals of the same species for an indefinite number of generations; Jensen's mouse carcinoma is still being transplanted in many laboratories. The same fact had been demonstrated in 1889 by Hanau, and in 1891 by Morau, but like Mendel's discovery, its significance had not been appreciated at the time and it had not been followed up. Although we have since learned that the information to be obtained from transplanted tumors is limited, especially in respect to the influence of heredity, these observations placed cancer research on an experimental basis, and the recent rapid progress in our knowledge of cancer has been largely due to the stimulus to investigation given by tumor transplantation work.

During the twenty-two years that have passed since these rediscoveries were made, genetics has become one of the most active fields of biologic research. Experimental cancer research has likewise been one of the most attractive subjects of pathology, although perhaps somewhat obscured by the contemporaneous development of the more hopeful science of immunology. In view of the relatively short period covered by these investigations, and the difficulties inherent in the problems themselves, it is not surprising that we are only just now beginning to secure evidence concerning the relation of heredity to cancer. In the following paragraphs I shall endeavor to present, as concisely as possible, the evidence that we now have concerning the influence of heredity on the occurrence of cancer.

A. Evidence Furnished by Human Pathology

Human material has furnished evidence that may be classified in two chief groups: (1) Statistical investigations, and (2) cancer families.

STATISTICAL EVIDENCE

Statistical evidence may be dismissed with the statement that, in the question of human cancer heredity, *all existing statistical evidence is valueless for any exact information on the subject*, and it must remain so until such time as we have necropsy records on all persons dying in several generations. When we consider how few persons have knowledge of a physician's diagnosis of the fatal illnesses of even their grandparents, to say nothing of their great uncles and aunts and of preceding generations, we at once recognize the limitations of clinical histories in casting light on the relation of human heredity to cancer. And even if we did have such records of clinical diagnosis we should be no better off, for the error in such diagnoses is far too large to permit us to use them.

We find that, even in large modern hospitals, necropsies show an error in clinical diagnosis in respect to cancer of anywhere from 20 to 50 per cent, depending on how large a proportion of the cases are of malignancy in the internal organs.[67] With such a great error in the diagnoses in large hospitals, where every modern diagnostic resource is available, what must the error be in the clinical diagnoses made on private patients under the varied and unfavorable conditions that often obtain even in present days, to say noth-

ing of the diagnoses in previous generations before the days of microscopy or modern methods of diagnosis?

In considering the relationship of heredity to cancer, even a single error in diagnosis might totally destroy the value of an entire family history, making it appear that cancer was present in a branch of a family when it was not, or that it had failed to appear in a certain branch in which it actually did exist. Therefore, the records that exist now, or that may be obtained in the future, can be of no value whatsoever for this purpose until they all contain a complete postmortem examination with microscopic control.

With these essential facts before us, we must dismiss the numerous discussions in the literature based on mass statistics. By so doing we lose nothing, for the conclusions are as contradictory as possible. On the one hand, we have the much-quoted and carefully compiled statistics of an expert statistician, Karl Pearson, using an absolutely worthless material, the histories of patients in a large charity hospital as to the incidence of cancer in their known relations. These failed to show any evidently greater proportion of cancerous relations in cancer patients than in patients with other diseases. Any medical man who has questioned the patients of such a hospital knows how absolutely worthless is the information that the patients can give in respect to family history. Most of them do not know how many and which of their relatives are living, to say nothing of the causes of death. Thus, in a discussion of the relation of heredity to cancer, Bashford[1] reports that in the histories of 2,932 cancer patients, in respect to familial occurrence of cancer, "no reliable statement

was obtainable for 2,263." That is to say, in less than one-fourth of the cases was there even a layman's knowledge of cancer in the family, although in the 4,526 parents there undoubtedly were not far from four or five hundred cases of cancer. To use refined statistical methods on such material is as useless as some of the attempts that are made to use the extremely exact methods of physical chemistry in interpreting biologic processes that even in controlled conditions show variations of 50 per cent.

It is only fair to Pearson to quote his own conclusion:

> The data do seem to justify further inquiry and to suggest to my mind that possibly the tendency to cancer does not run strongly in families. I admit that I should accept this only with reluctance, for general health, I find from my own investigations, is inherited exactly as any physical character like shape of the head, and length of life, is inherited also. It is difficult to conceive that longevity and general health can be inherited if the tendencies to particular diseases do not largely run in families. Cancer may be an exception, of course, and certainly the above results, without being convincing, do call upon us to pause and ask for further inquiry.

From this it is seen that Pearson was much more conservative in his deductions than most of the writers who have quoted his carefully analyzed statistics as weighty evidence that there is no hereditary influence in cancer.

On the other hand, we may find as many sets of statistics as we wish, which, like those of Williams,[63] show that a very considerable number of the relatives of cancer patients have had cancer; but they are not usually so controlled as to be of any value, even if such mass statistics could mean anything. About the only thing we can deduce from them is that most of the published statistics indicate that usually a larger pro-

portion of the relatives of cancerous subjects have been cancerous than of the relatives of non-cancerous patients. Few investigators, like Pearson, find the proportion of cancerous relatives the same in the two groups, and still fewer, if any, find more cancer among the relatives of the non-cancerous subjects.

Of material of this sort, perhaps the best is that considered by Little. This is contained in the family history records of the Eugenics Record Office of the Carnegie Institution, which have been furnished by persons of intelligence, conscientiously endeavoring to provide accurate family histories for scientific purposes. Analysis of these records shows that cancer occurs much more frequently among the descendants of cancerous parents, or in persons with cancerous relatives, than is to be expected from the general cancer mortality figures. However, we have here the usual defect in that the occurrence or absence of cancer is based on only the layman's belief concerning the cause of death of relatives, and the vital statistics used for comparison are of no more accuracy than any statistics not based on necropsy records, and probably give too low a cancer rate.

CANCER FAMILIES

Much attention has been given to the occurrence of families in which a strikingly large proportion of members are cancerous. The existence of such families cannot be denied. Some of these families have become classical in cancer literature. Such is the Bonaparte family; for Napoleon I, his father, his brother Lucien, and two of his sisters, Pauline and

Caroline, all were believed to have died of cancer of the stomach. One of the most remarkable is the family of Madame Z, reported by Broca in 1866, and mentioned in virtually every discussion of heredity in cancer since that time. Many more such families might be described. The chief trouble with most of these reports is that they do not include all the non-cancerous members of the family, and hence we cannot always be sure that the incidence is really so exceptional. Furthermore, they have, of course, the defect of depending only on family traditions and belief as to the cause of death.

In family records with a high incidence of cancer, no matter how high the proportion is, the possibility that the heaping up of cases in these families may depend on chance cannot be evaded. Granted that of the entire population past forty about 10 per cent will have cancer, the laws of probability would determine the occurrence of occasional families in which a high proportion of cancer cases would occur if heredity had no influence at all. Bashford[2] gives the table on page 164 showing how large a number of cases of cancer are to be expected on this basis, independent of any other influence than that of chance.

Likewise, there should be fortunate families that escape cancer through pure chance. As far as I can learn, no one has sought families that show an immunity to cancer, although such family records should be more attractive than the other kind.

But when we find families that have many cases of a certain sort of tumor which is not common, or a tendency to

*Occurrence of Cancer in Families, According to the Laws of Probability**

Number of Cancer Deaths in Family	Per Hundred Families of		
	6 Members, 3 Men, 3 Women	8 Members, 4 Men, 4 Women	10 Members, 5 Men, 5 Women
None	51	41	33
One	36	39	39
Two	11	16	20
Three or more	2	4	8
	100	100	100

frequent location of a certain tumor in a certain place, the law of probability becomes inadequate. We have just such records.

Undoubtedly the retinal glioma families afford the most striking examples of such unquestionable heredity influence. Glioma of the retina is a rare neoplasm, which is striking in that it often occurs in infants or even at birth. Its familial occurrence is equally striking, and we have numerous records of such families as the following:

1. Newton has reported a family of sixteen children, of which ten had died of retinal glioma, the disease being bilateral in seven cases. Two of the others died in infancy, and four were alive and well. Both parents were free from tumor, but a brother of the father was believed to have died of the same disease.

2. Wilson reported a family in which eight children had retinal glioma.

3. Purtscher has described a glioma family: A man who

* Including only persons living thirty-five years or more.

died of sarcoma of the arm had eleven children; two of six boys died of glioma of the retina (at nine and three years); a daughter had bilateral glioma (verified by Fuchs), which retrogressed spontaneously. Her only child, a boy, died of

Fig. 20.—Glioma of retina (patients of Dr. L. Comas of Santiago). The boy is the only survivor of five children with retinal glioma, both eyes having been enucleated. The sister shown in this picture died shortly after the photograph was made.

glioma. Two children of the members of the family, who remained tumor free themselves, developed glioma; one died and in the other the tumor retrogressed during ten years while under observation in the clinic of Fuchs.

4. Comas has described a striking instance of familial glioma: Among eleven brothers and sisters, five have had glioma of the retina. Of the five, three sisters and two brothers, only one brother is alive; he is now twelve years old and enjoys good health, although blind. Both his eyes were enucleated, the left when he was two years old and the right six months afterward (Fig. 20). Recently, Dr. Comas writes me, the father has died from gastric cancer. The mother is in good health, and the other children, one of them sixteen years old, are also in good health. The illustration (published with the permission of Dr. Comas) shows the mother, the blind brother, and one of the sisters who died shortly after this picture was taken.

It may be suggested, not without justification, that retinal glioma is not a typical and unquestionably malignant neoplasm, for it is often bilateral, does not commonly produce remote metastasis, and may even retrogress spontaneously (witness one of Purtscher's cases). I therefore add some other examples of familial neoplasms.

Silcock describes the following instance: A mother and daughter each suffered from melanosarcoma of the choroid of the left eye, each identified microscopically. The mother's father and each of her twin sisters had had an eye extirpated because of disease, but that this was melanosarcoma in all three cases is not known.

Williams[69] has collected a large number of family groups in which several members of the same family have died of similar or identical sorts of neoplasms, some of the instances being very striking, as are also the families described by Bashford,[3] Pel, Peiser, Watkins, Richards, and Oidtman.

As especially significant may be cited the interesting cases reported by Burkard of twin sisters, aged twenty-one, who developed each a fibro-adenoma of the left breast, each of the same microscopic structure, at almost the same time and in the same part of the breast. This recalls the remarkable family described by Critzmann, in which all members who were *not* twins died from cancer, all the twins escaping. Such an instance must be related to Galton's family, remarkable for the number of twins; whenever single children were born they always had six fingers and six toes, but the twins always had the normal number.

Another striking instance is reported by Hedinger of primary cancer of the liver in two sisters examined at necropsy within one week. No cancer was known in the family, but Hedinger believes it impossible that two such rare tumors could have occurred in sisters without a familial organ disposition. Another case of rare tumor in sisters is reported by Primrose, namely, primary "carcinoma" or cancroid of the appendix.

Interesting data are given by Peller from his analysis of a questionnaire sent out to the entire medical profession of Austria, from whom 389 replies were received; but here the factors of selected material and uncontrolled data make the significance of the reported material of uncertain value, for it is probable that observations in which many of the members of a family are cancerous are especially often recorded because they are especially striking.

Perhaps the most reliable family records of cancer in the literature are those reported by Warthin,[64] which have the

virtue of being based on histologic examination in at least many of the cases, and in being collected in a university hospital population probably with better information as to family history than is likely to be the case in large city hospitals with a foreign-born clientele. He cites with diagrams several families in which a striking history of cancer was obtained. In one, of forty-eight descendants of a cancerous grandfather, seventeen had died or been operated on for cancer, and many of the survivors were below the usual cancer age when the paper was published. The preponderance of carcinoma of the uterus (ten cases) and of the stomach (seven cases) is striking. Another family, in which the father and mother escaped cancer, although each had cancerous brothers and sisters, consisted of three daughters, all of whom had uterine or ovarian tumors. Especially striking is a family in which a cancerous father and a cancerous mother had six children, all of whom died from cancer, as did the only grandchild, that is, of the entire family of nine members in three generations, all died from cancer, as did the paternal great grandfather.

Warthin[65] thus sums up his study:

> In the histories of cancer cases coming from the state of Michigan and examined at the pathological laboratory of the university, about 15 per cent show a striking history of multiple family occurrence. When the difficulty of obtaining good histories is considered, this proportion is relatively high, and, on the whole, corresponds fairly closely with the percentage obtained by Williams. We must conclude, then, that a definite and marked susceptibility to carcinoma exists in certain families and family generations. This family tendency is usually most pronounced when there is a history of cancer in both paternal and maternal lines. In such families there is an especial tendency for carcinoma to appear at an earlier age than in the forebears, and in these younger individuals the cancer usually shows an increased malignancy.

Wolff, in his great compilation of cancer literature, says that recent authors find that from 11 to 18 per cent of their cases show evidence of a hereditary influence. After discussing this evidence, he concludes:

> Nevertheless, we must admit that heredity may be a factor for predisposition to cancer, for it is admitted that heredity is seen in nevi, warts and other skin abnormalities which are known to be closely related to cancer formation; furthermore, heredity is understandable on the assumption that abnormalities in fetal development, which likewise are often the starting point of a cancer, may repeat themselves in several members of a family or of a generation.

He cites a report by Rüder, in which seven boys, from five months to ten years of age, in one family exhibited epithelial "carcinoma" of the skin, in a form of papillary nodules up to bean size, while five girls of the same family showed none. The formation of these nodules was preceded by an inflammatory reaction where exposed to light. The course was slow, but nothing is said as to the outcome. The parents of these boys were healthy, but a grandfather had the same disease.

Those authors who consider that tumors arise usually or always in some embryonal rest of necessity lay much weight on heredity. Thus, Ribbert, for instance, maintains that irritation cannot cause cancer unless there are already present the necessary germ cells, which, like all other anomalies of the germ-plasm, are transmissible. He believes that ordinarily tumors develop spontaneously without exciting cause, solely because of the presence of anomalous predisposing germ cells. This view can scarcely be held now in the light of the newer studies on the experimental production of

cancer, unless we agree to the proposition that nearly all individuals have such anomalous germ cells located in any part of the body that we choose to irritate with our cancer-exciting agent.

The only study of heredity in human cancer in which the mendelian principles of heredity are considered is that of Levin, who used material collected by field workers of the Eugenics Record Office at Cold Spring Harbor. Unfortunately, these field workers were not physicians, and the data that they collected must have been limited to what the members of the investigated families knew or believed concerning the ailments of their relatives and ancestors. There were two "fairly complete" and three "fragmentary" records available, from a study of which this conclusion is reached:

> The incidence of cancer in these families is not greater numerically than would be found among the population of the community as a whole. But there are several points in the analysis which indicate that cancer may be influenced by heredity. A cancerous fraternity usually shows in a previous generation a cancerous member either on the maternal or paternal side, or both. In other words, a cancerous fraternity is usually derived from the union of two germ-plasms, each of which is characterized by the presence of germ cells that are non-resistant to cancer.

It was also noted that there is a distinct family susceptibility of organs; in one family all the women with cancer had uterine involvement "except one in the omentum"; in another family group the males had intestinal cancer, the females breast cancer. Analysis of the collected statistics gave Levin evidence that *resistance to cancer is a dominant character*, the absence of which creates the susceptibility to cancer.

Benign tumors, and especially various cutaneous growths that are essentially benign neoplasms, often exhibit a striking and undeniable hereditary occurrence. Several such records of dermatologic heredity are collected by Meirowsky and Bruck. Hereditary telangiectasis is also well known, the literature having been reviewed by Goldstein. Multiple benign cystic epithelioma is one of the growths that has a distinctly familial distribution, and these growths,[44] which usually more or less resemble carcinoma histologically, sometimes become malignant. As illustrating the familial character of these growths may be cited the case reported by Heidingsfeld, in a man of sixty-five, whose four children, like himself, exhibited the growth on the nose; his maternal uncle and aunt had a similar growth, his mother had died at thirty without having any growths, and there had been no cases on the paternal side. Probably this is the type of growth referred to by Wolff as cutaneous epithelioma.

Another form of benign neoplasm with an extremely marked hereditary character are the multiple cartilaginous exostoses. The literature of this topic has recently been reviewed by Maynard and Scott, who reported the occurrence of a family with sixteen known cases in three generations, an important feature being that the mother who transmitted the condition apparently did not herself have the disease. This has been observed in other families with this disease and is of much significance in respect to the mendelian principles of transmission of inheritable characters, as will be shown later.

Von Recklinghausen's disease, or multiple neurofibromatosis

with its various related and complicating conditions, has a most striking hereditary character, at least one-fifth of all patients showing close relatives with the same rare disease, which is especially significant in the fact that there is a noteworthy tendency to malignant transformation. The disease appears not only often in several members of a family but also for many generations, its character being so striking that the lay patient is usually well aware of similar conditions in his relatives and ancestors. For example, Harbitz has described a family in which the disease was known for five generations, it being of significance that in one generation it was transmitted by a woman who herself was not affected, although it was present in two of her sisters. The literature on this subject has been discussed especially by Langer and by Herxheimer and Roth. Davenport found evidence, from an analysis of 243 cases, that the hereditary factor behaves as a dominant, coming down equally well in either male or female lines, and affecting the two sexes alike. Sometimes, however, there is a failure of dominance and generations are skipped.

Possibly of some relationship to these conditions is the central nervous sclerosis associated with multiple symmetrical adenoma sebaceum, as indicated by the family reported by Berg, in which the father had tuberous cerebral sclerosis associated with adenoma sebaceum and a large, mixed, embryonal type of renal tumor; the daughter with the same nervous system disease and the sebaceous adenomas had a small angiofibroma of the kidney, and the paternal grandfather died with a large renal tumor but without the nervous and cutaneous lesions.[21] This disease is commonly associated

with renal, cardiac and retinal[62] tumors, as well as various developmental defects, which facts bring closely together the potential relationship of inherited developmental anomalies and consequent hereditary neoplasms.

B. Animal Experimentation

TRANSPLANTED TUMORS

In the period of active investigation of transplantable tumors in animals that followed the demonstration by Leo Loeb and by Jensen that series inoculation of rat and mouse tumors is readily carried out, there was naturally not a little study of the influence of heredity on the inoculated tumors. At this time it was not so fully appreciated as it now is that an inoculated tumor is something quite different from a spontaneous tumor. A transplanted tumor differs from a spontaneous tumor fundamentally in that it is never a growth of the cells of the inoculated animal, but it is a growth of the cells descended from the mouse that furnished the original spontaneous tumor from which the transplanted growth was obtained. For example, a mouse inoculated with a strain of the Jensen carcinoma, which has been carried through myriads of generations of transplants during the twenty and more years since Jensen first started the transplantation, is growing a tumor composed of cells derived from Jensen's original tumor mouse and not from its own tissues. The mouse bearing an engrafted tumor is merely furnishing the soil on which some grafted tissue is growing, exactly as a culture tube furnishes a soil on which bacteria are growing.

That the inoculated cancer is fundamentally different from

the spontaneous cancer is shown by the fact that successfully inoculated growths often disappear spontaneously, and that protection may be furnished by various procedures of immunization, phenomena which are never seen in spontaneous tumors. Furthermore, animals that are immune to tumor inoculation may develop spontaneous tumors,[4, 10, 58] and by painting the skin with tar, true carcinomas may be produced in mice immune to grafts of the same sort of tumors.[16]

Therefore observations on the influence of heredity on the susceptibility of animals to transplanted tumors can have no direct bearing on the question of susceptibility to spontaneous tumors, since the resistance to one bears no direct relation to the resistance against the other. The chief things of interest learned from the inoculated tumors in respect to heredity are the following:

1. Close relationship of animals is favorable for inoculation. An animal inoculated with its own spontaneous tumor is more likely to develop growths from the inoculation than any other animal of the same species;[35] its close relatives are more likely to give positive results than unrelated mice, and the likelihood of successful inoculation becomes more and more remote, the more different in origin and in character the inoculated mice are from the originator of the tumor. Growing a transplantable tumor for several generations in a particular strain of animals may enhance its virulence for that particular strain of animals and not for others. These and other related facts indicate that even with transplantable tumors there are differences in susceptibility that are connected with the heredity of the animals, a point recognized in the pioneer investigations of Morau.

2. Certain strains of animals are insusceptible to tumor grafts to which other strains of the same species are susceptible. This has been frequently observed, and the differences in susceptibility may be either absolute or only quantitative. For example, Haaland found that a certain tumor grew in nearly 100 per cent of Berlin mice, in 24 per cent of Hamburg mice, and was practically innocuous to Christiania mice. Again, Loeb has described a tumor originating in a Japanese waltzing mouse, which grew in nearly 100 per cent of this sort of mouse but not at all in common laboratory mice. Many other similar instances have been reported.

3. Heredity influences in a constant manner the susceptibility of a given strain of animals to inoculation with cancer. For example, Tyzzer[61] studied a carcinoma which arose in a Japanese waltzing mouse and which could be inoculated into mice of the same type with a large percentage of success, but which did not grow in certain "common" strains of mice. When Japanese waltzers were bred with these common mice the mice of the first hybrid generation were all susceptible, but the second and third hybrid generations made by cross breeding the first generation hybrids were insusceptible. The mice of the first hybrid generation, although susceptible to tumor inoculation, did not show the waltzing character of the susceptible parent strain, whereas the waltzing mice (recessives) that appeared in the second and third hybrid generation were not susceptible to inoculation with the dancing mouse tumor. Further studies carried out with numerous back crosses gave results that indicate that susceptibility to *grafted* tumors is not inherited as a single

mendelizing factor, for they do not furnish a ratio characteristic of a single factor inheritance. Tyzzer and Little believe that both susceptibility and non-susceptibility are inherited as a complex of mendelizing factors, perhaps as many as twelve or fourteen in number.* Susceptibility to this tumor might seem to be a dominant character, since it appears in the first hybrid generation; but its failure to appear in the subsequent hybrid generations does not conform with the behavior of a dominant unit character.

Loeb and Fleischer[32] have experimented with crosses of strains of domestic mice with differing susceptibility to transplantable cancer and obtained results not altogether in agreement with those of Tyzzer. For example, in the first hybrid generation the susceptibility to inoculation was intermediate between that of the two ancestors, and not as high as in the more susceptible. The second and third hybrid generations showed very little susceptibility, but in the fourth and fifth generations there was increased susceptibility. They agree with Tyzzer and Little in believing that, if susceptibility to these inoculated tumors is a mendelian process, it must depend on multiple factors. In later experiments,[33] using different strains of animals, they obtained entirely different results, indicating the lack of fixed principles applicable to all transplanted tumors, and all strains of animals. In one strain a pure line was extracted with a susceptibility different from that of the rest of the strain.

In rats also the transplantability of tumors has been ob-

*This conclusion has been reinforced by Little in a subsequent communication on the same material (Jour. Cancer Res., 6, 106, 1921).

served to be influenced by heredity; but in Roffo's experience this behaved more like a simple mendelian character than in the observation of Tyzzer and Loeb with mice. On the other hand, Morpurgo and Donati were unable to demonstrate that twenty-nine offspring of rats bearing inoculated tumors were more or less susceptible to inoculation than the twenty-eight offspring of rats of the same strains that were immune to inoculation. This again disagrees with the observations of Levin and Sittenfield, who found also in a relatively small number of animals (twenty) that a transplantable rat sarcoma that gave 86 per cent of takes gave but 25 per cent in the offspring of immune rats, a figure indicating that resistance to this transplantable tumor behaves as a dominant character. The number of animals used in these two last sets of experiments is so small, however, that the results have little if any value.

SPONTANEOUS ANIMAL TUMORS

Except for the extensive studies of Loeb and Lathrop and of Slye, which will be considered later, most of the evidence as to inheritance of a tendency to spontaneous tumor development in animals is of a somewhat casual nature. However, there are several interesting observations on this point. Perhaps the oldest record of this sort appears in the classical treatise on tumors by Virchow, "Die krankhaften Geschwülste," published in 1864. Here, in discussing the melanosarcomas of horses, Virchow says:

> Brugnone, who first seems to have described this disease of horses, although under the name of hemorrhoids, reported that a white stallion introduced this disease into the animals of a herd in Sardinia, and that

his progeny developed melanosarcoma, whether male or female. Gohier has told of a report by Gallety-Latournalle that a young white stallion affected with black growths transmitted this condition to all its white progeny, while all those that were not white remained free. As a result, the disease spread itself over the entire province of Bresse and its vicinity.

Coming to more modern times and experimental methods, in 1898 we find Eberth and Spude describing the occurrence of a family of mice with mammary gland tumors. In 1907, Tyzzer[59] made observations on a number of mice in respect to the occurrence of spontaneous tumors in the offspring of tumorous and non-tumorous ancestors; but the breeding was not followed through generations, enough to establish any basis for deduction as to how any possible hereditary influences might work. One family of mice (C), descended from a mouse with a papillary cystadenoma of the lung, exhibited three similar tumors among twenty-four offspring, none of which lived over fourteen months. Family B, consisting of twenty-nine offspring of a mouse with a lymphoma, produced one lymphoma and one lung tumor, but only seven of these twenty-nine lived to be one year of age. Family A contained ninety-eight offspring of a mouse with a lung cystadenoma, of which sixty-five lived more than six months, and of these twenty (32 per cent) presented tumors, of which seventeen were tumors of the lung.

The conclusion was reached from these observations that they "indicate that one of the factors in the development of tumors is to be found in an inherited character or peculiarity." Still earlier, Loeb had suggested heredity as an explanation of so-called cage epidemics in laboratory animals and the occurrence of "epidemic" conjunctival carcinoma in cattle.

Murray investigated the influence of heredity on the occurrence of spontaneous tumors by breeding together animals descended from cancerous females, or by breeding cancerous females with males descended from cancerous females, and by breeding together the offspring of such matings. Among 340 female mice so obtained, which reached an age of six months or over, sixty-nine, or 18.2 per cent, had some form of tumor (sixty-two being of the mammary gland), whereas in 223 females without known tumors in either their mothers or grandmothers only twenty-three, or 8.6 per cent, had tumors. The value of this study is limited by the fact that the ancestry of these mice is known for such a short distance; but as far as it goes it indicates, says Murray, that:

> Female mice in whose ancestry cancer of the mamma has occurred not farther back than the grandmothers are distinctly more liable to develop the disease spontaneously in this organ than those in whose ancestry cancer is more remote. The increased liability is probably of the nature of a predisposition of one particular tissue or organ system to undergo cancerous transformation under the wear and tear of life. The differences between the two groups are apparent at all ages, and the age of maximal incidence does not appear to have been lowered in the predisposed group. The magnitude of the difference is such that it cannot be accounted for by the chances of random sampling.

In such a method of selection as employed by Murray, however, there exists a fundamental source of error, for selecting merely cancerous and non-cancerous *individuals* it was perfectly possible for some of the cancerous mice to have been members of strains or families in which the tumor rate was low, the cancerous individuals having been exceptional members of these strains; equally well, the non-cancerous individuals might have been exceptional members of strains

or families in which the cancer rate was high. It is of interest to note that among the mice of immediate cancerous ancestry in Murray's experiment were eight cases of lymphoma, all occurring in the descendants of two mice with mammary gland carcinoma. Although there were but four squamous-cell carcinomas, three of them occurred in sisters in a single litter. These two last observations, together with those of Tyzzer, suggest that type and location of spontaneous tumors may be influenced by heredity; but the number of cases and character of control does not by any means establish this as a general law.

Another item bearing on this subject is given by Creighton, unfortunately without sufficient details, in these words:

> I was enabled, by the kindness of Mr. F. W. Twort, to use a whole series of microscopic specimens from thirty cases of mouse-cancer, female and male, which came all from one or two cages in the following circumstances: A breed had been started two years before in the country as a pastime. Cases of tumor occurred from time to time, of which the animals died, microscopic specimens being made from each of them as they occurred. The fatalities continued, no new blood was introduced, and at length the whole of the mice, males as well as females, died of one kind of cancer or another, so that the family was literally exterminated in the space of two years.

A much more extensive series of observations than any of the foregoing has been reported by Loeb and Lathrop, based on the existence in the stock of mice bred by Lathrop, for commercial purposes, of strains in which subcutaneous (presumably chiefly mammary gland) tumors were found with almost constant frequency, the rate varying widely in different strains. Only females over six months of age were considered. Unfortunately, these tumors were not all ex-

amined microscopically, nor was there systematic necropsy investigation of mice in which no external cancer occurred; but it is understood that the figures are based solely on the presence or absence of visible or palpable mammary gland tumors, diagnosed often only by observation of the gross appearances. If so, this fact needs to be kept in mind in analyzing the results, which should be considered as applying exclusively to macroscopically recognizable mammary gland tumors. Just how much of an error this will introduce into the figures is uncertain, and we cannot be sure that the proportion of error will be approximately the same in different series, since it would be possible for one series to have a considerable proportion of internal neoplasms not present in another strain. Loeb is of the opinion, however, that omitted internal tumors could not have been sufficiently numerous to modify their statistics seriously.

The main points developed by Loeb and Lathrop are these: Heredity undoubtedly is an important factor in determining the incidence of cancer, for strains can be established which run an almost constant proportion of subcutaneous cancer for several generations. These rates may be as high as from 58 to 65 per cent. They also found that a certain relationship exists between tumor frequency and tumor age, the latter seeming to be as characteristic for a certain strain as the tumor rate, or perhaps more so. When strains known to differ in their tumor rates were crossed, it was found that the hybrids might show tumor rates corresponding to those of either parent, or intermediate between the rates of the parents. Even when the two parents have a similar rate, the offspring may

have a different rate, although in such a hybrid cross the rate is usually similar to that of the parents.

The relations between tumor age and tumor rate, previously mentioned, are interpreted by Loeb and Lathrop as best explained "if we assume that the hereditarily transmitted constitution, so far as it represents the tendency of the organism to develop tumors, depends on the coöperation of multiple factors. These multiple factors determine the intensity of the tendency to tumor development in a certain individual. In general, the greater is this intensity, the earlier do the tumors appear, and the greater is the probability that in related individuals there exists likewise a tendency to the development of tumors. It is furthermore probable that in addition to the general factors determining the intensity toward the development of cancer, there exist factors which determine specifically the tumor age in certain individuals and strains."

A most extensive and carefully controlled investigation on the influence of heredity on the incidence of tumors in mice has been conducted by Maud Slye* under the auspices of the Otho S. A. Sprague Memorial Institute. This work has continued for more than twelve years, being the continuation of a study in genetics begun under the direction of Prof. C. O. Whitman, and has been carried out with a stock of mice of known ancestry for many generations. These mice are all the descendants of a limited and carefully selected stock, bred together according to definite plans designed to give evidence as to the

*A review with full bibliography is given by Slye in the Journal of Cancer Research, 7, 107, 1922.

influence of heredity on the incidence of spontaneous tumors in mice, and hence including strains of highly cancerous ancestry and strains with ancestry free from cancer. They represent strains in which cancer is very common, strains in which it never occurs, and strains of intermediate character. It must also be emphasized that not one of these mice has been subjected to any artificial influences that might modify its life. In no case is a spontaneous tumor used for inoculation, or operated on, and no mouse born in this laboratory is ever used for any experimental work whatever. From the moment of its birth, every effort is directed to the one object of permitting each mouse to reach a maximal age. Long experience and great care have made it possible to limit to a large extent the epidemic infections that constantly threaten such large colonies of mice under even the best of conditions. Up to the present time more than 40,000 mice have been examined postmortem, and all lesions that might possibly be cancer, or concerning which there was any doubt whatever, have been examined microscopically by Miss Holmes and myself. For example, every pneumonic lung is sectioned, no matter how obvious the pneumonia, since the inflammatory lesion might possibly conceal a lung tumor. All told, there have been at least 5,000 spontaneous tumors, mostly malignant, observed in this stock; and as all the mice, whether evidently cancerous or not, have been submitted to necropsy, the material is adequate in amount and quality to furnish evidence against which the question of chance or inadequate controls cannot be raised. Were it not that every dead mouse is thus thoroughly investigated, and that the average age at death

is, for a mouse community, very high, there would not be nearly so much cancer material.

Out of this work many facts have come and much has been learned concerning the influence of heredity not only on the occurrence of cancer, but also on its behavior. Some of the outstanding results are the following:

1. *Cancer in mice appears in most of the forms seen in man, and in far greater variety than had previously been supposed.* Since most of the mouse tumors that have been studied elsewhere were those observed by animal breeders, and generally in comparatively young mice, almost the only mouse tumors that were known for some time were mammary gland tumors. Only when large numbers of mice were kept to a maximal age, permitted to die a natural death, and then studied carefully by necropsy, did the great variety and abundance of mouse tumors outside the mammary gland become known. Although mammary gland carcinoma is by far the commonest growth, nevertheless not a few other growths are found. Thus, in the first 6,000 mice were 160 with primary tumors of the lung, chiefly papillary adenomas and carcinomas; in the first 10,000 mice there were twenty-eight primary liver tumors, this number having been greatly increased since that time; in 12,000 necropsies, no less than eighty-seven unquestionable sarcomas were found; in 19,000 mice there were twenty-eight cases of tumor of the testis; in 28,000 mice there were seventy-one cases of squamous carcinoma of the skin or mouth, fifteen cases of typical basal-cell carcinoma of the head, four squamous-cell carcinomas in the stomach, and several others in different locations: in

22,000 mice there were forty-four with ovarian tumors, mostly solid papillary adenomas, in 33,000 mice there were sixteen primary renal and four suprarenal tumors; in 39,000 necropsies were found twenty-two uterine tumors, eleven of which were leiomyomas, and no unquestionable carcinomas. Not a few other tumors have been observed in these mice, which will be reported later. The importance of the demonstration of this abundant variety of tumors in mice lies in the fact that it adds greatly to the existing evidence of a fundamental similarity in neoplastic disease of mice and of man. Nearly all tumors found behave in much the same way, occur at a corresponding period of life, in response to similar conditions, and present exactly the same histologic structure as similar tumors in man. The chief difference lies in distribution, the mammary gland carcinomas being by far the most frequent, whereas carcinomas of the stomach and uterus are almost unknown in mice, the same being true for nearly all animals except man.

2. *The tendency to develop cancer, or the capacity to resist cancer, is unquestionably influenced by heredity.* Strains have been established in which, among many hundreds of individuals, through as long a period of observation as twenty-five or thirty generations, not a single case of tumor growth has been seen. Also, strains have been established in which the occurrence of cancer is so common that it becomes the sole cause of the natural death of the animals. Since every mouse that dies of anything except senility might possibly have developed cancer had it lived out its maximal possible span of life, it is difficult to secure 100 per cent cancer strains;

yet families have frequently been obtained in which all the deaths for one or more generations have been from cancer, and strains with figures approaching 100 per cent tumor incidence for several generations have been obtained.

Since cancer is a disease developing late in life, what is transmitted is merely the tendency, or resistance to the tendency, to acquire cancer, never the disease itself. But, of course, it is true of all characters that only the tendency to them is inherited, since in the fertilized ovum which carries the tendency none of the characters in which it is manifested have yet appeared; some of the characters appear in fetal life, some not until after birth.

3. *The resistance to cancer in these mice behaves in breeding, in Slye's experience, like a typical mendelian dominant character. The susceptibility to cancer behaves as a mendelian recessive.* When a cancer mouse, derived from the crossing of cancer mice is crossed with a mouse free from cancer and derived from ancestors that never have shown cancer for many generations, the *resulting hybrids of the first generation never show cancer.* If such hybrids are bred together or with other hybrids of similar ancestry, cancer will appear in the offspring in mendelian proportions, and strains of (1) pure cancer mice, (2) pure cancer resistant strains, and (3) heterozygous strains can be extracted, exactly as with any other inheritable "unit character." To quote from Slye:

> Cancer and non-cancer tendencies segregate out and are transmitted as such. They are therefore unit characters. A specificity of tissue type in specific organs from ancestor to offspring segregates out and is transmitted as such. It is therefore a unit character. Since these things are unit characters, it is possible to manipulate them by selective breeding

and thereby to implant them indelibly in any species, *or to eliminate them permanently and completely from any species.* Cancer and non-cancer behave like the absence and presence, respectively, of a mechanism fitted to control proliferation and differentiation in regenerative processes; and an animal either has this mechanism or lacks it, no matter to what species he may belong.

This fact has been observed so many times and with such constancy that Slye feels certain that her work establishes her conclusions beyond any doubt. It is, of course, quite to be expected that susceptibility to cancer should be a recessive character; for, if susceptibility were dominant, cancer would be far more prevalent than it is. The usual statement that a deleterious dominant factor eliminates itself by destroying the species in which it occurs does not hold for cancer, since this disease does not usually manifest itself until after the reproductive period is almost or entirely completed.

4. *Not only the incidence of cancer is influenced by heredity, but also its site and its character.* For example, in certain strains, sarcoma is very common; in others it is seen rarely or never. In some strains one seldom sees any form of malignancy except mammary gland cancer. Slye has developed one strain of mice whose inbred and hybrid derivatives have yielded more than a hundred primary liver tumors, although in all the other mice examined postmortem in her laboratory not a single liver tumor has been found, and only two other cases have been reported from the thousands of mice examined in other laboratories. Another strain has yielded a considerable number of tumors of the testis, although not a single case has ever been reported from other laboratories. A similar tendency for other tumors to appear chiefly or exclusively in

certain tissues in certain strains has been observed by Slye. It may be recalled that Loeb reports that the tumors of the Lathrop stock are mostly mammary gland carcinomas, whereas Tyzzer[60] had a remarkably high proportion of lung tumors and a low proportion of mammary gland tumors among his cases of spontaneous tumors, and Murray observed lymphomas in a certain strain of mice. Indeed, the difference in location of neoplasms in respect to organs in different species is of itself an hereditary character, for in the cow we find the mammary gland immune, the suprarenal and liver susceptible; in swine, the embryonal adenosarcoma of the kidney is the prevailing tumor; in rats, sarcomas are more numerous than carcinomas; in negroes, uterine leiomyomas seem to be exceptionally common.

5. *Behavior of tumors is influenced by heredity.* This statement is based on the observation that the localization of secondary tumors seems to be determined largely by heredity. Similar types of mammary gland tumors in mice have been found to produce much pulmonary metastasis in some strains, and none or little in other strains. Furthermore, the strains in which secondary tumors occur frequently in the lungs are also the strains in which primary pulmonary tumors are common. A similar observation has also been made for the primary and secondary liver tumors. It may be mentioned that Wood has observed in rats that in some strains a transplanted tumor produced many more instances of lung metastasis than in other strains inoculated with the same tumor.

6. *Inbreeding is not, of itself, responsible for an increased susceptibility to cancer.* I make this statement in this way be-

cause it has been suggested that Slye's high cancer rates were the result of inbreeding, a statement that is not warranted in the light of any appreciation of the principles of inheritance. Inbreeding merely concentrates existing characters, but does not produce new characters. Therefore, inbreeding of cancer-resistant strains produces cancer-resistant strains, while outbreeding of cancer-susceptible strains with other susceptible strains produces cancer susceptible strains. An inbred strain may produce 100 per cent of cancer or 0 per cent of cancer, depending on the character of the strains that are inbred.

While we have no similar material to compare with Slye's, in which the complete ancestry for many generations is known, all animals are permitted to reach a maximal age, and every dead animal for from twenty to thirty-five generations has been submitted to careful postmortem study, yet such study as others have made of the influence of heredity on spontaneous cancer serves to corroborate at least the *fundamental* point: that heredity is a most important factor in determining the absence or occurrence of cancer.

I have previously referred to the evidence produced by Virchow, Tyzzer, Loeb and Murray in respect to spontaneous tumors in animals, which agrees in indicating the importance of heredity in determining the occurrence of cancer, and also to some extent in determining the site and character of the neoplasm. To this list may be added two more recent contributions which bear directly on the latter point.

A Swiss investigator, Stilling, had been carrying on transplantation experiments, using a definite strain of rabbits which he raised himself. During these experiments he found

tumors in the uterus of several animals. He waited years until he had accumulated thirteen such animals and carried out a series of inoculation experiments with them. His death interrupted these experiments before he had given more than a few short communications concerning transplantable tumors before a local medical society. A pathologist, Beitzke, examined the records Stilling left behind him and reports the results. Beitzke says:

> He [Stilling] bought almost *no* rabbits, but raised his own stock, which not only permitted him to control the relation of his experimental animals, but in a certain sense to raise a whole tumor race. Unfortunately, no mention was found in his records that he had undertaken an exhaustive investigation concerning the influence of heredity.

Stilling attributed his success to the fact that he kept his animals until they were old, the youngest tumor being in a four-year, the oldest in a seven-year rabbit. He also laid weight on the fact that most of the cases occur in rabbits of the same strain. This contribution is especially valuable because rabbits seldom exhibit spontaneous tumors, for we can find in the literature records of but twenty-eight cases of rabbits with tumor growth, all told,[57] exclusive of the thirteen found by Stilling in one small strain of rabbits. Therefore, the element of chance may be entirely excluded as accounting for the occurrence of Stilling's cases.

Equally true is this of the experience with rat sarcomas in the Crocker Fund Laboratory, Columbia University.[8] Here numerous experiments have been carried out with rats infected with a certain tapeworm, *Tænia crassicollis*, which passes its encysted stage in the liver. In some of the infected

rats, sarcomas develop in the liver as a result of the irritation or growth stimulation. It has been found that different strains of rats differ greatly in their tendency to develop sarcomas in response to this common stimulation of the liver tissues, some giving a high percentage and some a low percentage of positive results. At the 1923 meeting of the American Association for Cancer Research, Wood reported that when rats that developed sarcoma were bred together, much higher rates were obtained in the offspring, such families sometimes giving 100 per cent of positive results.

Another piece of work which may bear on the subject of heredity and tumor formation is that of Stark, on the lethal neoplastic process discovered by Bridges in a fruit fly, *Drosophila melanogaster* (amelophila). This appears in the form of black granules in the bodies of the larvæ, affecting males only, although not attacking sex structures, and causing death of all the affected larvæ. The growth consists of a solid mass of large cells, producing much pigment which resembles melanin. Unfortunately, we know so little about the pathologic anatomy of insects that it is not possible to prove that these growths are true malignant neoplasms identical with mammalian cancer; but this much is in favor of such a conclusion: (1) The tumors consist of atypical cellular growths; (2) they invariably kill the organism they attack; (3) bacteria cannot be cultivated from them; (4) sterile eggs raised under aseptic conditions may produce larvæ exhibiting these growths; (5) the growths may be transplanted into other larvæ, and into adult flies; (6) metastases may form consisting of cells identical with those of the original growth; (7)

irregular mitotic figures have been noted in rapidly growing tumors, and (8) the tumors develop in embryonic rudiments, destined to develop the adult organs during the pupa stage.

If this growth of the fruit fly larvæ is a true tumor, it furnishes a remarkably clear instance of a neoplasm that occurs solely on a basis of heredity which has been worked out conclusively. In the affected strains it is found that one-fourth of the larvæ die, and these are all males; that is, one-half of all the males die. Therefore, this inherited lethal growth behaves in inheritance as a sex-linked recessive factor.

MECHANISM OF THE HEREDITARY INFLUENCE

In view of all the experimental evidence cited above, and the absence of any experimental evidence that contradicts it, the conclusion seems inevitable that the incidence, character, location, and behavior of tumors depend to some extent, at least, on the inherited qualities of the animal and of its tissues. This being granted, the next question is: How does heredity determine susceptibility or resistance to tumor formation?

Apparently this may be answered as follows: Tumor formation is the result of stimulation of the tissues to growth, the stimuli being of various sorts and non-specific. Some stimuli produce marked proliferative effects in proportion to the retrogressive effects, and such stimuli are particularly capable of leading to neoplastic proliferation, that is, roentgen rays, coal-tar. The same amount of stimulation does not produce equal amounts of proliferative reaction in all individuals, even when of the same species, that is, negroes are

more likely to develop excessive amounts of connective-tissue growth (keloids) in response to cutaneous injuries than are white men, and some white men develop more scar tissue than others from similar wounds. Not all roentgen-ray workers develop the same degree of hyperkeratosis from the same amount of exposure, and some develop roentgen-ray cancer much sooner than others. Hence there are individual variations in both amount and character of proliferative reaction to a common stimulus, and these variations undoubtedly rest on an hereditary basis, in part if not wholly.

Evidently, then, heredity may determine whether the proliferative reaction that follows injury assumes a neoplastic character or not, just as the Crocker Laboratory rats do or do not develop sarcoma in the liver tissues about the encysted tenia, according to their ancestry. This has been pointed out especially in connection with the study of the lung tumors in Slye's mice, which show that mice with cancer heredity react to non-specific inflammatory conditions in the lungs more often with excessive proliferation which leads to malignancy than do mice of non-cancerous ancestry. All mice of tumor age have suffered more or less from inflammatory conditions in the lungs, with proliferative reactions. In some of the mice of cancer ancestry, but only in about 10 per cent of those involved in this study, the proliferation assumed a definitely neoplastic character. On the other hand, mice not of cancer ancestry subjected to corresponding lung injury very rarely, if ever, reacted with proliferation to a degree even suggesting tumor formation. Nor is this all of the story. Since this study was made, we have learned more of

organ specificity in cancer heredity, and we now know that if certain strains are selected it is possible to secure a breed of mice nearly all of which develop lung tumors, and others which never develop lung tumors in response to exactly similar conditions of lung injury.

A nicely comparable instance is cited by Bateson, who, speaking on observations on inherited deformities of the feet in chickens, says: "When the incubators are not running uniformly, many of the chickens are born with deformed feet. Such abnormality, however, is found with especial frequency in particular strains of birds, though eggs from other strains exposed to the same conditions may give perfectly normal results. The *liability* is the thing transmitted, but without the appropriate conditions the effect is not produced." That is to say, it is not the characters themselves that are inherited but the tendency to develop them. For example, we have the following example from plant genetics: Red and white primroses breed true;[54] but if red primroses are raised in a greenhouse at from 30° to 35° C., the blossoms are all white and in appearance they differ not at all from white primroses. If after many generations of growing white flowers they are transplanted outdoors, they again breed red blossoms as before. Therefore, the red primrose cannot be said, when growing in hothouses, to transmit redness, but only the capacity to react to a certain environment by producing red pigment.

A striking illustration of what seems to be an example of another disease in mice that behaves exactly as if determined by a mendelian unit factor has been furnished by Hagedoorn-La Brand. A breeding experiment was under way in which a

colony of mice, composed of Japanese mice, large albinos, and hybrids of these two, was under observation. This colony was attacked by an epidemic staphylococcus infection, which killed all the Japanese mice, but attacked none of the albinos, although the latter often ate the dead infected Japanese mice. No animals attacked by the infection recovered. *In the first hybrid generation, no mice died*, although quite as much exposed as the others, thus indicating that the resistance of the albinos depended on a single dominant genetic factor. This was further corroborated by the observation in the other generations of hybrid crossings. In the second hybrid (F 2) generation, of 125 animals ninety-one lived and thirty-four died, the theoretical expectation on the foregoing assumption being 93.75 to 31.25. Of crosses between F 1 and Japanese, of fifty-seven animals twenty-five lived and thirty-two died (theory, 28.5 to 28.5). Of crosses between F 1 and albinos, of fifty-one only one died (theory, no deaths). These results correspond remarkably well with the assumption that the albino mice possess one gene, the presence of which protects them against death from this infection, and which is lacking in the Japanese mice.

Presumably related to this sort of inheritable predisposition to an infectious disease is the inheritable deficiency in complement observed by Moore. This deficiency is associated with a lack of resistance to infection, and it behaves as a simple mendelian recessive, hybrids of the first generation having as active complement as that of the normal parent.[26]

In Slye's experience, the hereditary factor of resistance to

cancer may become so high in pure strains of selected mice that no ordinary amount of proliferative stimulus ever overcomes it, for strains of cancer-resisting mice have been developed which have never shown cancer during at least thirty generations, which would correspond in human life to close to a thousand years. Conversely, the capacity to resist cancer may be so effectively bred out of mice that virtually all of a selected strain develop malignant neoplasms from the ordinary proliferative stimuli occurring under even the best of living conditions. Only experiments as yet not performed will show whether the maximal experimental proliferative stimulation may overcome the resistance of pure non-cancer strains of animals. Evidently in the heterozygous human race, maximal stimulation is almost always capable of overcoming such resistance as exists, since so large a proportion of people exposed to excessive amounts of Roentgen rays have developed cutaneous cancer, but even so, we do not know of any particular form of tissue stimulation in man that leads to 100 per cent cancer production. Conversely, cancer often develops in tissues in which there has apparently been no unusual amount of injury or stimulation; that is, in man, cerebral gliomas occasionally develop after a definite trauma as an apparent sequel, but in most cases of cerebral glioma there is no history of trauma to the head, and in retinal glioma we see many cases occurring in a single family with no suspicion of any injury whatever to the retina. In this last case the hereditary influence is so great that merely the ordinary physiologic wear and tear seems to be sufficient to lead to malignancy.

C. Relation of Animal Experiments to Human Disease

As to the bearing of the experimental evidence on the problems of human cancer, the following facts must be considered:

1. Cancer in animals is, in all essential respects, the same disease as cancer in man.

2. The laws of heredity are fundamental biologic laws applicable to every living thing, whether plant or animal. Mendel worked out the principles of inheritance with garden peas, and these principles have been found to hold good for all multicellular living things, whether plants or animals, whether peas or mice, insects or cows. This must inevitably be so, since all multicellular creatures take origin through fertilization of one cell by another, and since the fertilized cell produces quite the same sort of being as the one from which it came. If the laws of heredity established with peas hold good for mice, they should hold for men, for there is far less difference between mice and men than between mice and peas.

3. We have, furthermore, found that these mendelian principles do appear in human inheritance, although as yet we have no completely satisfactory evidence of mendelian inheritance in human cancer. Because man is a slow-breeding animal with very small families, it is not possible to study all sorts of inheritance in the human species, but there are some striking pathologic conditions which may be followed. For example, in hereditary hemophilia and in color blindness we find perfect illustrations of an inherited sex-linked recessive unit character. While we cannot usually secure sufficient data to test out the mechanism of human inheritance, Fischer reports that in the crossing of Europeans with Hottentots,

transmission of characters occurs in accordance with mendelian expectations.

Another illustration of human heredity conforming to the mendelian principles is seen in the separation into four groups of the human red corpuscles in respect to iso-agglutination.[45] Fischer, indeed, says that "all known normal and pathologic characteristics that are transmitted by heredity follow the mendelian laws."

Therefore, if it is accepted that an important element in the occurrence of cancer in mice or other animals is the inherited character of the tissues, the same thing in all reasonable probability must be accepted for man. Furthermore, as pointed out previously, we do undoubtedly have instances in which the tendency to cancer has been inherited in man.

Thus, among Warthin's carefully studied material appear families in which the cancer occurrence corresponds beautifully to the mendelian expectation, and in Levin's analysis of human cancer from a geneticist's point of view, the evidence led him to interpret it as indicating that resistance to cancer behaves as a dominant, susceptibility as a recessive, character.

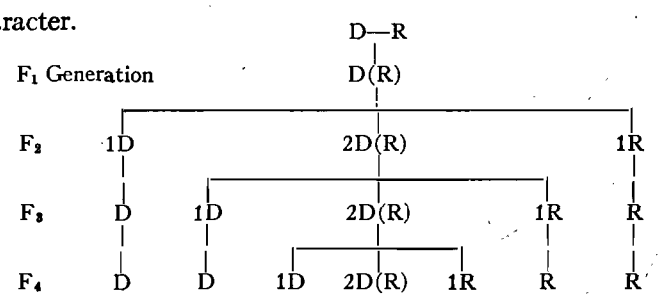


Fig. 21.—Typical mendelian inheritance: *D*, Dominant; *R*, recessive; *D* (*R*), presence of both factors, or heterozygous.

If we accept Maud Slye's contention that resistance to cancer behaves as a dominant character, and susceptibility as a recessive, we can understand the fact that human cancer commonly appears as an isolated condition in only a few members of a family, is often entirely absent in families of

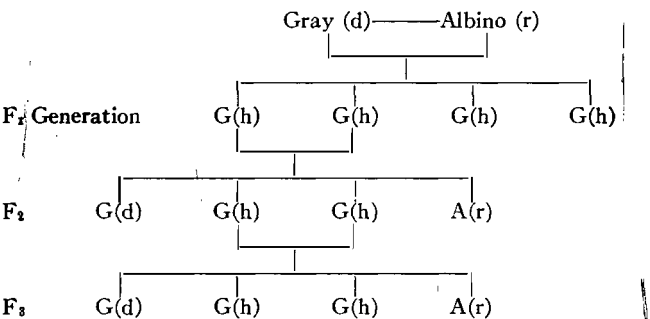


Fig. 22.—Typical mendelian inheritance in crossing gray and albino mice.

large numbers, and occasionally appears in a large proportion of the members of another family. As shown by the typical mendelian chart (Fig. 21), a recessive character does not appear in the first hybrid generation formed by crossing a recessive with a dominant character. If the heterozygous and dominant offspring of this generation are bred with dominant, the recessive never appears (Fig. 23). When heterozygous individuals are bred together (Fig. 22), the recessive character does appear, but only in the ratio of one in four of the offspring. If two recessives are bred together, however, then the offspring all show the recessive character. If heterozygous offspring are bred with pure recessives, half the offspring exhibit the recessive character (Fig. 24).

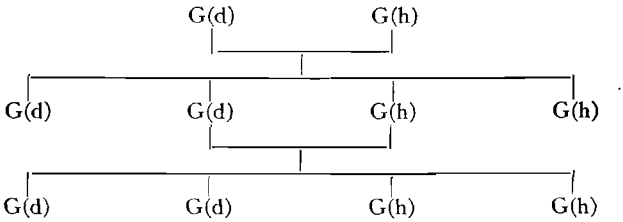


Fig. 23.—Inheritance in dominant mice bred with heterozygous mice.

Grayness is dominant, albinism is recessive. In the first hybrid generation the offspring will appear gray, but all still carry the recessive gene, *i. e.*, they are heterozygous. When these are bred together, the mice of the F_2 generation yield offspring in the following proportions: one pure (dominant) gray which does not carry the gene for albinism, two

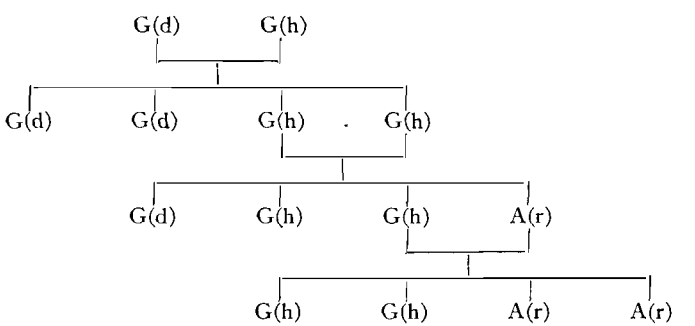


Fig. 24.—Way in which a recessive character reappears when heterozygous offspring are bred together, or when bred with recessives.

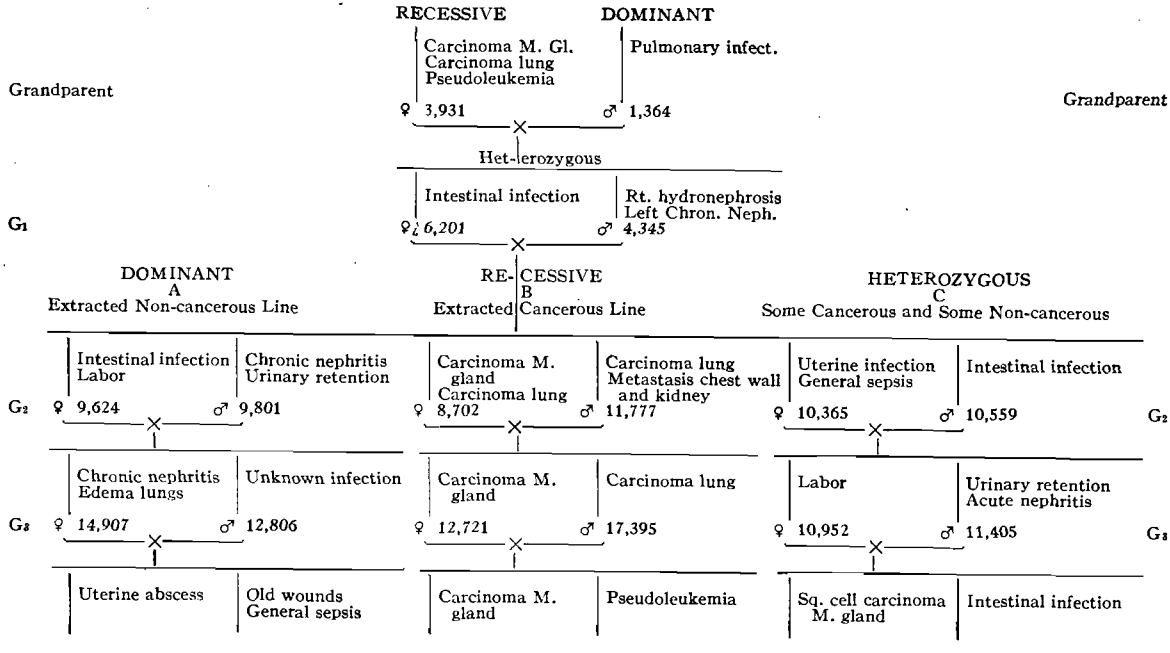
heterozygous grays carrying both genes, and one albino (pure recessive) which does not carry the gene for grayness.

In Figure 23 dominant mice are bred with heterozygous mice (derived from the crossing of gray and albino mice). As the dominant gray gene is always present in the offspring,

they always appear gray, although half of them have the capacity to transmit albinism when mated either with albinos or with heterozygous grays, as shown in Figure 24.

Transferred to the terms of human cancer, if this is a condition determined by a recessive unit character, then we should expect that in the heterozygous human race, breeding indiscriminately in respect to cancer ancestry, the recessive character of tumor susceptibility might crop out almost anywhere in a given family group, and ordinarily involve only a small proportion of the entire family. If, through chance, two individuals who inherited the tendency to cancer, which ordinarily would not manifest itself until after the reproductive period is over, should mate and bring forth offspring, it might be expected that these would all inherit the cancer susceptibility, and the demonstrated existence of "cancer families" agrees with this hypothesis. Equally well does the more common occurrence of families that show no cancer correspond to the expectations of this hypothesis.

The fact that either, but not both, of two parents had cancer would not require that the offspring should develop cancer, since the other parent might be resistant (and dominant) to cancer (even if he or she had cancerous relatives) and the offspring might correspond to a first hybrid generation none of whom has cancer. If one parent has cancer and the other parent is heterozygous to cancer, which should be the usual situation in the family history of descendants of a single cancerous ancestor, then the first generation should show some cancer cases (pure recessives) and some heterozygous offspring which do not have cancer themselves, but all of which


RECESSIVE
DOMINANT
Carcinoma M. Gl.
Carcinoma lung
Pseudoleukemia
Pulmonary infect.
Grandparent
♀ 3,931
♂ 1,364
Grandparent
Het-erozygous
Intestinal infection
Rt. hydronephrosis
Left Chron. Neph.
G1
♀ 6,201
♂ 4,345
DOMINANT
A
Extracted Non-cancerous Line
RE-CESSIVE
B
Extracted Cancerous Line
HETEROZYGOUS
C
Some Cancerous and Some Non-cancerous
Intestinal infection
Labor
Chronic nephritis
Urinary retention
Carcinoma M. gland
Carcinoma lung
Carcinoma lung
Metastasis chest wall and kidney
Uterine infection
General sepsis
Intestinal infection
G2
♀ 9,624
♂ 9,801
♀ 8,702
♂ 11,777
♀ 10,365
♂ 10,559
G2
Chronic nephritis
Edema lungs
Unknown infection
Carcinoma M. gland
Carcinoma lung
Labor
Urinary retention
Acute nephritis
G3
♀ 14,907
♂ 12,806
♀ 12,721
♂ 17,395
♀ 10,952
♂ 11,405
G3
Uterine abscess
Old wounds
General sepsis
Carcinoma M. gland
Pseudoleukemia
Sq. cell carcinoma M. gland
Intestinal infection

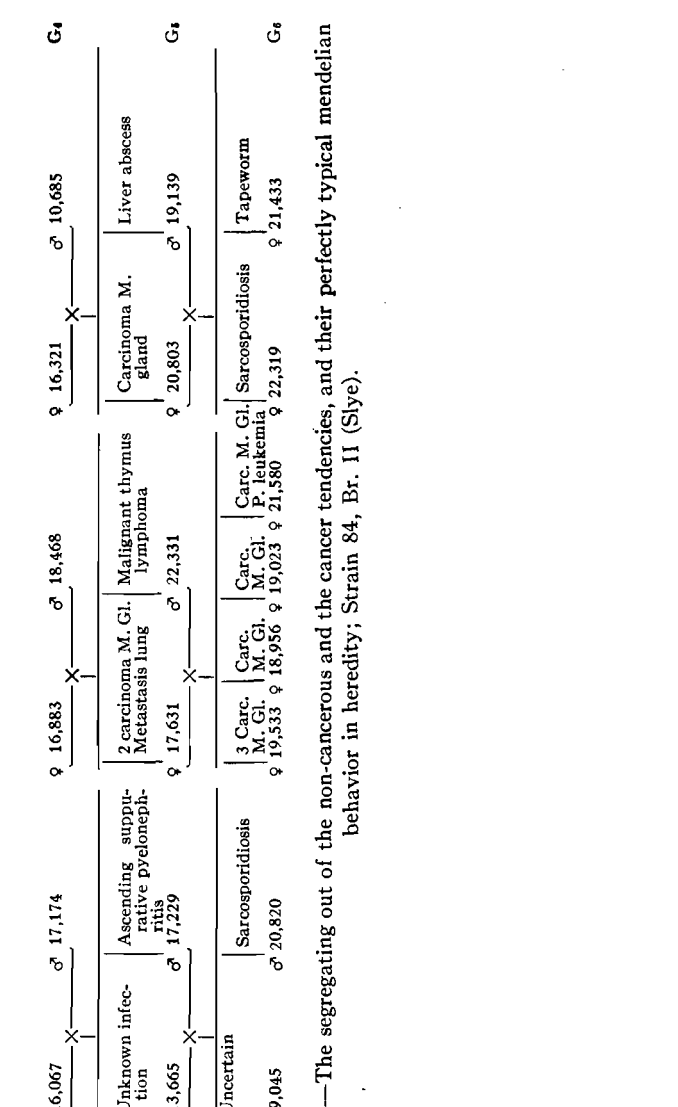


Fig. 25.—The segregating out of the non-cancerous and the cancer tendencies, and their perfectly typical mendelian behavior in heredity; Strain 84, Br. 11 (Slye).

may transmit the tendency to cancer. It is also perfectly possible for heterozygous and dominant resistant individuals to mate with one another for several generations without the recessive (cancer) appearing; but, when heterozygous offspring of such unions mate, cases of cancer might appear. This is illustrated by Slye in such a chart as the one here reproduced (Fig. 25). Here pure non-cancerous (dominant), pure cancerous (recessive), and mixed (heterozygous) strains are shown extracted from common ancestors. Note how in the heterozygous strains (*C*), cancer crops out at intervals (16,321, 20,803) after three generations of direct ancestors with no cancer. This heterozygous strain continued through (Fig. 26) exhibited in the thirteenth generation a mouse (30,908) with lung tumor despite the fact that its direct ancestors had shown no tumors for eight generations. On the other hand, none of the mice of the dominant, cancer-resistant strain (*A*) ever exhibited cancer during fifteen generations for which they were followed, whereas the recessive, tumor-bearing strain (*B*) continued to produce mice succumbing to neoplasms in every generation.

With human families, cancer appearing at long intervals in such a strain as *C* would ordinarily be interpreted as an example of cancer appearing in an individual without cancer ancestry, which is entirely contrary to the fact. The heterozygous human being could transmit cancer tendencies unrevealed through an indefinite number of generations, provided it failed to mate with recessives or other heterozygotes; but when cancer did come out it would be as definitely inherited as if each ancestor for several generations back had

had cancer. Failure to appreciate the manner in which inherited characters are transmitted has caused most of the confusion resulting from the impossible attempt to learn the hereditary relation of cancer by analyzing mass human statistics.

Certainly these considerations fit well with what we do know of human cancer. Until some one has carried out the arduous studies necessary to confirm or refute Slye's conclusions as to the exact way in which the demonstrated influence of heredity is transmitted, it may be fair to consider them as at least offering a reasonable explanation of the influence of heredity on human cancer. It probably will be a long time before we shall have enough reliable information, controlled by necropsy records, to determine the influence of heredity on human cancer by direct observation. Perhaps the easiest way to test the validity of the hypothesis that in man, as in mice, resistance behaves as a dominant inheritable character and susceptibility to cancer as a recessive, will be by securing records of the offspring of matings in which both parents had cancer. Here we should expect that all, or, allowing for premature death, nearly all, of the offspring of such a union that reach advanced age would develop cancer. Such statistics should not be impossible to secure, since they involve only two generations. But as yet, at least in America, we probably cannot find two generations in which we can be sure of all the final diagnoses. Possibly in some more advanced country, such as Switzerland, where necropsies are more usual, the necessary data can be obtained.

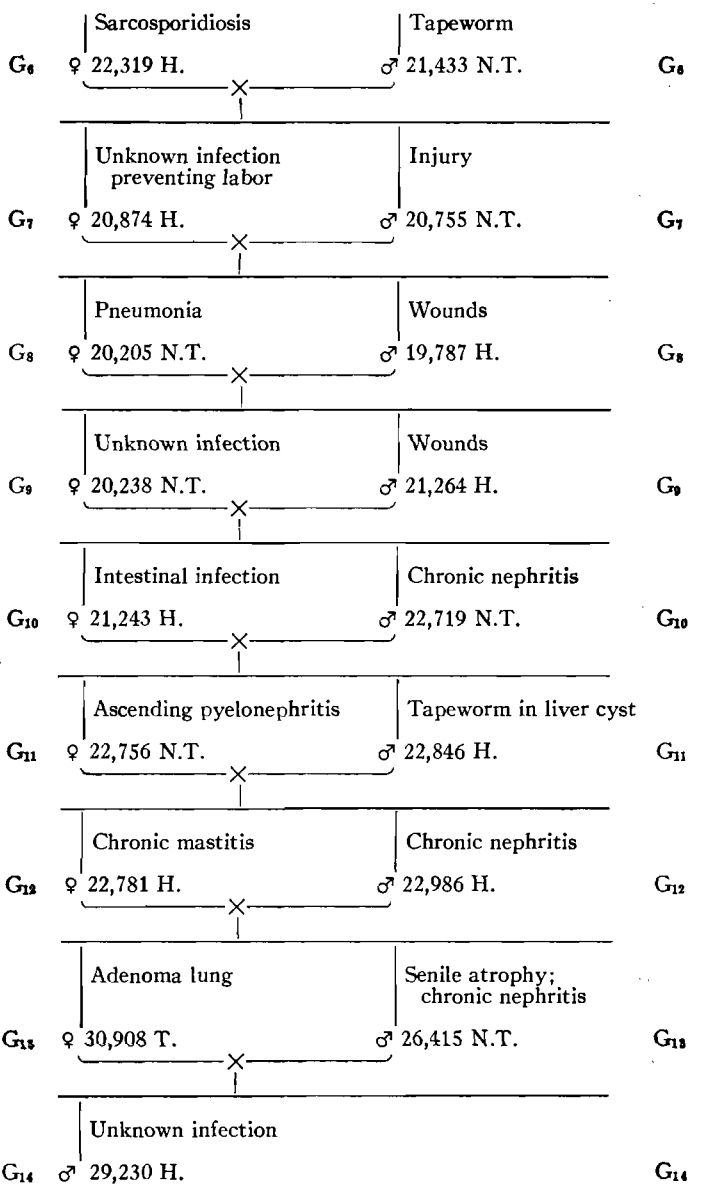


Fig. 26.—Heterozygous branch continued through the fourteenth generation; Strain 84, Br. C. (Slye): *H*, heterozygous; *T*, tumorous; *N.T.*, non-tumorous; *G*, generation.

SUMMARY

The coincident development of the science of genetics and experimental cancer research has begun to yield evidence bearing on the relation of hereditary influences to cancer occurrence. Human statistical evidence is not of sufficient accuracy or extent to render it of any value in the study of this subject. The occurrence of cancer families is unquestionable, but of doubtful value because of the possibility that such occurrences may depend solely on chance. Family occurrence of rare neoplasms, such as glioma of the retina, multiple neurofibromatosis, and multiple cartilaginous exostoses, cannot be dismissed as depending on chance. Human evidence being inadequate, we are compelled to rely on evidence from observations on animals. It is known that the principles of inheritance are the same in all species of animals as well as plants, and that cancer, in its fundamental respects, is the same in man as in other mammals; therefore the drawing of conclusions in respect to heredity and human cancer from observations on experimental animals is justifiable. Such observations have shown repeatedly that an important element in the occurrence of spontaneous tumors in animals is determined by the heredity of the animals under study. Slye has produced, solely through breeding, strains of mice that have never developed tumors in twenty and more generations, strains of mice in which the natural death of the adults is by cancer, and strains with less degrees of frequency of cancer occurring according to the mendelian expectation. In these animals the capacity to resist cancer behaves as a dominant character, the susceptibility to cancer as a recessive. There

is evidence available which supports the inference that in man also the susceptibility to cancer behaves as an inherited recessive character.

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EUGENICS

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The term "eugenics" has come to be used loosely in so many senses today that its real significance is by no means clear to the average person. The funny, or the would-be funny, speak of it as choosing your grandfather and remark facetiously about the twins Eugene and Hygiene, and the average newspaper is likely to use the term in heading the columns which deal with anything from the crusade against venereal diseases to birth control.

Perhaps the best way to arrive at a satisfactory understanding of what eugenics is will be to enumerate some of the things it is not. It is not prenatal culture, whatever that may be. There are still many persons apparently who believe the myth that mental impressions of a mother can in some way be stamped into the unborn young. Even were this true—and it is not—the facts would not pertain to eugenics. Neither is eugenics a crusade against venereal disease, although the newspapers herald almost all legislation which has to do with prenuptial medical inspection as "eugenics legislation." Some of it is, but most of it is not. Nearly all such laws are directed toward purely hygienic measures designed to prevent the spread of venereal disease, and they are more accurately classified under the caption of sex-hygiene. Only as such regulations have bearings on selective death rates or birth rates are they of eugenical significance.

On the other hand, as regards laws for the sterilization of certain constitutionally undesirable classes, the purpose is eugenical. Again, eugenics is not advocacy of an attempt to breed super-men by state enactment; nor is it a plan to mate human beings like animals. In fact, there is nothing in the idea repugnant to our ideals of morals, love, marriage, or parenthood.

The word is derived from the Greek "eugenes" which means "well-born"; the science concerns itself with race betterment through good ancestry. The fact is undeniable that there are individuals endowed by heredity with good physical and mental attributes, and there are those who are constitutionally inferior in one or the other, or both of these respects. The eugenicist simply points to the desirability of having more of the first, fewer of the second type. He recognizes that the question of breed, of the natural endowment of its citizens, is of fundamental importance to any nation.

The idea of eugenics is not a new one. At nearly every period of history there have been certain individuals who have seen the necessity of a state eliminating its supply of defectives and of conserving the better stocks. The term *eugenics* was coined by Francis Galton in 1883, and we may look to him, therefore, for a definition. He says, "Eugenics is the study of agencies under social control that may improve or impair racial qualities of future generations, either physically or mentally."

MENDEL'S LAW

Relation to Mental Diseases and Defects.—It is becoming more apparent every day that human structures and apti-

tudes no less than the traits of plants and the humbler animals are subject to the well-known laws of inheritance. Certain insanities in man, for instance, behave as mendelian dominants, and hereditary feeble-mindedness acts as a mendelian recessive, as surely as yellow dominates green in crosses of the garden pea, or wrinkled surface is recessive to smooth. And as any one of these characteristics can be removed in subsequent generations by the plant-breeder, no less surely can the terrible maladies of man just mentioned, as well as others, not spoken of, be largely eliminated if we but follow the obvious path marked out by our present knowledge of heredity.

Here in the United States we are in the midst of one of the most important experiments in government the world has ever known, American democracy; an experiment the fate of which unquestionably will be determined by the educated men and women of the next few generations. For human society has become so complex that it can no longer be entrusted to the whims and the prejudices of the unenlightened. It must be guided by broad, sympathetic understanding, by intelligent management, and by a desire to promote the well-being of others.

Relation to Democracy and the State.—Democracy, government by the people, requires mutual understanding and cooperation; it means consensus of opinion. And this opinion, in turn, is only the outward manifestation of the ideals which make each individual what he is. And what is he? He is the expression of certain inborn mental predispositions plus the effects of environment and training.

The biologist, working year after year on problems of heredity, seeing literally the futility of trying to gather grapes from thorns or figs from thistles, recognizing the impossibility of turning draft horses into racers, realizing, in short, that "blood will tell," the biologist, I say, is firmly convinced of the fundamental importance of inborn tendencies in determining what an individual shall become. The Hapsburg lip is traceable through eighteen generations from a fourteenth century duchess, but just as surely in evidence throughout the ages are the Hapsburg madness and the Hapsburg morals. Authorities on the subject of human heredity, such as Karl Pearson of London, from the results of long study based on many measurements and tests, both mental and physical, assert that heredity is from five to ten times as important as environment in determining what a given individual shall become.

Since it is mainly the innermost qualities of men which determine what as citizens they shall be in disposition, character, and intelligence, and inasmuch as such qualities are handed on in inheritance no less certainly than the more obvious characteristics of stature, complexion, or bodily structure, it is clear that the question of human heredity is of fundamental importance to our nation.

Influence of Environment.—Do not misunderstand me. I would not in the least minimize the part of environment and training, but I would emphasize the importance of the fact that the effects of environment and training depend on how a given inborn constitution reacts. Heredity determines what one *can* become; environment and training supply,

in the main, the means of becoming it. In brief, the issue of human life depends largely upon the endowment individuals have to start with, but obviously the best of predispositions may be warped by thoroughly unwholesome experiences and surroundings, or suppressed by lack of opportunity or wrong training.

We talk much in these days about training for leadership. Training whom? Give the rose the same earthy salts, water, and atmosphere provided for the jimson, and instead of this poisonous weed with its nauseating odor, we find the raw materials transformed into a thing of fragrance and beauty, by virtue of the rose plant's inner mechanism. Each produces its kind. So, training and education cannot create ability; they can only reveal and perfect what is there.

Relation of Stock to Government.—We hear much today about equality of rights, the rights of this class or of that, but there is a significant silence regarding the obligations of the class in question. Yet, rights in a true democracy imply also duty, service of each for all. No country can be wisely governed unless its citizens are willing to select those best qualified by nature and education to formulate and administer its laws, not in the immediate interests of any class even though it be a majority class, but in the interest of the whole nation. Yet, withal, the government must be the expression of the natural inclinations of those governed. Government can only do what can be done with its people. Hence, the unescapable necessity of a fundamentally well-disposed stock with which to begin.

TESTS OF INTELLIGENCE

But have we any light on the real situation in America today? While various significant studies have been made in recent years, perhaps the facts which are attracting the most attention at present are the results shown from the army intelligence rating. This rating was based on tests prepared by our American psychologists to determine just what each individual conscript was best fitted to do as his part toward winning the late war. While these tests can be and have been criticized from many points of view, the fact remains, when all is said and done, that they are statistically valid. The best evidence of their reliability is the closeness with which the later performance of many of the tested individuals corresponded with the forecast. They were not tests of schooling or of memory, but were intended to be tests of intelligence, power to reason, to see relations, to grasp situations as a whole. These are largely inborn qualities. There were two sets of tests: one, the *alpha*, for men who could read and write English readily, the other, the *beta*, for the illiterate, the non-English speaking, and those who could not read and write English well. The results were tabulated according to a scale which ranged from A to E, in which A and B were regarded as superior, C as average, D as inferior, and E as very inferior. Of our white recruits, only 12 per cent proved to be superior, 66 per cent were average, and 22 per cent inferior. Such tests are also commonly expressed in terms of mental age based on comparisons with school children. While such comparisons do not tell the full story of the respective abilities of adults and school children, graded at the

same level, to be self-supporting and even socially valuable citizens, nevertheless, such a scale is of value in classifying individuals according to their relative mental capacities. It at least shows the spread of the capacities tested. It is a momentous fact that 47.3 per cent of our white recruits graded below the mental age of thirteen years. And unquestionably the army possessed a higher average of intelligence than would be found among the same number of individuals taken at random from our population, because the obviously feeble-minded and those who were otherwise mentally defective had already been weeded out before the tests were made. Yet, the fate of a democracy must be determined by the intelligence of its voters, and we may well remember also that intelligence cannot be bestowed by a majority vote.

The Average Man.—The truth is that most of us have little suspected the amount of low-grade intelligence there is in our population. We have a mistaken idea of the abilities of the so-called average man, so keenly played up to by the politician, the advertiser, and the newspaper because his kind, of necessity, constitutes the most numerous class in the community. So much is he extolled and courted that most of us take considerable pride in proclaiming ourselves average men. And yet on the basis of intelligence tests we find this composite creature located well down in the laboring class with a mental age of not over thirteen years.

According to the illiteracy commission of the National Educational Association there are more than 4,300,000 known illiterates entitled to vote in this country, of whom more than 3,000,000 are of native birth. The commission

is convinced, moreover, that the 4,931,905 acknowledged illiterates in the United States constitute less than half of the actual number, because of the many overlooked in the census-taking or who concealed their illiteracy.

National Menaces.—While many factors may tend toward national deterioration, the four most prominent ones which are operative in, or which threaten America, are: (1) War; (2) the unwise charity which not only permits, but encourages the production of unfit strains; (3) the immigration of types which in desirable natural attributes do not measure up to our standards; and (4) the infertility of our better stocks.

In staying the hand of war we have, of course, escaped one serious menace to our blood. For it is clear that any race must be carried on by what is left after war has taken its toll. And just in proportion as it takes a toll of men of above average physical efficiency, energy, and intelligence, just in that proportion are future generations impaired. How serious such reversed selective action is, is determined by the deadliness of the warfare and the length of time it continues. Fortunately for us in this respect, our time in the war was brief.

But as noted, war is only one of several factors in racial deterioration, a factor which because of its dramatic nature thrusts itself on us, but which, deplorable as it is from the standpoint of inheritance, is less threatening than certain of the other dangers enumerated. We look grave at the suggestion of what may happen to our race as the result of the destruction of half a million able-bodied men in war, and well we may, yet we face with complacency what is happening

to our race through the celibacy, the delayed marriages, and the infertility after marriage of thousands on thousands of our mentally and spiritually most highly endowed men and women. Yet from the standpoint of racial preservation, what is the difference how parenthood is prevented, so long as such frustration is a fact?

But, it will be inquired, has not the mosaic of good and bad strains in society always existed? Has not each been producing its kind for a long time? Why grow agitated over it just now? To answer this let us look at what human affairs would be under conditions of nature, uninfluenced by our modern altrusim. It is evident that if the weak, the insane, the feeble-minded, and the pauper were left to nature, they would die of disease, the rigors of the climate, or from inability to secure food; and that, too, long before they could mature and produce their kind. If this happened generation after generation, the race would in time become purged of the physically and mentally incompetent. But with our improved methods of sanitation, with our care of the sick, with our charities and philanthropy, we protect and foster such misfits, permitting them to grow to maturity and produce their like. In other words, we have, temporarily at least, so eased the rigors of what the biologist calls *natural selection* that decadent stocks are not only holding their own, but some of them are increasing relatively faster than normal stocks. Moreover, they are contaminating sound strains. It is clear, therefore, that if we do not use our intelligence and substitute some other check, we are headed toward disaster.

Results of Protection of Misfits.—Now there is no one who

will deny that the altrusim which prompts our action is based on the noblest motives of the human heart, and no one, least of all the eugenicist, would advocate abandoning these derelicts to the painful and pitiless method of elimination by natural selection. But what the eugenicist would suggest is that we look beyond the present generation of decadent strains and ask ourselves the question why they should not be the last of their kind. Why not prevent such social maladies instead of turning them loose as a scourge on humanity and then striving ineffectually to cure them? It is obvious that on a dangerous mountain highway we can build a strong railing at the top of a precipice to prevent accidents, or we can establish ambulance and hospital service at its foot so that unfortunates who plunge over may be tenderly cared for or decently laid out by the undertaker. It is all a matter of judgment. At present in our charitable work we are using mainly the hospital and undertaker combination.

Lest it be thought that the alarm over the deterioration of our blood as a nation is based on rhetoric rather than on reason, I wish briefly to present a few significant facts.

Perhaps no danger is more threatening than the spreading of mental and neural defects, particularly insanity, feeble-mindedness, and epilepsy. There has been great activity during the past few years in the study of the mentally diseased and the mentally deficient, and it is the consensus of opinion of those qualified to judge that certain of the various forms of insanity are based largely on inherited neural instability, that at least two-thirds of feeble-mindedness is inherited, and that much of epilepsy has a heredity basis.

Statistics of Mental Diseases and Criminalism.—A conservative estimate places the total number of insane in the United States today at 250,000. These are maintained at an annual cost of over $33,000,000. They outnumber the students in our colleges and universities. The state of New York is spending for her insane alone one-fifth of her total revenue, and one-third of the entire state income of Massachusetts is being spent in the support of individuals requiring state care. Conditions approaching this are being disclosed in other states.

Again, it is a conservative estimate which places the number of feeble-minded in the United States at 300,000. Of these, only some 35,000 are in special institutions. For example, of Massachusetts' 15,000 feeble-minded, only 3,000 are receiving state aid, which means that a large proportion of the remainder are continuing to reproduce their kind without let or hindrance.

The probable number of epileptics may be set roughly at 200,000. While many epileptics are harmless enough, many also are particularly prone to criminal acts, and where an unusually brutal crime is committed, it is likely to be the work of a criminal epileptic. A survey made of the epileptics of New Jersey shows that they double in number every thirty years. There are no reasons for believing that conditions are materially different in other states.

With our improved modern tests the grade of intelligence of subnormal individuals can be determined reasonably well. Careful application of these tests in representative institutions has shown that from 30 to 60 per cent of our crim-

inals are mentally below par, that probably 60 per cent of our drunkards were mentally unstable or deficient to begin with, that a vast proportion, in some cases over 90 per cent, of the population of our almshouses are feeble-minded, as are also a notable proportion of disreputable women. Many of these feeble-minded individuals are of the higher grade known as moron. Their intelligence may approach that of a twelve-year-old child and they are readily overlooked by the casual observer.

The recent report of the Wisconsin Mental Deficiency Survey conducted under the auspices of the National Committee for Mental Hygiene and a special state committee reveals conditions which are probably typical of other states. The total population of Wisconsin is about 2,700,000. A careful study was made of the various state and county penal and charitable institutions, and of 8,000 representative school children. According to the estimate in this report, there are in all 18,000 feeble-minded individuals in the state. This is 2,000 more than the estimate from the army count made during the war. Of these, only 1,126 are in the two state institutions, and 433 others in special classes in the schools. On the general estimate that there are one-third as many insane as feeble-minded, the number of insane in the state is recorded as about 6,000. Of the approximately 400,000 school children in the grades of the public schools, it is estimated that 40,000 are so handicapped mentally as to be unable to compete on equal terms with their fellows. Of these, 2,800 are classified as actually feeble-minded, but if we add the borderline cases, the total rises to 7,200. About

800 children in the public schools of the state are afflicted with epilepsy and 1,200 are classed as of psychopathic personality; that is, they are neither feeble-minded nor insane, but are characterized by frequent behavior difficulties. This record of mental ills is surely enough to give any state cause for serious thought.

The Cost of Mental Diseases and Criminalism.—The various states of the Union are together directly paying well over $100,000,000 every year in the support of their defectives and degenerates, and indirectly, vast additional sums, since, as just seen, these classes are a bountiful source of our delinquents, paupers, inebriates, and criminals. And the states continue placidly to do this year after year, ignoring the fact that through the application of a few common-sense principles this vicious or defective horde might, in the course of a few generations, be materially lessened.

Contamination of Good Strains.—But bad as are these visible, measurable conditions, the disconcerting fact confronts us that as regards feeble-mindedness, at least, they represent only part, possibly the least dangerous part of the situation. When feeble-minded mates with feeble-minded the offspring are all feeble-minded. When feeble-mindedness is crossed into normal stocks, the defect, following the mendelian law, may become largely or wholly obscured in the immediately resulting offspring. Nevertheless, it is likely to reappear in later generations, with qualities undimmed. Such traits constitute what the geneticist terms a recessive. If an individual who carries feeble-mindedness as a recessive marries one who is likewise a carrier, a common occurrence,

one out of four of their children will probably be mentally defective, and two out of four may, like themselves, transmit the condition. This explains, for instance, how feeble-mindedness may often appear among the children of apparently normal parents. The most disquieting part of the situation lies in the fact that in a fairly stable population where a relatively small proportion reveals a recessive defect such as feeble-mindedness, there is always, through contaminations which have gone on generation after generation, a much larger percentage of the population who, though apparently normal, are carriers and therefore transmitters of the defect. Thus such evils are not being confined to the originally defective strains, but are thrusting theftuous roots into our better blood.

Without entering into the details of their rather intricate calculations, it may be stated that two of our most careful investigators in the field of heredity, Professors East and Punnett, have each come to the startling conclusion that with 300,000 visibly feeble-minded individuals in the United States, with its population of over 100,000,000, there must be between 7,000,000 and 10,000,000 people who are carriers of feeble-mindedness, any two of whom chancing to marry would probably have one child out of four mentally impaired, and two children out of four capable of transmitting mental impairment. This means that even if, in the United States, we could blot out all actively feeble-minded at one stroke today, we should still have this enormous reserve of carriers who, marrying as usual, would produce a resurgence of approximately 100,000 active cases in the next generation.

It should be noted that these calculations are for feeble-mindedness alone and include neither epilepsy nor the insanities.

Birth Rates of Normals and Defectives.—As matters now stand, however, we not only have this unavoidable increment launched on us every generation, but we are doing little to stay the torrent which is issuing from the matings of the plainly feeble-minded, who family for family are outbreeding normal strains. In a recent survey of certain counties of Pennsylvania Dr. Key discovered that not only was the birth rate of defective mothers more than twice that of normal mothers, but that the survival ratio of the young of such defective mothers was also more than twice that of the children of normal mothers. Dr. Key found that 60 per cent of the good-for-nothings, drunkards, criminals, and sex-offenders of the regions studied belonged to ten feeble-minded family strains.

It is becoming more apparent every day as methods of precision are beginning to take precedence over guesswork that many of the "down-and-outers" are not so because of lack of opportunity, but because of inherent incapacity. In the industries this is unquestionably an important factor in the problem of "labor turn-over." For example, in a number of the Journal of Delinquency (March, 1917) before me I find that in a representative group of 107 unemployed men who applied for charity recently in Portland, Oregon, about one-fifth proved to be of the moron grade of feeble-mindedness, and all were considerably inferior mentally to an ordinary group of successful men. Other studies of similar nature are bringing the same significant facts to light else-

where in the country. And let us not forget that in a democracy the vote of each of these has just as much weight as that of the most enlightened citizen.

THE SOLUTION OF THE PROBLEM

What are we going to do about it? The student of heredity can only present the problem. The answer must come from the public. Little can be done, even though we get suitable legislation, without public opinion supporting it. Are we going to go on placidly permitting the production of defectives and delinquents?

One thing we can do is to set about preventing parenthood to the obviously unfit. The only feasible way of doing this on the great scale that such a movement requires, if it is to save our race from further serious contamination, is to segregate these mentally eclipsed unfortunates into colonies for the separate sexes. To be sure, this is a stupendous undertaking, but what else can be done? The problem is not one which will stand still while we deliberate about ways and means of doing something at some indefinite future day. It is a menace to our very life blood as a nation.

Colossal as the undertaking seems, as a matter of fact, the initial cost would be the greatest item of direct outlay, for such colonies, once established, can by wise management be made largely or wholly self-supporting. We have considerable evidence based upon the actual experience of well-managed institutions that most feeble-minded persons under proper supervision can do much work that is helpful to the institution or the state and healthful for themselves. Data

from various sources all agree in showing that the economic value of the feeble-minded, above the grade of idiot, is more than the cost of their care and maintenance. A recent example is that of twenty-five boys from one of the New York State custodial asylums, who were sent up into the Adirondacks for a month of camping, and given a lot of seedling spruce to set out. They did their work in a spirit of play, and yet at the end of their visit they had reforested a considerable area. A fair estimate placed the net value of the work to the State at $1,000, yet the cost of their transportation and keep for the entire period amounted to only $400. The fact is that many feeble-minded individuals are physically strong, good-natured, irresponsible children, who remain happy and contented if kept under reasonably comfortable conditions. It should be borne in mind, moreover, that with the reduction of the feeble-minded there would also be a lessening in our expenditures on paupers, criminals, inebriates, and delinquents.

EFFECT OF IMMIGRATION ON NATIONAL INSTITUTIONS

Another matter that requires our gravest thought is that of immigration. It is evident that what our democracy will be depends in large measure on the natural abilities and inclinations of ourselves and of our fellow-countrymen. The main problem, indeed, becomes largely one of who our fellow-countrymen are, since because of numerical superiority their wills must in large measure prevail. As long as they are of the same race or stock as we are, opinions will doubtless be fairly harmonious, ideals much the same. But the standards of a different race or stock are likely to differ greatly from

ours. Our present institutions, social, political, religious, are largely northern European in origin. The precious things for which our American government stands, peace, justice, honesty, protection of life and property, personal freedom, are but the embodiment of the united wills of the individuals who have made our nation.

The intellectual, moral, and spiritual characteristics which constitute the source of our social institutions and government are in the main but the outward expression of the strong inherent trend that is a part of the very being of our race. Change our race and inevitably our institutions must change. Free institutions are but the expression of free men, and the spirit which makes men free and keeps them free is inborn. Initiative, courage, enterprise, high ideals, and creative imagination on the part of the individual citizen will inevitably be expressed in the institutions created by such citizens; and the roots of all these qualities are innate. The lethargy of the dullard will never kindle into a glow from the flaming torch of freedom. The frenzy of the fanatic will never lend itself to the establishment of that dispassionate justice which is our ideal. The lawless spirit of anarchy can never express itself in peaceful pursuits and orderly institutions. So, does it not behoove us to scan with anxious eye our citizenry to see what we are doing to insure worthy heirship to our heritage of democracy? Are these benefits to accrue to the descendants of the original stocks which colonized America and made the United States what it is at its best, or are they to be for alien blood? If the latter, then how sure are we that our institutions will continue to exist?

Proportional Statistics of Native and Foreign-born.—Most of us, indeed, little realize how much of the population of the United States today is made up of people of foreign birth or of the immediate children of the foreign-born. According to the census of 1910 there were 13,245,545 foreign-born individuals in the United States; that is, one out of every seven inhabitants. But, if to the foreign-born we add those with one or both parents foreign-born, the total rises to approximately 30,000,000 or one-third of our entire population. During the decade 1900–1910, 8,500,000 foreigners came to the United States, of whom some 5,250,000 remained to make a permanent home. The estimate is that in general four-fifths of the immigrants remain permanently in America. During the first three-fourths of the nineteenth century immigration, on the whole, probably strengthened America, since it was made up of energetic, progressive individuals belonging to races closely allied to the original colonists. Later, however, there followed a deluge which unquestionably was not up to the average of its own country. The earlier immigration was independent; the later, largely dependent.

We hear much in these days about the economic and immediately social problems of immigration. But important as these undeniably are, they are insignificant compared with the biologic problem involved. It seems never to occur to most of us that sooner or later, in a few generations at most, we must drink the blood of this stock into our own veins through interbreeding.

Comparison of Natural Increase with Immigration.—With a total population of over three and a half million, three-

fourths of the inhabitants of New York City are of non-English speaking people. The native white population of native parentage constitutes less than one-fifth of the total population of New York City; less than one-fourth the population of Chicago, Boston, Cleveland, Detroit, and Milwaukee; and little more than one-tenth that of Fall River, Massachusetts. In only fourteen of the fifty largest cities of America does the native population constitute half of the total.

In the state of New York with its 9,000,000 inhabitants we find 840,000 Russian and Finns (the Russians being mostly Russian Jews); 1,000,000 Germans; 470,000 Austro-Hungarians; 125,000 Canadians, mostly French-Canadians; 720,000 Italians; 880,000 Irish; 310,000 British, and 90,000 Scandinavians.

In a single ward in the city of St. Louis there are: 2,301 foreign-born Germans; 2,527 foreign-born Italians; 7,534 foreign-born Russians; 900 Austro-Hungarians; 495 foreign-born Roumanians; and 14,067 others of foreign parentage; as well as 1,602 negroes. Surely such figures as these must drive home to us the magnitude of our immigration problem!

The rapid and steady increase in population in the United States during the past thirty years has been due largely to immigration and the high fecundity of the immigrant women, rather than to the productivity of native stock. For instance, the births in the state of New York in 1912 were a few over 216,000, but the number of immigrants settling in New York that same year was over 239,000. Moreover, the foreign family, as nearly as can be estimated, outbreeds the native

family in the ratio of at least five to three. In Massachusetts, indeed, where for many decades birth statistics have been taken on a basis of nativity, the records show that the birth rate of this native group is only fourteen per thousand, while the death rate is eighteen per thousand. The native American stock in general, in fact, appears not to be holding its own. According to the twenty-eighth report of "The Immigration Commission," 13.1 per cent of American women under forty-five years of age who had been married ten to nineteen years, were childless; and of those who had children, the average was only 2.7 children per woman.

Sprague, from a study of vital statistics, calculates that for the American stock of the East, at least, every mother must average 3.7 children for the stock barely to maintain itself. The American women just mentioned, therefore, were falling far short of the percentage required. Speaking of the celebration of the three hundredth anniversary of the landing of the Pilgrims, Holmes, from a study of this stock in California, graphically points out (Journal of Heredity, November, 1918) that if its present birth rate continues for another 300 years, it will be possible to put all surviving descendants back into the Mayflower without overcrowding.

Percentage of Mental Diseases in Immigrant Stock.—The importance of immigration to our democracy, of course, hinges on whether the contribution we are receiving is a desirable one. It takes but a glance at available statistics to see that much we are receiving and have received in recent years is wholly undesirable. For example, when the foreign-born population of New York was 30 per cent, the foreign-

born constituted over 43 per cent of the population of her insane asylums, and in New York City approximately 65 per cent of the insane. From a special report on the insane and feeble-minded in the United States, based on the census of 1910, we find that while foreign-born whites constituted 14.5 per cent of our total population, they made up 28.8 per cent of the total number of inmates in our asylums for the insane.

Percentage of Crime in Immigrant Stock.—Again, according to Fosdick, there is a direct connection between the presence of foreign races in America and crime. In our large cities the percentage of arrests of foreigners is in excess of their relative proportion of the population, and not merely for misdemeanors which might be due to ignorance of minor police regulations, but for serious crimes, such as assault, burglary, and murder. Of 148 foreign-born charged with homicide in New York City in 1915, sixty-five were born in Italy and twelve more were of Italian parentage. We find reports that crime has greatly diminished in certain communities in Italy, and our government commission which was investigating the matter was told that it was because the criminals had gone to America.

Percentage of Crime in the United States.—As regards crime, when we compare the United States with other civilized countries, the result is appalling. For example, in the year 1916 London, with a population of over 7,250,000, had only nine premeditated murders, while Chicago, with about one-third the population of London, had 105 such murders; that is, nearly twelve times as many. In 1918

Chicago had twenty-two robberies for every one in London. From 1916 to 1918 Glasgow had thirty-eight homicides, while Philadelphia, but slightly larger, had 281. Cleveland, one-tenth the size of London, had three times as many homicides in 1917. And so for various other American cities.

The Cost of Crime.—How many of us realize that in the United States crime costs us annually at least twelve times as much as our combined army and navy and over three times the amount of our total internal revenue and customs receipts? In a recent article in *Business*, published in Detroit, Edward H. Smith shows that the cost of crime in our country is at least ten billion dollars annually. This is over two and one-half times the total national receipts for 1923 and three times the national budget for the same year. His figures have been gathered over a number of years from such sources as the police departments of our larger cities; the New York Stock Exchange; the Association of Railway Executives; the National Surety Company; the Insurance Company of North America; the National Vigilance Committee of the Associated Advertising Clubs of the World; the National Association of Credit Men, and kindred organizations.

Our army intelligence rating, already referred to, which was applied to conscripts during the late war, also sheds a flood of light upon the quality of much of the foreign-born population of the United States. While in the white draft, as a whole, 22 per cent were found to be of inferior intelligence, the percentage rose to 46 for the foreign-born when grouped apart from the others. The peoples of different nationalities differed somewhat, one group exhibiting as

high as 70 per cent of inferior intelligence. Of our negro troops, 89 per cent rated under the mental age of thirteen. An almost negligible number of individuals of superior intelligence were found among the foreign-born. Then why hurry to make them citizens? The fate of a democracy must be determined by the intelligence of its voters.

A new flood of immigration started after the war; 800,000 arrived in the year ending June 30, 1922. All unprejudiced observers tell us that our experts and consular agents were correct in their predictions as to the mental and physical inferiority of this material. At present the influx has been checked by our new Immigration Act.

Intelligence Ratings of Immigrants.—Recently, for the Congressional Committee on Immigration, Dr. H. H. Laughlin of the Eugenical Record Office examined 210,855 inmates in 445 of our 667 State and Federal custodial institutions with reference to such conditions as feeble-mindedness, insanity, epilepsy, crime, tuberculosis, blindness, deafness, deformity, and pauperism or dependence on the community. Taking all defects together, he found that the foreign-born showed almost double the proportion yielded by the native-born of native parents; that while the foreign-born make up 14.70 per cent of our total population they constitute 20.63 per cent of the inmates of our jails, almshouses, and institutions housing the insane, feeble-minded, epileptic, chronically diseased, crippled and deformed. While it is clear that to make a fair comparison with similar conditions among individuals of native parentage, certain corrections should be made such as the possibility that foreigners are more likely

to be placed in such institutions, that there are relatively more adults among the foreigners, that environmental pressure is more severe for them, and the like, nevertheless, with all possible corrections made, the facts are far from reassuring. Dr. Laughlin compared the numbers of individuals in each racial group found in these institutions with the total number of the same group found in the population of the United States. A group which furnished such inmates in the same proportion that it furnished inhabitants to the United States was said to fulfil its quota by 100 per cent. In such a comparison some very instructive facts are brought to light. Thus, in *insanity*, Ireland leads with a percentage of 305, that is, over three times its legitimate allowance; Russia is second with 266 per cent; and Scandinavia third with a percentage of 193; while native whites of native parentage constitute 73 per cent. In *crime* the three highest in percentage are the Balkans, with 278; Italy, 218; and Russia, 126, as compared with a native quota of 82. For *dependency* the score reads: Ireland 634, Great Britain 218, the Balkans 121, native 104; for *epilepsy:* Great Britain 146, Russia 117, Ireland 108; for *tuberculosis:* the Balkans 379, Scandinavia 214, Russia 200, native 89. When it comes to feeble-mindedness, deformities, deafness, and blindness, the native whites of native parentage would seem to be inferior to the foreign-born, but this is probably due to the fact that such conditions are easily detected and that such immigrants have been excluded under our laws. This supposition is borne out by the fact that among the children of immigrants these defects show a disproportionate increase.

We have not time to review this study in detail, but there are certain outstanding facts that should be mentioned. Taking defectiveness as a whole, Ireland stands first, with a quota fulfilment of 209 per cent; Russia-Finland, second, with a quota of 184 per cent; and the Balkans third, with 175 per cent. Thus the problem cannot be resolved into a question of Northern and Northwestern Europe versus Southern and Southeastern Europe as has been commonly supposed. The country with the worst record, Ireland, lies in the north and west division of Europe; that with the best record, the present Czecho-Slovakia, and parts of Jugoslavia and Poland, in the south and east division. The north and west division has the worst record for insanity and dependency; the south and east for crime, feeble-mindedness, epilepsy, and tuberculosis. No one country has a monopoly of all defects.

It is obviously impossible, therefore, to keep out undesirable European aliens by rejecting immigrants on a basis of race or nationality. The only satisfactory outcome can be reached by careful selection of the immigrant in the land of his origin, and not only the individual but the family of which he comes must also be taken into consideration.

It is certainly high time that we give this whole question of immigration the most serious consideration of which we are capable. Since, sooner or later, we must inevitably mingle our life blood with that of these invading hordes, our very existence as a nation is at stake.

It remains for us as a people to decide whether we shall continue to leave the determination of the character of our future population to the large employers of cheap labor, to

the railroad and steamship agents and brokers, or to sentimentalists or interested organizations who care nothing about the inborn fitness of the immigrants they bring, or whether we shall insist upon a proper regulation of this flood, so that we may receive only an honest, intelligent, industrious stock capable of understanding and upholding our laws and institutions. To continue to absorb these aliens with as little selection as we have done in the past is nothing short of criminal carelessness.

The Duty of the Better Strains.—But perhaps, from the standpoint of social welfare, the most serious of all the conditions which threaten our civilization is the declining birth rate of those who represent the higher reaches of intelligence and ability. Are not the able-bodied and able-minded men and women who refuse to marry and rear children fit to carry on civilization as much shirkers in their duty to their nation as the coward who slinks away from the dangers of war? Why in all fairness should we not broaden the term "slacker" to include the race-slacker? If it is necessary for the defense of our race to send the flower of our manhood to death on the battle-field, what about the flower of our womanhood? What about the capable man who remains unmarried? Why go out and fight for a race that will soon not exist? Surely it is just as important to give lives *to* the nation as to give lives *for* it. Is there anything of greater importance in the world than the breeding and rearing of future good citizens? If the increased leisure which comes to the successful nation means merely relaxation and amusement with consequent loss of the sense of responsibility, if

it means leaving the nation to the procreative recklessness of the illerate foreigner or the mentally subnormal, then, indeed, is the prospect a gloomy one.

But do not misunderstand me. I am not advocating that the better stocks enter into a breeding competition with the mediocre and inferior. If anything is certainly obvious it is that the world is not in need of a general increase in population. The serious feature of the present declining birth rate is its selective nature. It is the superior types which are declining, while the inferior are coming to outnumber them more and more.

WORLD POPULATION AND FOOD SUPPLY

Taking the world population as a whole the average birth rate is too high for safety. The ultimate check to any population whether it be that of lower animals or of man is lack of food. It is the old story: population tends to increase in geometric ratio; food not so rapidly. The final stark question is that of food, and who shall eat it? If mankind is not intelligent enough to take his own evolution in hand and keep it within the limits of his food supply, then nature will do it for him in the same old crude, ruthless way: war, famine, and pestilence will become the final arbiters.

Professor East, in his *Mankind at the Crossroads*, has brought together enough data on world populations and world food supply to give pause to even the most thoughtless individual. Viewing the world country by country he finds that, conservatively estimated, there is a total increase in world population of from twelve to fifteen millions a year; that is, nearly

twice the total population of that Belgium we were hustling to feed a few years ago. Twelve to fifteen million more mouths to be fed each year! The tremendous acceleration going on in population may, as East points out, be seen from the fact that from the time of the first records of man on earth up to 1800, a period of some 500,000 years, he reached, as nearly as can be estimated, a population of 850,000,000; but by 1900, just one hundred years later, this number had doubled, since the present population is 1,700,000,000 with a probable error of not over 40,000,000. At its present rate of growth Knibbs estimates that the world population will double in sixty-one years. Of course, such a rate of increase will not, cannot, go on for any considerable period of time. It must gradually slow down as the saturation point is approached. But what reasonable human being wants to see his nation reach a saturation point where each person can have barely enough to sustain life?

East's figures on the future agricultural possibilities of the world are also enlightening. After pointing out the fallacies which underlie the wide-spread belief that the situation will be readily met through improved methods of agriculture, improved varieties of plants and animals, the unlocking of new stores of energy, or the chemical production of synthetic foods, he goes on to show that there are probably about 13,000,000,000 acres of land on the earth available for food production. Allowing 2.5 acres as the minimum which will maintain each individual on the present dietary standard of the European peasant, the world can support 5,200,000,000, a population which at the present rate of increase will be

reached in a little over one hundred years. This means that even the end of the present century, at this rate of increase, will see all the more habitable agricultural regions of the globe filled well toward the saturation point. Countries which can now export food will be kept busy supplying the home needs. Even today neither overpopulated Europe nor Japan can wholly feed themselves. What will happen when they can no longer secure food from the outside?

With facts like these confronting us the futility of dreaming about the abolition of war, until the fundamental question of world population is settled, is evident. When the pangs of hunger cause a nation to begin to tighten its belt, it goes without saying, that nation is going to set forth to get food at any cost. Even defeat, with loss of millions of men, can be viewed with equanimity, since this relieves the pressure in the homeland. Some of the grim results of striving for "a place in the sun" have only too recently been before us to require comment.

Professor East's figures for the United States are particularly interesting. Of the 1,903,000,000 acres in the United States, he finds approximately 47 per cent in farms, of which 55 per cent are improved. Of the remaining 1,022,-000,000 acres, after subtracting untillable land: deserts, forests, swamps, non-irrigable lands and areas occupied by cities, towns, roads and railways, only 314,000,000 acres of usable new land is left, and this, in the main, probably not as good as that at present under cultivation. This means that we can add barely 35 per cent to our present farm area. So, with anything like the present rate of increase, we shall

not have to wait till a dim future for filling up. Our youngest children, or at least their children, will have to face the possibility of feeding 300,000,000; and yet, according to the estimates of both Pearl and East, in the United States *200,000,000* is approximately our saturation point.

THE SOLUTION OF THE PROBLEM

What's the answer? Who knows? Whether you have the answer or not, I think you will agree with me that a general increase in population is not needed. Medical research seems to hold out promise of an ultimate annual death rate of as low as sixteen per thousand, hence, a birth rate of sixteen per thousand also will be all that is necessary to keep a population stationary. The present birth rate, according to the best figures available, for the world at large, is in excess of this by at least nine per thousand of general population.

The decline of a nation is a function of the loss of certain qualities possessed by its leaders, indeed, the loss of its leaders. Suppose the abler one-tenth of America should be exterminated today, where would we be? And remember that capacity for leadership is largely an inborn, not an acquired, characteristic.

The thoughtful student of heredity sees the dangers confronting us and is doing his best to shout for help. He is advocating two distinct programs: he would, (1) prevent the mating of the unfit, and (2) encourage the reproduction of the best. Through the first he hopes to avoid further contamination of normal stocks and to bring about the gradual reduction of defective ones. Through the second, he hopes

to augment the numbers of the sadly depleted superior strains.

As to the future of America, if we have the brains, energy, and courage necessary, she will be perpetuated as a great civilization, but the all-important question which no one can answer at present is, have we? For our democracy to continue successfully, it is plain that its constituency must be made up of an intelligent, well-poised, well-disposed people: a people which is astute enough to realize that in times of peace no less than during the crisis of war, modern government demands all of wisdom, of ability, of technical knowledge, and of zeal for public welfare that the nation can muster; a people which, appreciating this fact, in the spirit of a true republic, is willing to choose by these standards those representatives who are to guide or administer its social and political institutions. Such a democracy can, in the last analysis, spring only from good blood. Are we preparing such a citizenship?

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