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DEPARTMENT OF GENETICS[1]

C. B. Davenport, Director

GENERAL STATEMENT: PROGRESS OF GENETICS IN THIRTY YEARS

Since this is the last Annual Report that I shall have the honor of submitting to the President and Trustees of the Institution, it seems appropriate to review the development of genetics during the 30 years in which I have directed this Department. In this development the Department has played an important part. It is impossible to measure the influence that the Department has had; most of it has been indirect; that is, the researches carried on here, indeed the very existence of the Department, have made impressions that have spread in ever widening circles throughout the world of biologists.

In 1902 when I suggested to the Trustees of the new Institution the establishment of a "Station for Experimental Evolution," the need for research in this topic was becoming recognized. The rediscovery of Mendel's laws had been made a few months earlier, de Vries's book on Mutations was showing the results of applying experiment upon evolutionary problems; the facts of organic variation were being analyzed by new statistical methods; cytology had advanced to a point where the rôle of the cell in heredity and development was fully recognized. My lectures at Harvard had dealt with the need for experiments in this field and, of my students, W. E. Castle had already begun experiments in genetics and H. S. Jennings shortly followed. Bateson, in England, had also started under the influence of Galton's researches; a few agricultural experimenters were securing data on plant breeding.

Today genetics is a leading biological discipline, has its own organizations in the United States, as well as other countries, and is represented by several leading genetical journals and many departments of genetics in the universities and agricultural institutes.

The early work of the Department was devoted first to a confirmation of Mendelian laws; then to a study of new phenomena. The personnel selected at the start included a graduate in botany (Dr. G. H. Shull), an entomologist (Dr. F. E. Lutz) and a cytologist (Miss Anne Lutz). Work was done on poultry because of the extraordinary number of characters that they reveal; with insects as the most rapidly evolving group of animals; with the evening primroses to throw some light on the unsolved problems that de Vries's work had pointed out. Miss Lutz early discovered and accurately described doubling of chromosome sets associated with well-defined mutants of Œnothera. Shull developed the principle of biotypes. Castle, supported by the Institution, worked largely in the field of multiple allelomorphs, using small mammals. While the Columbia group developed the chromosome map, Belling at our laboratory opened up the field of trisomes and chromosomal interchange in Datura which Blakeslee and his coworkers have so extensively cultivated.

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In 1910, Mrs. E. H. Harriman established the Eugenics Record Office to collect human records to be used in the study of heredity in man, following the Mendelian principles of analysis. That this led the way to the great development of human genetics in the last two decades is merely a fact of history. In January 1918, the Institution accepted the gift of the Eugenics Record Office, whose function was defined as the gathering of data on human heredity and research on such data.

All of this work and that of scores of geneticists throughout the world have thrown new light on heredity, variation, individual development and evolution.

At the beginning of the century, the development of the individual was one of the great mysteries. There was no clear notion of the internal factors that control the path that the developing egg takes in becoming a child. A second mystery that seemed quite separate was that of heredity, by which the special traits of the parents were led to reappear in the offspring. Through the studies of the past three decades not only in genetics but also in other sciences, such progress has been made that we see more clearly the mechanism of ontogeny and realize that it is at the same time the mechanism of heredity.

This mechanism is the set of thousands of genes arranged with extraordinary precision in the dividing nucleus and passed on in equal number and kind to each of the two daughter cells that arise by division of one. Associated with the genes, and of equal importance, is the set of hundreds of kinds of molecules in the cell-protoplasm. It now becomes clear that the genes by themselves do not cause the development of the egg and embryo. As enzymes they accelerate the chemical changes going on in the cell-protoplasm and thus determine the time and place of occurrence of each embryological process. The relation of genes and cell-protoplasm is that of two interacting chemical agents. The end product—the kind of tissue produced, or of intercellular substance formed—depends upon the agents involved.

The exponents of the gene theory sometimes stress the vast age of the genes; pointing out that they go back hundreds of millions of years to the beginning of life. But the egg protoplasm is no less old and its specific properties—the kind of molecules which it comprises—have come to the present time out of the remote past.

Development, with its wonderful potentialities, thus depends upon the remarkable properties of the organic catalyzers. The simplest of this type of agents are the bacteriophage and filterable viruses, then come the bacteria and the yeasts. The great results produced by these minute bodies gives an insight into the vigor of the enzyme-catalysts; and assigns the beginning of vital activity to the origin of such enzymes.

Great light has been thrown on the factors of organic evolution. First of all, mutation has been shown to be ubiquitous and constantly occurring, though always limited in kind to the nature of the mutating substance. Secondly, the chromosomes have been shown to undergo such changes as would produce, environment being suitable, new species, each with several new characters and constant in their reproduction.

Altogether, the conclusion seems justified that genetics has thrown much light on evolution and the development of the individual. Incidentally, it has prepared the way for a new attack on old problems from a new vantage ground. For research tends to go in spirals, but ever deeper and deeper.

In the Department of Genetics the year has yielded new data of general interest. Among these may be mentioned the discovery that, in general, all genes are important for the life and reproduction of each living cell of the body. Thus they perform a general cell-metabolic function as well as a specific organ-producing function. The number of gene loci in one organism, *Drosophila*, has been estimated by experimental methods and found to be about 2500. These genes are undergoing slow changes, mutations. These changes may be hastened by the use of X-rays; but most of such changes are non-viable. That such changes occur just through the passage of time, so that aged seed show an excess of mutations, has recently been demonstrated in *Datura*. Even the chromosomes, so precious a device for securing the transmission of the full complement of genes to each cell, may form new associations of their parts and in this way establish in *Datura* pure breeding types ("new species"). On the other hand, new crucial evidence of the importance of the non-nuclear parts of the cell is furnished by the higher rate of transmission of leukemia through the mother.

Certain of our recent genetical results have an importance for medicine. Thus mice, susceptible to inoculated leukemia, have been renderd immune to the disease by recovering from slight infection with it. Also a substance that we had previously discovered, prolactin, proves to be useful in inducing flow of milk in recent mothers who need such a stimulus.

Of other discoveries in heredity, mention may be made of the further development of a general theory of heredity; the discovery of a particular gene which is chiefly responsible for sex determination (in *Drosophila*). On the strictly human side, striking metamorphoses of the bodily proportions in growing children have been discovered, which afford new evidence of the parallelism of growth of young children and the lower Primates.

DETAILED REPORTS ON CURRENT INVESTIGATIONS

THE GENE

RÔLE OF GENES IN THE CELL

Demerec has continued, during the past year, his study of the rôle that the genes play in the vital functions of a cell. He has found that a deficiency for certain minute regions of a chromosome upsets the normal functions of the cell to such an extent as to prevent the development of even a few cells, perhaps a single cell, containing that deficiency. These deficiencies are called "cell lethals."

During the past year the X-chromosome of *Drosophila melanogaster* has been surveyed for cell-lethal regions by means of the X-ray. A total of 72 minute deficiencies, involving 18 known loci, was produced. Of these 34, involving 13 tested loci, were studied for cell-lethal effect. In 12 of these loci the deficiency caused cell death; only one, cut (ct), did not show this

effect. The conclusion seems warranted that sometimes the deficiency of a single locus causes death in even minute groups of somatic cells. Consequently, the genes of these regions, or loci, are essential for the vital functions of the cell.

The foregoing discovery indicates that genes are performing a more important function than mere determination of the development of various morphological characteristics, such as color of the body and shape of the organs. They are apparently taking an active part in the vital functions of every cell of the organism. In fact, those various morphological characteristics may be regarded as a sort of by-product of these fundamental chemical reactions. Demerec believes these findings support the view that genes are the lowest units among living organisms, and that the history of evolution has been the accumulation of single genes and subsequent differentiation among them. From this point of view a completer knowledge of the genes may help toward an understanding of organic evolution.

NUMBER OF GENES IN THE X-CHROMOSOME OF DROSOPHILA MELANOGASTER

Through studying the results of bombardment by X-rays of about 2500 r-units dosage of the X-chromosomes of the germ cells of *Drosophila*, Demerec finds the frequency of changes in loci is 12.5 per one hundred chromosomes investigated. The total number of changes observed for 22 loci, in 633,787 chances to detect a change, was 156, which indicates that the average change per locus was 0.0246 per cent. By dividing the frequency of changes in all the loci by the average frequency of change per single locus, an estimate of about 500 was obtained as the number of loci in the X-chromosome. If the other chromosomes of *D. melanogaster* contain the same number of genes per unit of length as the X-chromosome does, a total of 2500 genes (loci) will be obtained. Since most of these play an important part in the individual cells, a vivid picture of the complicated nature of these functions is obtained.

EFFECT PRODUCED BY X-RAY ON X-CHROMOSOME OF DROSOPHILA MELANOGASTER

From numerous experiments in subjecting the X-chromosome to X-rays, the conclusion is drawn that lethal changes and inversions are the most frequent intrachromosomal changes induced. Visible gene changes are comparatively rare. These lethal (that is, fatal) changes comprise two groups, namely, lethal gene changes and gene deficiencies, and of these the latter group is probably the more numerous. Of the 72 deficiencies of known loci found in the experiments, 56 were tested with adjacent loci, and 31 were found to be deficient for one known locus only, 19 were deficient for two known loci, 5 for three and 1 only was deficient for five known loci. Hence, most deficiencies include only a minute region of the chromosome. Indirect evidence suggests that in several cases a single locus may have been deficient. Thus it is known from the work of Sturtevant that the loss of the bar locus produces a wild-type phenotype and that such a loss is not a lethal one when homozygous. All known deficiencies for other loci have a homozygous lethal effect. During Demerec's studies, 18 losses of bar locus were observed, 11 of

which were not lethal and 7 were connected with a lethal effect; accordingly, it is probable that the bar locus alone was affected in the 11 cases; and that a deficiency in an adjacent locus was responsible for the lethal effect in the 7 other cases.

Demerec thinks it probable that these deficiencies are gene eliminations due to chemical changes induced by X-rays. It is improbable that a change in several adjacent loci would be produced by a direct hit of a single electron. X-rays may, accordingly, be considered as producing a change in the environment in the gene which in turn affects either a single gene or several adjacent ones. In four cases, so far, it has been found that a visible gene change occurred in a locus adjacent to the deficient loci. Also, a changed gene may produce changes in adjacent genes. As pointed out in last year's report, most gene changes probably eliminate from the gene the power of reproduction which would be equivalent to the elimination of the gene itself, *i.e.* to the formation of a deficiency.

The length in the gene-string of deficiencies is far below the length of deletions described by Muller, in which a large section of the chromosome is eliminated. It seems probable that these changes originate differently; that deficiencies originate through direct gene changes, and that deletions are produced by mechanical processes in which a chromosome forms a loop which later becomes eliminated. Inversions, in which a section of the chromosome is inverted, probably originate through the same process as that which produces deletions, except that the loop does not break off but opens up, making new connections. Of the four types of changes induced by X-rays, therefore, gene changes and deficiencies probably originate through chemical changes in genes, and inversions and deletions are probably formed by a mechanical process in which a sector of the chromosome is inverted or eliminated.

The relationship between changes in adjacent loci is more involved than indicated by the evidence presented from changes in the bar locus. It has been found that out of 11 changes where two bars were present in the same chromosome, 9 included both bars and only 2 included one bar only. This suggests that the frequency of change in more than one locus may be a function of either the distance between adjacent loci or of the chemical similarity of these loci, or most probably, of both.

A GENE RESPONSIBLE FOR INTERSEXES IN DROSOPHILA

A widespread search is being made for the internal factors that determine the sex of the individual. The X-chromosome as a whole is one factor. Mr. Lebedeff has found that a recessive gene of the third chromosome of *Drosophila virilis*, called intersex (ix), stimulates the development of the male reproduction system in homozygous females. This gene has no effect on developing males. Three allelomorphs or modifiers of this gene have been isolated, giving three types of intersexes. Females homozygous for type 1 are almost normal externally, except for the rudiments of male genitalia and undifferentiated ovaries and rudimentary testes. Females homozygous for type 3 have incompletely developed male external and internal genitalia,

gonads and rudimentary ovaries, though infrequently female external and internal genitalia may be present in these individuals, and the shape of their abdomen is female. Females homozygous for type 4 are morphologically almost normal males except for the more or less underdeveloped testes. The majority of 1×2 and 1×4 females are hermaphrodites, both in primary and secondary sex organs of both sexes. Finally, 3×4 females are male-like excepting for underdeveloped testes and the shape of the abdomen, which is intermediate between male and female. It is concluded, therefore, that the ix gene plays a major part in the sex determination of *D. virilis*. The sex-determining mechanism of this species is apparently dependent just as much on the quality of genic material as it is on the number of sex determining genes involved.

CHROMOSOME STUDIES

THE EVOLUTION OF CHROMOSOME COMPLEXES

The major problem in our Department is that of evolution, and long experience points to the conclusion that the clue to evolution of organisms must be sought in large part through following the evolution of their chromosomes. As pointed out in last year's report, the study of the evolution of chromosomes has been advanced by determining the difference between the chromosomes of species in terms of the segmental interchanges which they have undergone. *Datura discolor* is one of the few species outside of the *stramonium* group which will cross with *D. stramonium*. Crosses with tester races of the latter species as a standard have led Dr. Bergner to the tentative conclusion that *D. discolor* has the modified chromosomes 1·11, 2·17, 12·22, 15·21 and 16·18 instead of the chromosomes 1·2, 11·12, 15·16, 17·18 and 21·22 of the standard *D. stramonium* tester race. The hybrid between the two species shows a circle of 10 attached chromosomes which would be expected if the chromosomes had had their ends interchanged in *D. discolor* in the manner indicated by the present evidence.

CROSSABILITY BETWEEN SPECIES

Related forms are more apt to be crossable than unrelated species of a genus, but Blakeslee's studies show that crossability can not be a certain test of taxonomic relationship. Mr. Murray has tested capacity for hybridization in all available species of *Datura*, to enable their chromosomes to be compared with those of *D. stramonium* as a standard. Sometimes the cross can be made only one way. For example, the cross between *D. stramonium* and *D. discolor* has succeeded only when the latter has been the male. Many attempts to combine species have been unsuccessful. Dr. Buchholz, with the assistance of Mr. Williams, has been investigating the growth of pollen tubes as a possible check to hybridization. In some cases the pollen of the species will burst in the style of another species, while in the reciprocal cross the pollen tube growth is normal. There are obviously other blocks to crossability than bursting of pollen tubes, and these are being investigated by Miss Satin.

MUTATIONS STIMULATED BY AGING SEEDS

In continuation of the research recorded in the last Year Book (page 39), Dr. Cartledge has been investigating the mutations shown by aging seeds of *Datura*. Tests of the pollen condition of now over 5000 plants grown from seeds of different age leave no doubt of the higher mutation rate from old than from freshly harvested seed. The suggestion made last year that stray radiation from an X-ray machine may have been responsible for the increased rate of mutation of stored seeds is not supported by further study, since aged seeds stored in another building gave even higher mutation rates than the first lot. The peculiarities found in derivatives from aged seeds are shown in the same way as those found in the pollen, chromosomes or offspring of seeds treated by X-rays or radium. Apparently, a number of initial cells take part in forming the developing stem and any one of them may undergo a mutational change, leading to a modified sector. Since these mutations, in very high proportion, bring about abortion of the pollen grains, such pollen abortion is the most delicate as well as the most convenient index of mutation rate in plants so far discovered. Cartledge has been able to distinguish, with a fair degree of accuracy, by surface appearance, pollen abortion types caused by chromosomal mutations and those caused by simple gene mutations. His ability to do this has been checked by the cytological findings of Miss Satin. The two types of mutation seem to be of about equal frequency. Together about one-half of one per cent of plants from seeds one year or less old show aborted pollen. On the average, there is an increase of slightly less than one per cent in the number of plants with aborted pollen for each year during which the seeds have been stored.

The pollen abortion used as an index of the mutation rate was observed in plants which grew from the aged seeds, and to the question whether the factors responsible for the abortion could be transmitted to the next generation Cartledge has obtained an affirmative answer, since he has recovered in the second generation both the gene type (18 cases) and the chromosomal type (13 cases). Mutations affecting the gametophyte, of which the pollen is a part, are in our experience more common than those affecting the sporophyte which form the visible part of the plants. The genes that produce "visible" changes are the ones commonly dealt with in genetic studies of plants. Blakeslee's earlier work with radiation treatment seemed to indicate that any stimulus which increased the rate of one kind of mutation increased the rate of other kinds of mutation as well, hence the adoption of pollen abortion as an index of the mutation rate. However, it seemed desirable to look for "visible" genes from the aged seeds. In progenies grown from 392 plants from such aged seed, five new genes have been recognized already in the seed pans, a mutation rate of 1.27 per cent. This contrasts with the mutation rate of about 0.04 per cent of new gene mutant types visible in the seed pans in all our experiments with untreated Daturas since 1919. Thus, the mutation rate of aged seeds is about 30 times the rate from controls.

The result from aging seeds has much of interest since it seems more likely to be related to processes going on in nature than artificial stimulation

by X-rays and radium. These processes may have some evolutionary significance.

Since the aged *Datura* seeds had been kept in varying conditions of moisture and temperature, which have great effect upon the viability of seeds, an attempt was made to discover seeds of *Datura* which had been buried for long periods in the soil, where they are known to retain their vitality for at least thirty years. We aimed to learn if aging under these more natural conditions would have any effect upon the mutation rate. Through the cooperation of Mr. H. B. Derr, County Agricultural Agent in Fairfax, Virginia, we have been able to secure over 500 germinations of *Datura* seed which had been buried for twenty-two, or more, years in the soil under his house. At the time of this report the mutation rate of these seeds has not been determined.

In seeking for the cause of the increased mutation rate in aging seeds, we are fortunate in having secured the cooperation of Dr. William Crocker and Miss L. V. Barton of the Boyce Thompson Institute, who are subjecting our genetically controlled seed to different environmental treatments in an attempt to learn the effect of varying the temperature, moisture and oxygen supply and other factors upon the mutation rate.

SUMMARY OF TEN YEAR BREEDING RECORDS OF 2n+1 TYPES

For ten years Blakeslee has cultivated a series of extra chromosomal types, which have been reared under comparable environmental conditions as well as comparable genetical conditions, since they are all within our highly inbred Line 1. The 2n+1 types, which have an unmodified chromosome as an extra are called primaries; those in which the extra consists of one-half chromosome doubled are called secondaries. Secondaries regularly throw a certain percentage of related primaries in their offspring.

A summary by Mr. Avery of the 10 year records on nearly 50,000 field-grown offspring of the 12 primary and 14 secondary (2n+1) types leads to the following conclusions: (1) Both primaries and secondaries differ widely in viability (transmission of the extra chromosome to their offspring). The highest viability is shown by 2n+23·24 with 33.4 per cent transmission and the lowest by 2n+19·20 with 2.8 per cent transmission. (2) The number of primaries thrown by their own secondaries also varies widely even when percentages are corrected for viability. This fact indicates that disjunctions responsible for 1n+1 primary gametes are not at random. (3) The number of secondaries thrown by unrelated primaries is extremely small (0.035 per cent). The number of secondaries thrown by their own primaries is slightly larger (0.088 per cent). (4) There is a marked difference in respect to the number of new mutations of unrelated 2n+1 types which each type throws (0.06 per cent from the 2n+3·4 type to 2.5 per cent from the 2n+19·20 type). Primaries and secondaries together throw 0.9 per cent unrelated 2n+1 types (1.1 per cent from primaries and 0.7 per cent from secondaries). Since over 13,000 normal diploids threw only 0.16 per cent 2n+1 types, it is evident that primary non-disjunction must be more frequent in 2n+1 types than in diploids. (5) Certain types are more frequent among the new mutations than others even when figures are corrected

for differences in viability. The conclusion is reached that chromosomes differ in their frequency of primary non-disjunction. These differences are not related to chromosome size.

EFFECT OF CHROMOSOMES ON ANATOMICAL STRUCTURE

Dr. Sinnott, with the assistance of Miss Helen Houghtaling, has prepared for publication by the Institution a report on their extensive studies on the effects produced by extra chromosomes upon the internal anatomy of the *Datura* plant. Most of the comparative work was centered on the structure of the flower stalk. Among those plants in which the normal chromosome complex is doubled, or trebled, the chief anatomical differences were associated with differences in cell volume which, in a given tissue, is roughly proportional to the chromosome number in the nucleus.

The mean value for the 12 primary mutants is for most characters very close to the value for normal diploid, thus supporting the theory of chromosomal balance.

The expected relation of balance between primary mutants and its two secondaries is often lacking in anatomical characters. For many traits, especially in the 2n+1·2 and 2n+9·10 groups, the primary is intermediate between its secondaries, but in other cases there is no sensible difference on the one hand, or the difference may be extreme on the other. This somewhat unexpected result supports the belief that genes bring about their effects not through acting alone, but through interacting systems.

Certain chromosomes tend to influence increase in cell size; others, increase in cell number. Anatomical "pattern" seems also specifically determined by the various chromosomes independent of cell size and number. Evidence is afforded that the various chromosomes differentially affect rates of development of certain anatomical traits.

GAMETOPHYTIC INHERITANCE

Increasing attention in recent years has been devoted to the gametophyte, a stage in the life history of the plant in which the cells have the haploid number of chromosomes and hence are the more highly unbalanced by abnormalities in chromosomal constitution. Mutations affecting the gametophyte appear to be much more numerous than those affecting the more noticeable characters of the sporophyte. Three genes when homozygous have the following chromosomal effects respectively: (1) Lack of pairing at reduction; (2) doubling of nuclei and formation of giant pollen grains with 2n and 4n chromosomes; (3) dyad formation with 2n eggs and sperms. In *Datura,* genes causing abortion of affected pollen grains are common and have been used by Cartledge as an index of mutation rates from aged seeds. Two of such pollen abortion genes have been located in a particular chromosome. Dr. Buchholz and his associates have discovered genes which affect the behavior of the mature pollen. The following genes have been located in a particular chromosome. One gene for short pollen tubes is in the 19·20 chromosome and another is in the 13·14 chromosome. One gene responsible for bursting of pollen tubes is in the 17·18 chromosome.

COILS AND CHROMOSOMES

Cytological research has revealed that at the stage when the chromosomes are about to separate, and immediately before their separation takes place, the gene strings often lie in a close coil which splits lengthwise into two coils. Attention has been called to the mechanical difficulty in some cases of separating two such coils. Laughlin has been investigating the conditions under which two such coils may be related to each other so as to be readily separable.

Let us assume, first, that in dividing lengthwise the helix (or "coil-spring") presents its flank toward the one and only external pole so that the axis of division of each particle passes through that pole; let us assume, secondly, that, after the chromosome has divided lengthwise, and the daughter chromosomes are still in place, the one polar center divides into two, which migrate to opposite poles of the still undivided cell. Under these circumstances the coil-spring chromosomes which divided longitudinally particle by particle, while oriented in reference to a single pole, can now separate and go to two poles without interference.

Laughlin has further analyzed the case of separable coils and drawn the conclusion that the linear distance along the spireme, or coiled string of genes, in one complete cycle or turn of the string in the coil is equal to the square root of the sum of the square of π times the diameter of the cylinder around which the helix is wound plus the square of the distance between similar phases of the helix (openness of the coil).

Again, the turning of the coil and the twisting of the pair of strings must always be in opposite or compensatory directions, if the divided coils are later to be pulled apart. If (viewed from that end of the axis toward which the coil is being wound) the coil is anti-clockwise, then the twist of the pair of strings (viewed from the free end of such pair of strings) must be clockwise.

There is a substantial leeway in the exact location and sharpness of twisted spiremes, depending upon the openness of the coil. The distance between similar phases must always be greater than the diameter of the spireme string—that is, the diameter of one gene, otherwise the coils will pinch and not pull apart easily. In some cases this distance between coils may be small and the two coils may pinch and lay the foundation for "crossing-over" or for the breaking of chromosomes. It has up to now been assumed that the chromosome on the eve of gene-duplication and separation is built along a straight axis. However, separation can take place even if the axis of the coil be strongly bent. The only condition is that whatever the shape or direction of the coil may be, every part of the coil about to duplicate must have "free view," that is, uninterrupted orientation toward the *one* pole.

A further consideration of the condition in which these coils can function leads to the conclusion that chromosomes must be composed of flexible material which is either brittle or weak enough to break under certain strains and stresses caused by differential pull and resistance, due to abnormalities in timing, orientation, or external (but not lethal) injury. Also, the gene molecules must constitute a single string, permitting the single molecule to duplicate itself. For, if a gene or bead were composed of a large mass of

molecules, each daughter molecule would find difficulty in being created at a point adjacent to the parent molecule.

In the case of special phenomena such as crossing-over, non-disjunction, deficiency, duplication, displacement of pieces of chromosomes and reversed order, such conditions as orientation, timing and change in the value of the distance between coils may be important. The interference with normal duplication and division may be caused by such external agents as radiation, heat, age, or chemical damage which may upset the normal division without causing death. If in the mechanical parallelism one desires to demonstrate crossing-over, it is necessary only to skip (or to double) one or two of the twistings in the course of winding the coil, thus destroying the consistent orientation in the cross-over region. The crossing-over will be found essentially at the affected point when one tries to pull apart the daughter coils in cell division.

TRANSMISSION BY INOCULATED CELLS

While in most studies in genetics we consider the union of two germ-cells as a forerunner of a development, there is a class of cases that lends itself to genetical treatment where somatic cells with characteristic power of self propagation enter into a soma, or adult body, and yield characteristic or specific results there. A case in point is found in the lines of leukemia which are being propagated and studied here by MacDowell, Potter and associates.

GENETIC AND NON-GENETIC VARIABLES IN SPONTANEOUS LEUKEMIA; THE CONSTITUTION OF THE SUBSTRATE

To learn the rôle of heredity or constitution in spontaneous leukemia one has to follow the mouse to very old age, in some cases even to beyond three years. Microscopic diagnosis of deceased mice, made by MacDowell and his group, reveals that in the inbred leukemic strain C58, of 604 mice diagnosable with certainty, 90 per cent had leukemia when they died. Considering the genetic uniformity of the strain, the failure of 10 per cent of the mice to develop leukemia suggests that non-genetic variables occasionally balance the genetic determiners.

The fact of such non-genetic variables stands out more clearly in the first generation of a cross between genetically pure (homogeneous) leukemic and non-leukemic strains, where 41.0 per cent of 105 diagnosable cases from leukemic fathers gave leukemia. Since this generation is genetically uniform, the occurrence or non-occurrence of leukemia is not due to genetic variation. The relative potency of non-genetic variables may be stated to be 10 per cent in the pure strain and about 50 per cent in the first hybrid generation. Thus the potency of the non-genetic influences upon the expression of leukemia varies with the genetic constitution.

In the back-cross generation, derived by crossing the first generation hybrid males to the pure non-leukemic strain, the incidence of leukemia is again reduced by about half, *i.e.* to 18.8 per cent in 101 diagnosable cases. A correlation is thus found between total leukemic heredity and incidence of leukemia.

MacDowell finds that one important influence on the percentage incidence of leukemia is transmitted by the mother alone. The incidence of leukemia in the offspring is greater in transmission through the mother than the father. In the first generation of the cross, the difference is 20.1 per cent, in the back cross 26.4 per cent. These differences are statistically significant. The absence of sex-lineage shows that the sex chromosome is not involved.

The remaining difference between the contribution of the two germ cells to the offspring is the cytoplasm of the egg, and so the constitution of the cytoplasm (substrate) must be regarded as the differential which is responsible for the higher transmission through the mother. To be sure, maternal transmission involves intrauterine life and nursing by a potentially leukemic mother, but through the use of foster mothers this last possible influence has been eliminated.

An excessive influence of the mother in determining traits of the offspring is not peculiar to the incidence of leukemia, since similar results are found for mammary carcinoma. In our standard strains of mice, the incidence of carcinoma of the breast is moderately high in the non-leukemic strain, while in the leukemic strain it is very low, being 0.2 per cent in over 700 mice. Reciprocal matings gave an excess of 11.3 per cent in the incidence of breast cancer in the females of the first generation when the mother alone belongs to the strain with moderately high tendency for breast carcinoma, as compared with matings when the father alone belongs to such strain. Owing to the complicated inheritance of leukemia, it is not surprising that the rôle of heredity in human leukemia and cancer is so obscure. Indeed, it is rare that leukemia occurs in two members of a human family. It is planned to investigate the non-chromosomal influences upon the occurrence of spontaneous leukemia.

For the investigation of non-chromosomal influences, a knowledge of the initial stages of leukemia is essential. The first clinical sign (splenic enlargement) represents already an advanced stage. With any strain that produces 90 per cent leukemic offspring, the chances of finding microscopically many early stages in a random sample of clinically healthy mice of suitable age are very great. Accordingly, samples of the tissues and organs of 100 animals of the leukemic strain have been preserved and studied histologically and cytologically by Misses Findley, Taylor and Plyler.

Potter and Miss Findley have first taken up the location of the earliest lesions. Already 2000 microscopic slides bearing serial sections from 34 mice have been surveyed. In 25 of these animals, lymphoid lesions of possible malignant or pre-malignant nature were found in liver and lungs; in 17 of these, similar lesions were also present in one kidney. In all 34 mice there was a striking absence of any abnormal activity in the lymph nodes or spleen.

Another approach to the problem of spontaneous origin of leukemia is to be found in the metabolic studies that are being carried on by Dr. Joseph Victor in the Department of Pathology, College of Physicians and Surgeons. While studying the influence of age of host upon metabolism of inoculated leukemic cells, Victor discovered that age brought characteristic changes in the metabolism of the lymph nodes of normal mice of the leukemic strain

that did not appear in other strains of mice. Moreover, in non-leukemic strains the aerobic and anaerobic glycolysis of normal lymph nodes were consistently reduced in the interval between 2 and 6 to 8 months; while in the leukemic strain there was an increase. Oxygen consumption is similar in leukemic and non-leukemic strains and is generally lowered by age; but in the leukemic strain alone, old, still non-leukemic individuals were occasionally found with increased oxygen consumption.

The metabolism of 23 clear-cut cases of spontaneous leukemia was found to be intermediate between that of normal and that of the highly virulent leukemic cells propagated by inoculation, and this is true for six criteria: oxygen consumption, measured with and without glucose; respiratory coefficient, with and without glucose; anaerobic and aerobic glycolysis. This demonstrates that the metabolism of lymph nodes of mice of the leukemic strain, measured before any cellular indication of the disease, approaches the metabolism characteristic of leukemia.

Following this significant lead, Victor has devised an apparatus for determining the metabolism of extremely small bits of tissue, such as a single normal lymph node. This may be removed without injuring the mouse and successive observations can thus be made upon the same mouse at different ages. Contributions seem now in sight toward an answer to the question: Is the constitutional factor that predisposes toward leukemia expressed through the altered metabolism which in turn favors the change of normal cells into leukemic cells, or is the peculiar metabolism an indication that such changes have already taken place?

IMMUNIZATION OF MICE NATURALLY 100 PER CENT SUSCEPTIBLE

Leukemic cells of a given line implanted uniformly in mice of a given strain multiply freely and kill the mice in a predictable time with a predictable gross and microscopic-autopsy picture. But such results do not indicate the nature of the relationship between cells and host. Last year it was reported that leukemic cells of the same line in susceptible hosts of different genetic constitution showed differences in their metabolism and in the number of certain cell constituents (mitochondria), but this influence of the host on the line of leukemic cells was not lasting. The cell lines used kill the hosts so rapidly that transfers to new hosts must be made every 3 or 4 days, so that possible modification of the host is not detectable. A new series of experiments is being carried out by MacDowell and Miss Taylor, in which a longer time is given for mutual interaction between cell line and host.

It has been known for some years that the life of the hosts can be lengthened by reducing the number of cells inoculated. Accordingly various dilutions as high as 1/200,000th of the standard dose of Line I were used and transfers were made from donors (strain C58) that lived 9 to 16 days. After 11 successive transfers were made with such dilute doses, no evidence of any modification of the cells by the hosts was found when transferred again in standard doses. However, in the course of these experiments appeared a clue which led to the proof that the host is actively modified by the leukemic cells. With sufficiently small doses the mouse may survive

even after the cells have multiplied to many times the number given in the standard dose. This shows that a change must have taken place in the host. This change is in the nature of a resistance, or immunity, whereby the leukemic cells are actually destroyed, although, at least in some cases, they have multiplied and become distributed in lesions in many parts of the body of the host. This resistance protects against subsequent doses of increasing magnitude. In some cases a single dilute dose has immunized against a standard dose, but the usual practice has been to approach the standard dose by a series of three or four steps at intervals of about 16 days. A surprisingly close correlation has been found between the dilution of the first dose and the proportion of the animals that survive, although the occasional death of an animal given less than 400 leukemic cells has delayed the solution of the technical problem involved in the successful immunization of every animal in a given group.

Using standard doses and standard technique of inoculation, leukemic cells of Line I have grown progressively in every one of the 2748 normal mice of strain C58 that have been inoculated in the last three and a half years in the Columbia University laboratory and at Cold Spring Harbor. Due to immunization by dilute doses, standard doses of Line I cells have failed to grow progressively in 70 mice of this same strain. Fifteen of these mice were again tested by standard doses a month after the first standard dose and all were still immune.

This demonstrates beyond question the active immunization of mice naturally 100 per cent susceptible to a standard dose of highly virulent leukemic cells. Preliminary microscopical studies of sections and peripheral blood by Potter show that the manner of regression is closely smiliar to that studied in a strain of mice naturally resistant to the same cell line. Following the active destruction of the inoculated cells, which in some cases had already infiltrated many tissues, a hyperplastic condition of normal lymphoid tissue has appeared. Obviously many questions are raised by these results as to the nature, specificity and persistence of this immunity, and its relation to subsequent incidence of spontaneous leukemia. The active immunization of the host in response to the presence of leukemic cells affects the interpretations of all observed phenomena and affords a lead of more than theoretical importance.

CHANGES IN VIRULENCE OF LEUKEMIC CELLS

Last year's report that virulence of leukemic cells depends upon the increase of proportions of large type cells in the inoculated material has received further support by Potter's findings that in a single line of leukemic cells in successive transfers there may be a decline in cell size and this is accompanied by a marked reduction in virulence. In later transfers the cell size increased and the virulence increased likewise.

Potter also found that the correlation between changes in cell size and virulence is very much weaker during the rapid changes in virulence in the first few transfers from a spontaneous case. For example, in this period a drop of thirty days in the interval before death may be *accompanied* by an increase of 3 to 5 per cent of large type cells; whereas a drop of 10 days in

the later history of a line may be *preceded* by an increase of 100 per cent in the proportion of large cells. Hence, changes in virulence during the first few transfers and changes much later in the history of a cell line are not under identical control.

Victor's metabolic studies support this conclusion. Different periods of a well-established cell line, showing different virulences, reveal marked metabolic differences, whereas in the early history of such lines changes in metabolism were only feebly correlated to changes in virulence. Thus it appears that changes in the size and metabolism of leukemic cells are certainly correlated with virulence, but they are apparently much more closely correlated with each other.

ORGAN SECRETIONS AS AGENTS IN GENETICS AND DEVELOPMENT

Hormones, it is now well established, exercise a determining control over the development of some organs and tissues of higher organisms and provide special conditions essential to the maintenance of life itself in all except its early and least differentiated stages. Some hormones, moreover, partly regulate and definitely condition the development and function of still other organs whose function it is to produce other hormones. Thus, during ontogenesis hormones are produced and released having a primary and also a secondary influence on development. It will be observed that the hormone-secreting glands, having taken over in part the control of the later development of the organism, have usurped, as it were, the function that the genes in their interaction with the cytoplasm exercise in all organisms. It looks as though the gene-cytoplasm reaction establishes, in different parts of the body, the endocrine system for the purpose of finishing off the body and controlling certain of its functions, especially the periodic ones.

Of the endocrine glands, the anterior pituitary gland produces more than one hormone with these remarkable properties, and that gland has been the center of interest of Dr. Riddle and his associates during the last year.

PROLACTIN

Since it has been shown that injections of that secretion of the anterior pituitary known as prolactin into mammals affect the milk secretions, and since the milk secretions are sometimes wholly inadequate in the mothers of new-born children, we have met a natural demand for its clinical use by providing some of our preparations of it to Dr. Raphael Kurzrok and Dr. E. G. Miller jr., Sloane Hospital, Columbia University Medical Center. Injections of prolactin produced no untoward reactions and was ordinarily successful in yielding results desired. Three commercial houses have undertaken to prepare prolactin for medical use and their task has been assisted by this Department. A certain instability has developed in some of the preparations so produced which disturbs the uniformity of the good results.

To measure the potency of a prolactin preparation two to five doves or pigeons are inoculated with it and the amount of enlargement of the crop-glands determined. During the present year Riddle, Bates and Lahr have discovered that different *races* of pigeons, or hybrids of different racial

composition, give quite unequal response to prolactin. Indeed, the response in certain hybrids may be from six to ten times that of other hybrids, or pure races. Here again our bird colony provides the best possible testing material for the hormone, since, during the past fourteen years of genetic breeding, standard animals of different endocrine races have been produced. Likewise, it is recognized that a constitutional or genetic factor greatly influences the amount of milk which different women may secrete. Our standardized races of pigeons seem to afford the best materials for determining the nature of the factor, or factors, that determine the response to prolactin and variation in milk secretion.

With the increasing demand for prolactin, it has become necessary to examine in the pituitaries of cattle the stage at which the supply is maximum. In this study, the Wilson Laboratories, of Chicago, have cooperated with us in securing pituitaries of known origins. From seven such classes of pituitaries the prolactin was extracted and assayed in our laboratory, with the results shown in table 1.

TABLE 1—*Prolactin content of cattle pituitaries according to age and sex*

	Source of anterior pituitaries						
					Cows		
	Embryos	Veal calves	Adult steer	Adult bulls	Not pregnant	Early pregnancy	Late pregnancy
Units of prolactin per gram of moist tissue	78	26	29	33	25	38	44

It appears that prolactin is present in remarkable amount in the pituitary of the calf embryo and is also found in unusual amounts in that of the pregnant cow. Of course, this large prolactin content may indicate a storing rather than a releasing of prolactin to the blood stream.

Since only mammals secrete milk, and but few birds produce a crop-milk similar to that secreted at the end of incubation by the pigeon, the question arose whether prolactin is present in other birds and lower vertebrates, and if so, what is its function? A series of tests by Riddle, Bates and Lahr showed that in fowls prolactin is concerned in the establishment of "broodiness," at least in those fowls that are laying eggs, but in races that do not go broody this state can not be induced by moderate dosage with prolactin. At six different periods of the year laying hens, in twenty-three cases, injected daily with ten to sixty units of prolactin have been made broody. Practically all of these birds began "clucking" on the third or fourth day, and sixteen of them began nesting eggs a few hours thereafter. Two of these hens were permitted to complete incubation of the eggs. Moderate dosage of non-laying birds, in thirty-two cases, of both broody and non-broody races uniformly failed to induce nesting, though nearly all partially

responded by clucking. Two male fowl given high prolactin dosage began to cluck on the fourth day, but remained uninterested in nest and eggs.

Further work has been done by Bates and Riddle on the purification of prolactin. It has been found that at pH 8.0 prolactin withstands boiling for one hour with little loss of potency and, it is believed, with complete removal of the growth hormone. By the rabbit ovulation test, cited below, direct evidence was obtained that one milligram of our prolactin contains only about one three-hundredths of a milligram of the gonad-stimulating hormone. It was also found that purified trypsin almost completely destroys prolactin at pH 8.0, in 2 hours at 37°C, indicating that prolactin is of protein nature. By the same treatment the gonad-stimulating hormone of the pituitary is rapidly destroyed.

Studies made on the specific power of prolactin to regulate the size of the gonads in adult fowl shows that in them, as in adult doves, the size of the testis is decreased, while the size of the hen's comb and oviduct, as well as the width of her pubic bones, are all decreased by prolactin and increased by gonad-stimulating hormone. Recently Riddle, Moran, Lahr and Bates have extended this study to the testes of a group of 42 old rats and obtained a wholly negative result with both hormones. In rats aged 1 year, or even in those of 3 months, fairly heavy dosage failed to affect testis size. However, this last may be an atypical mammalian case. So far as present observations go, the anterior pituitary gland probably has not one, but two, hormones with which it regulates, both upward and downward, the activity of the germ glands and thus indirectly the state of the uterus, mammary gland and other secondary sex characteristics.

If prolactin does in fact cause regression of the ovary, with suppression of its production of the ovarian hormone which now appears to be a cause of many mammary and uterine tumors, prolactin is indicated as a specific remedy or counter-agent for this type of tumor. In an uncompleted effort to find in animals suitable ovarian and uterine tumors for a test of this matter, Riddle, Bates, Moran and Lahr have examined 241 old or adult fowl, treatment being given in several cases. For initial tests of treatment of human mammary tumors some prolactin is being supplied to others.

IDENTIFICATION OF THE PITUITARY HORMONE WHICH CAUSES OVULATION IN THE RABBIT

During the past few years it has been known that some substance derived from the anterior pituitary causes ovulation in the rabbit. But it has not been known whether the hormone causing this ovulation is the luteinizing, the gonad-stimulating or a still different one specific for ovulation. Recently Riddle, Moran, Bates and Lahr have apparently resolved this question by injecting a large number of suitable rabbits with minimum ovulating doses of a series of pituitary hormones which had been previously assayed on pigeons. These tests show that this reaction is produced by the gonad-stimulating hormone and by that pituitary hormone only. In all present attempts to purify the several anterior lobe hormones it is important to know that a separate or otherwise unknown hormone is not indicated by the ovulation test, and we have been able also to put this result to practical use.

With this sensitive reaction, we have checked our assays—as made on the testis of the immature pigeon—of the gonad-stimulating content of various pituitary preparations, and have thus learned the amount of gonad-stimulating hormone which is still present in our best prolactin preparations.

ENVIRONMENT AND THE PITUITARY GLAND

Many of the organs and processes of the body take on new levels of activity under the cyclical or temporary direction of the anterior pituitary gland. We therefore have special reason to search for those conditions which normally induce the pituitary to issue its commands—to release or to withhold its various hormones. There is already good reason to suspect that, in birds at least, the release of certain pituitary hormones is somehow governed by cyclical changes in the environment. The changes in temperature and ultra-violet light which accompany seasonal change are agents particularly suspected of influence in the regulation of parts of the work of the pituitary. With the aid of Dr. Schooley some tests have been made of this hypothesis.

A SEPARATE PITUITARY HORMONE WHICH STIMULATES THE THYROID GLAND

Since 1929 some investigators have considered it nearly certain that the pituitary principle which maintains the thyroid in its usual state of activity is distinct from other known pituitary hormones. Satisfactory proof for this view has been lacking, and only during recent months has such proof accumulated from the work of two or three laboratories. To this crucial evidence this Department has made two contributions. As was reported last year, nearly but not quite all preparations of the gonad-stimulating hormone examined by us were also capable of stimulating the thyroid gland. The histological study of dove thyroids treated with some of the exceptional preparations now convince Riddle, Lahr and Bates that marked gonad-stimulation occurs independently of thyroid stimulation. Again, Riddle, Smith, Bates and Lahr have demonstrated that serum from the pregnant mare—which is very rich in the gonad-stimulating hormone—and pregnant urine preparations have no effect whatever on the thyroid controlled basal metabolism of ring doves. These results provide conclusive evidence that the pituitary principles which stimulate the gonads and the thyroid are quite distinct.

EFFECTS OF ANTERIOR PITUITARY HORMONES ON THE BASAL METABOLISM

To learn the effects of several pituitary hormones on the respiratory metabolism, Riddle, Smith, Bates and Lahr injected these hormones into doves. It appeared that such hormones yielded a decrease in basal metabolic rate when measurements are made on ring doves at a low temperature (15°C). There was no effect at 20°C on metabolism. But at 30°C a wholly different and fairly discriminating result was obtained. The gonad-stimulating hormone, it should be noted, obtained from mare serum or, admixed with the luteinizing hormone (Prolan B), from pregnant urine, has no effect on the metabolic rate. Thyreotropic hormone preparations were found to increase the metabolic rate about 15 per cent; prolactin, to increase about 20 per cent; whole pituitary extract, including the growth hormone, to

increase 50 to 65 per cent. A tentative analysis of these data suggests that in our birds the thyreotropic hormone affects metabolic rate by its action upon the thyroid; prolactin by its action upon the adrenal or a similar organ; and the growth hormone—indicated as having a strong additional effect—perhaps by its action on the growing tissues of the whole body, but probably the effects attributed to the growth hormone are not produced by any one substance.

BASAL METABOLISM OF DOVES AND PIGEONS

The study of the metabolic differences associated with race, sex and hybridity has been continued in collaboration with Dr. F. G. Benedict, director of the Nutrition Laboratory, and with the assistance of Mrs. Guinevere C. Smith. An investigation of metabolism during adolescence in the Tippler race of pigeons has been concluded. The study of the effect of advanced age, to supplement Dr. Benedict's work on man and rat, is being continued. The effect of a flight of six miles upon the metabolism of homing pigeons has been studied. During the first forty minutes following this flight an increase of as little as 9 per cent in well-trained birds, and as much as 80 per cent in a poorly trained one has been found.

The removal of the pituitary gland in doves, done by Dr. C. S. Moran, has been under study, and yields the result that within ten days following hypophysectomy the metabolism is decreased by not less than 25 per cent.

TRANSMISSION BY SEX-CELLS

INHERITED BEHAVIOR PATTERNS IN MICE

Observations on living mice carrying the gene for "Shaker," discovered some years ago in MacDowell's mouse colony, indicated that the lesion responsible for the Shaker behavior was probably in the brain rather than in the ears, long supposed to be the location of the defect in the closely similar Japanese waltzer. This has been confirmed through cooperation with Dr. Klaus Zimmermann of the Kaiser Wilhelm Institut für Hirnforschung, who finds that the location of the defect responsible for the Shaker behavior lies in the *area striata*.

Since the appearance of the Shaker mouse, the list of genes responsible for similar behavior patterns has been increased in other colonies by three. Two more genes may now be added to the list, making seven in all.

A strain of mice characterized by the peculiar behavior pattern called *circling* has been under observation by Mr. Laanes for the last five years. He has found that in young animals, this trait is expressed in various ways; some offspring of recessive matings have been normal. Breeding tests show that offspring from pairs of such normal parents, from pairs of circling parents and from matings between normal and circling parents, are very nearly identical; the only deviations that might approach significance were in the opposite direction from the parents.

During the last two years, Mr. Laanes has been making observations upon hybrids between circlers and a strain in which no abnormal behavior pattern has been seen. The first generation of the cross was entirely normal. The second generation (F_2) and back cross to the pure strain yield circlers in

proportions that indicate the interaction of two recessive autosomal genes segregating independently, whose influence is overcome by non-genetic variables in 17 per cent of the cases.

GENETICS OF CLADOCERA

During the past year tabulation and checking of the data obtained during the course of the sex-intergrade and excavated-head selection experiments (1917 through 1927) have been continued by Professor Banta and Miss Wood. Tabulation and graphs by single and five-generation averages have been completed for the sex intergrade selection experiments and are well under way for the excavated head-selection experiments.

GENETICS OF THE PARASITIC WASP HABROBRACON

Professor P. W. Whiting, who has worked at this department during a large part of the year, has continued his genetic studies on *Habrobracon juglandis* (Ashmead). This species has, during the past five years in the hands of Dr. and Mrs. Whiting and their associates, produced about sixty mutations of which some are important for the problem of sex determination; for this is one of those forms in which the females are produced sexually and the males by haploid parthenogenesis, having only one chromosome instead of two in each set.

Whiting has already advanced a theory to account for the feminization of the genitalia in certain haploid mosaic males. This theory postulates that the female is digametic, X/Y, and produces from unfertilized eggs two kinds of haploid males, X males and Y males. Females arise from a union of the X egg nucleus with the Y sperm, or the reverse. Diploid males derived by sexual reproduction come from union of gametes X with X or of Y with Y. Selective fertilization is involved, since fertilized eggs in most cases produce females. To establish the theory, proof was sought from the study of a sex-linked factor. Such a gene, *fused*, was discovered as closely sex-linked. Also, two other factors loosely linked with fused were also sex-linked, while other genes found belong to other chromosomes.

The theory has been tested by various observations. It has been shown that females of a certain strain crossed to males of various mutant types produce daughters which, if bred as virgins, produce a small percentage of females in addition to the usual males. These impaternate females may be either homozygous or heterozygous for any factor for which their mothers were heterozygous, and the homozygotes are numerically equal to the heterozygotes, according to expectation. Whiting, on the other hand, in a new strain that produces females parthenogenetically, finds that when the mothers are heterozygous for the gene fused and for various non-sex-linked factors the impaternate daughters are heterozygous for fused, as expected by theory, while for other genes they are either homozygous or heterozygous. In this strain also many haploid mosaic males are produced, giving further evidence of feminization of genitalia.

Dr. B. R. Speicher, associated with Dr. Whiting, has been investigating the earliest stages in the development of the egg of *Habrobracon*. By the use of the valuable Feulgen method of staining the structures of the egg, he has

been able to study these stages in the unfertilized eggs, which produce haploid males; the eggs fertilized by unrelated sperm, which produce females only; and the eggs fertilized by closely related sperm, which produce females or diploid biparental males or which fail to hatch.

GENETICS OF THE THOROUGHBRED HORSE

The Measure of Racing Capacity described in the last report has been applied by Laughlin to about 3000 additional horses. The special efforts of the year in a new direction have been the perfecting of the prediction-index as to racing capacity. The problem was to develop the theory and practice of weighting the several individual kinships which enter into the particular prediction-basis. The Near-kin Prediction-basis Index family derived is $\frac{\Sigma(FC \cdot K_{fc})}{\Sigma K_{fc}}$, in which FC is the value of the Fluctuation Center and K_{fc} the modal value of that center (one "offspring value" unit $\pm$ 0.5) as an index of accuracy of prediction (fig. 1). Experience shows that if the sires have an extremely high index of racing capacity (*e.g.* 132), their offspring will fluctuate around a more mediocre point (109.59); or if the sire index be low (100), his offspring will again fluctuate around a more mediocre point (103). Similarly with the dam; although her index alone is a slightly better prediction basis for racing capacity in the offspring than that of the sire alone. Using this regression phenomenon in index-making, one enters the sire, for example, as a factor influencing offspring quality, not at the racing capacity of the sire himself, but at the fluctuation-center of the average racing capacity of the offspring which sires of that particular racing quality on the average produce.

To determine the relative stress to be laid upon any fluctuation-center value in making up the total prediction index, the modal value K at each such center has to be taken into account, as indicated in the formula above. Any kin-group can thus form the basis for an offspring-prediction basis, but the closer the kinship and the more kin there are included in the index, the better will be the prediction of Nature's behavior.

The principal advance of the year in researches on the genetics of the Thoroughbred horse has consisted in demonstrating more definitely the principles and technique for evaluating and coordinating the individual near-kin into a prediction-index for offspring values. Besides thus perfecting the specific formula for the inheritance of racing capacity as such, a substantial contribution has been made to the principles of index-making which, in general, evaluate independent pieces of quantitative evidence and assimilate them into a logical prediction-index of high practical value.

GENERAL FORMULA OF HEREDITY

Laughlin has continued work on a general formula of heredity applicable to any quality which is definitely measurable in the individual and which has an hereditary tendency. This formula in its definitive form, with accompanying photograph of its geometrical model, in a specific case is shown in figure 2. In general the formula is $k = f\ (M,R)$ as defined in last year's

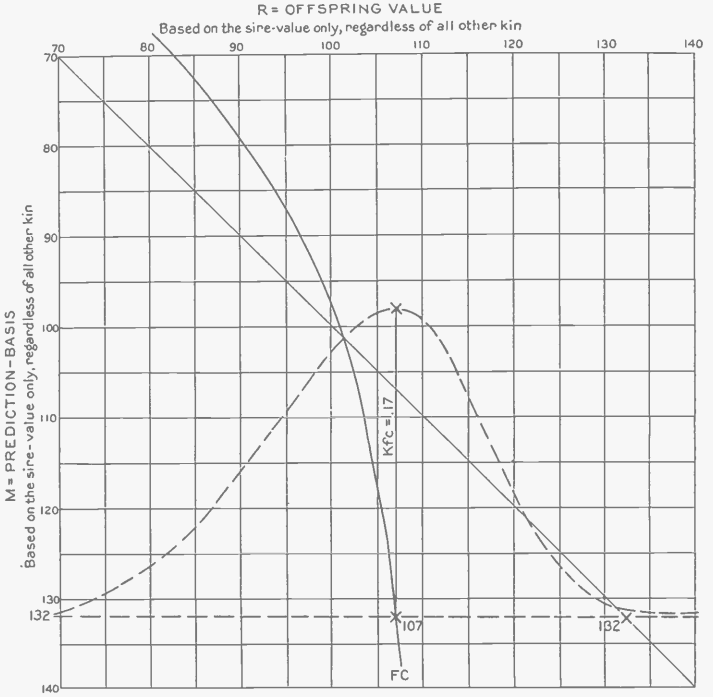

FIG. 1

DETERMINATION OF VALUE AND PROBABILITY OF AN INDEPENDENT CAUSAL FACTOR IN THE PREDICTION-INDEX

EXAMPLE:

CAUSAL FACTOR: Racing capacity in a definite kin. Herein measured racing capacity in the sire as one of the causal factors of the degree of such capacity in the pre-selected offspring.

VALUE OF THE INDIVIDUAL ANCESTOR:

(a) As a performer, racing capacity (RC) ..... = 132.00
(b) As a sire, fluctuation center of racing capacity in offspring... = 109.59

PROBABILITY *i.e.* frequency of offspring at FC ±.5 one R-unit = K_{fc} = .17

By making a computation for each causal factor (herein each near-kin) used in the particular prediction-basis the following formula is derived:

$$\text{NEAR-KIN PREDICTION-INDEX} = \frac{\Sigma(\text{FC}:K_{fc})}{\Sigma K_{fc}}$$

report. The mathematical model, called Manerkon, is a skewed saddle, or skewed camel's hump, depending on the particular formula. The illustration is based on Galton's studies on inheritance of stature derived from measurements of 1028 British children and their 255 mid-parents. In the model M, or the prediction-basis (the fore-and-aft coordinate), is the height of the mid-parents; the thing-predicted, or R (the right-and-left coordinate), is the adult-height of the child; while K (the vertical coordinate) is the probability that a pre-selected adult child, with a given M or prediction-basis (that is, whose father and mother have definite given adult statures), will fall within an arbitrarily selected stature-range. In this particular case the stature-class-range = R ± 0.5 inch. Due correction is always made for sex.

Goodness of prediction by K = f (M,R) depends upon: Accuracy of measurement; significance and inclusiveness of M, the prediction-basis; the "strength of heredity," and the degree of blood-purity of the subject population in regard to the subject trait.

Two immediately discernible qualities of the mathematical model for K = f (M,R) connote excellence-of-prediction. These qualities are diagonalness of the axis (in reference to M the prediction-basis; and R the thing-predicted, fig. 1), and the steepness and narrowness of the model as a whole (in reference to R, the thing-predicted; and K, probability). These two geometric qualities measure the ability of the particular prediction-basis (M) to predict by what probability (K) the value of the thing-predicted (R) will fall within a given measured class-range. Another essential geometric quality of this mathematical model is of frequent use; every cross-section right-and-left (like so many slices of bread) always shows a probability-curve with area equal to 1.000, that is, the summation of all vertical probability-strips (for all prediction-classes one R-class wide) of the thing-predicted must summate into a probability of 1.000 or certainty.

Referring again to the mathematical model (fig. 2) for K = f (M,R) given any selected M and R, one can find the corresponding K, either by substituting the selected values of M and R in the Specific Formula, or by locating the manerkon-surface-point common to the selected M and R, and then by reading the coordinate value of K on the "post" (at upper left-hand corner).

In the present (fig. 2) specific formula, M = Height of Mid-parent in inches; Mid-parent = (Height father + Height mother × 1.08) ÷ 2; R = Arbitrary selected adult offspring-stature in inches ±0.5 inch. This locates the offspring-prediction-range of one inch. K = Probability that the given M will produce the arbitrarily selected R.

Laughlin notes that his general prediction-formula is a combination of two geometries. First, the two-dimensional Cartesian, in which R = f (M). This alone would suffice except for the fluctuations of offspring values. Second, the DeMoivrian geometry of probability in two-dimensions. This second is then superimposed at right angles on the first. This three-dimensioned figure Laughlin calls the "Manerkon" from manton ("M") meaning prophecy; ergon ("R"), meaning the actual thing; and eikon ("K"), meaning likelihood.

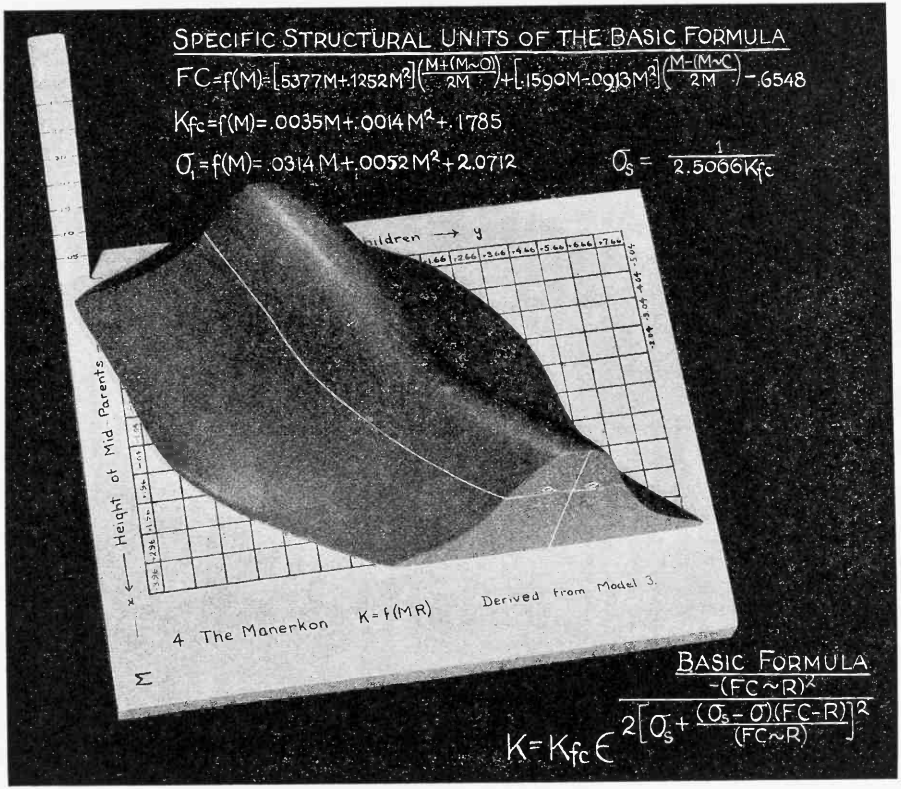
SPECIFIC STRUCTURAL UNITS OF THE BASIC FORMULA
FC=f(M)=[.5377M+.1252M²](M+(M~O)/2M)+[.1590M-.0913M³](M-(M~C)/2M)-.6548
Kfc=f(M)=.0035M+.0014M²+.1785
σi=f(M)=.0314M+.0052M²+2.0712
σs = 1/2.5066Kfc
Children → y
Height of Mid Parents
4 The Manerkon K=f(MR) Derived from Model 3.
BASIC FORMULA
K=Kfc ε^(-(FC~R)² / 2[σs+(σs-σ')(FC-R)/(FC~R)]²)

FIG. 2

In the further development of $K = f(M,R)$, a large series of specific formulæ of heredity must be computed, that is, the general prediction-formula must be applied to a great many cases for a specific trait or quality in a definite species or stock. In such a series, further perfection of the formula is looked for mainly in the generality or constancy of the mathematical nature of each of the three structural units. These three units, each represented by a two-dimensioned Cartesian curve, are as follows: $FC = f(M)$, $K_{fc} = f(M)$, and $\sigma = f(M)$. The standard deviation σ may be σ_S (that is, for the particular M-class, if the R-class distribution be symmetrical) or, if skewed, $\sigma_R + \sigma_L = 2\sigma_S$. FC is always computed on the R-scale, K_{fc} on the K-scale, and $\sigma_{S,\ R\ or\ L}$ on the R-scale.

HUMAN GENETICS

COMPARATIVE HUMAN AUXOLOGY OF WHITE CHILDREN

Infants

A much-prized opportunity has been seized by Davenport to participate in a study of development of infants at the Normal Child Development Research Clinic, Babies Hospital, Columbia University Medical Center, L. Beverley Cheney, director, Myrtle B. McGraw, assistant director. Here physical measurements are made on about 15 infants beginning a few days after birth, and repeated fortnightly at first and then monthly. These measurements run parallel to the psychological and physiological studies.

Child Development

The studies in child development that are being pursued by Davenport have been continued at Letchworth Village with the generous cooperation of Dr. C. S. Little, superintendent, and Dr. E. J. Humphreys, clinical director. In this work Miss Lillian B. Frink, who previously had spent two years in studying the families of these particular children, has assisted as recorder and Mr. William Drager as statistical assistant. All individuals of the series have been seen at six-month intervals. All measurements made on about 70 individuals, who have been repeatedly measured for six to ten years, have been plotted to record the course of individual physical development.

The following studies have been published:

The Thoracic Index—This is the ratio of transverse chest diameter to chest depth. This index is very different in the various genera of mammals. Thus it is about 165 in some of the most primitive mammals; about 165 to 120 in various burrowing mammals, 150 to 120 in fliers; 145 to 90 in various arboreal species; 100 to 75 in running forms. In adult man the index is about 135. However, this index changes greatly during development, being, on the average, about 60 at the end of the first month of gestation; rising to 100 at the end of the third month, to 113 at birth and to 129 at 4 years. Thus in the human fetus and infant this index passes through a series of changes like that of the Primates. However, in the macaque monkey the adult index is just under 95; the orang goes on to 150 or more. Man starts like the other Primates, but reaches a different goal in which his broad chest and shoulders

permit the free movement of his arms to and fro past the body axis. In relation to trunk height, the chest breadth in boys tends to diminish to early adolescence and thereafter to increase slightly.

The Intermembral Index.—This is the ratio of arm length to leg length. In *Homo* at the third month of gestation this index is about 125; falls to 92 at birth, and reaches 84 at adolescence; and then rises slightly. The intrauterine growth is like that of the apes, but whereas the chimpanzee retains in the adult the fetal indices of around 107 the human child goes further toward reduction of this ratio. This reduction of the intermembral index in man is a highly adaptive result. Certainly an index of 135 as in the tree-inhabiting gibbon would be a handicap to terrestrial man. In the case of other biped mammals (Kangaroo, jumping mouse, Tarsius) the fore limbs have become greatly reduced as compared with the hind limbs; it seems probable that the same thing has happened in man and that, accordingly, his ancestors had an intermembral index of not far from 135 and were arboreal.

The Brachial Index.—This is the ratio of the distal segment of the arm to the proximal segment. In the human fetus this ratio increases from 75 at 3 months of gestation to 90 at birth and then falls rapidly to 78 at adolescence. This extraordinary change in the index finds a meaning when comparative growth studies are compiled, showing that the brachial index of the Primates rises during gestation to 80 or 85 (as in *Homo*), but, unlike man, after birth goes on to 94 in the chimpanzee and 107 in the gibbon. Thus the final proportions of the human arm are seen to be due not merely to a difference in relative growth of two of the segments, but to a constant adjustment to fetal, infantile and adult needs.

Criticism of Physical Anthropometry

With Steggerda and William Drager, Davenport published a critical examination of anthropometric methods used by themselves. While some extrinsic errors have been largely eliminated by checking each other's technique, it is found that the accuracy of measurement (taken repeatedly by one observer on one adult subject) varies markedly in the different dimensions. Thus stature, the largest dimension, has the "probable error of a single measurement" of medium size (2 mm.). It has a coefficient of variation (or relative variation) of only 0.19 per cent, the smallest of all. On the other hand, height of nose bridge, the smallest dimension, has a probable error of the single measurement of 1 mm. and a coefficient of variation of 11.2 per cent, or sixty times that of stature. The dimensions of the head have a small error, while of mobile, soft parts like waist girth, the error is high. It appears also that stature decreases by about 7mm., and sitting height by 9 mm., between morning and afternoon, specifically between 10 a.m. and 4 p.m.

At different seasons of the year the increase in certain dimensions of the body is very unlike. Thus the monthly increase in stature is greatest in the spring and least in the summer. Increases in weight are greatest in April and October and least in June. Growth is relatively slow also in mid-winter.

RACE DIFFERENCES IN THE GROWTH OF INDIANS, NEGROES AND DUTCH

Steggerda has, with some aid from Mrs. Steggerda, continued his comparative study of growth of children of different races. Despite considerable difficulties in securing the ages of Negroes and Indians, Steggerda has been able to reach a conclusion concerning the comparative development of the different races of the three groups being considered: Dutch, Negroes and Navajo. It appears that the Navajos are the shortest; the Negroes being closer to the White standard than to the Indian. In development of all races, studied alike, the curve of growth of the females show a decussation with the curve of the males at ten and a half years, when the females become taller than the males. In all cases, also, at about thirteen and a half years a second decussation in the developmental curve appears, at which time the males become taller than the females.

An important conclusion is drawn from the comparative study of these races, namely, that the differential characteristics are already apparent at six years of age and persist throughout life. Thus, Negroes have longer appendages and shorter trunks than the Indians, and this is already true of the children at six or seven years of age. Similarly, the cephalic index for adult Navajos is very high, about 85.4 for the males and 86.1 for the females. Younger children, in general, have higher cephalic indices than adults, but the indices of the Indian children are exceptionally high as compared with those of White children.

The following table shows the number of individuals in each of the developmental series:

Race	Location	Measured	
		Number	No. of times
Dutch Whites	Holland, Michigan	232	3
Maya	Yucatan, Mexico	170	4
Navajos and Zunis	Arizona and New Mexico	100	2
Negroes	Alabama	108	2
Total		610	

FAMILY STUDIES AMONG THE INDIANS

Since our developmental studies are at the same time genetical studies, Steggerda is plotting extensive family pedigrees. From such pedigrees some interesting data concerning the reproduction of the Maya Indians appear. Thus, 34 Piste mothers whose reproductive span has been completed, produced 264 children, or an average of 7.8 children for each woman. The chances are that the birth rate is even higher, since it is difficult to secure accurate information on infant mortality. Of these 264 children, 90 died young, which is approximately 34 per cent. This figure is also lower than the actual mortality rate, since many early deaths are unrecorded. When the family data are fully tabulated, it will be possible to compute not only the average number of children for a larger number of mothers, but also the average age of the mother at the birth of her first child, which appears at

present to be much younger than among White mothers. It will also be possible to determine the number of legal husbands and wives per individual, which is also higher than for Whites, although Steggerda finds reason to believe that the number of promiscuous unions among the Maya is no greater than that found among equal classes of Whites.

DERMATOGLYPHICS

A paper has been written by Steggerda with Professor Harold Cummins of Tulane University, which is about to appear in the American Journal of Physical Anthropology. This deals with the fingerprints of the Maya Indians. It considers 127 Indians from Yucatan. In this series 33 per cent were whorls, which is slightly less than found in other collections of North American Indians, but considerably higher than recently found in the Dutch children, where the incidence was only 20 per cent. In the Maya the frequency of arches was 7.6 per cent. This is higher than generally found among the Whites. The hypothesis that a greater frequency of whorls occurs among the broad-headed than among the long-headed was tested by comparing the whorls of Maya and Dutch children, and the conclusion was reached that no relationship exists between the type of fingerprint and cephalic index.

Mrs. Steggerda has for a long time been interested in racial differences in palmar dermatoglyphics. It has been known that three of the main lines on a Negro palm generally fall in positions 7, 5 and 5, while in Whites these lines terminate most generally in positions 11, 9 and 7. In the Maya Indians 27 per cent have an intermediate position of these lines, namely 9, 7, 5; 22 per cent fall into the 7, 5, 5 group; and 17 per cent in the 11, 9, 7 class.

OTHER STUDIES AT YUCATAN

Census, Soil and Food Studies of the Maya

As pointed out last year, Steggerda has made a census of the entire village of Piste and this he revises each year. By this means he is able to acquire facts concerning reproduction and thus to secure correct dates of birth of the different children. Incidentally, he noted that Piste, a town of 372 persons had 17 new houses built in the year ending March 1934; 9 others had been repaired or changed in some way or another. It must be remembered that there were only 111 houses in Piste; if compared with a stable New England town, or even a Pueblo village, this is a great change; but the Mayan "homes" are less durable in construction than Pueblo or White man's houses. Steggerda has gathered data concerning migration and immigration at Piste, and will be able to compare this with a Pueblo group of the southwestern Indians, concerning which data are being secured by Dr. S. D. Aberle. Bearing upon the migrations among the Maya Indians in the past, Steggerda is making a detailed study of the changes in the soil with the cooperation of Dr. Oswald Schreiner of the United States Department of Agriculture.

Forty different Maya foods have been sent to the Nutrition Laboratory in Boston for analysis. In addition, samples of the daily food consumed by six Maya laborers for three successive days were analyzed at Dr. Benedict's laboratory.

Steggerda took about one thousand feet of moving-picture film showing preparation of food and other domestic activities of the Maya.

Comparative Mental Tests

Steggerda has applied several mental tests to the Indians, but finds that certain difficulties are encountered, such as uncertain age (which is required for determining intelligence quotient); speed, which the White race alone stresses; language, which requires that those tests should be selected which can be given by pantomime; different cultural backgrounds, which makes necessary the elimination of many tests that would be otherwise valuable. The environment in which the tests have to be made must be selected with care. The tests were usually given in the native's home. In Steggerda's experience the best tests are: Knox Cube imitation test, Stringing of Beads test, Form Discrimination test, Seashore Music test, Designs test, Color Blindness test, and test for taste, using phenyl-thio-carbamide.

Dental Studies

Steggerda has continued to cooperate with Dr. Weston A. Price on the problem of dental caries. He has secured and sent to Dr. Price samples of saliva from Navajo Indians, samples of food from the Maya, and secured other data that may throw light upon the immunity of dental caries enjoyed by the Maya.

INHERITANCE OF ACQUIRED CHARACTERS

The old idea of transmission to later generations of the effect of an injury still holds sway even among educated people. An opportunity came to Davenport to "run down" a case of an injury to the finger which was believed to have resulted in its shortening; and in consequence a shortening of the corresponding finger of a child of the injured person. However, short finger was found to be a family defect. Light is thus thrown on the development of the idea of inheritance of acquired characters. An accident calls attention for the first time to a defect. The defect is ascribed to the accident. Subsequently the affected individual has a child with the same defect and this defect is ascribed to the accident that happened to the mother. The chain of evidence seems to the casual observer complete. The one fact is missing that the first observed defect is congenital, antecedent to the accident.

STUDIES IN SENSORY THRESHOLDS

Blakeslee has gathered additional statistics on the differences between people in sensory reactions. Tabloids, each containing 5 mg. of mannose, were submitted to 250 biologists at a dinner. 15 per cent received no sensation of taste from the tabloid, 20 per cent pronounced it sweet, 10 per cent said it was bitter, and 55 per cent both sweet and bitter. Different individuals had different thresholds at which they could sense these two stimuli.

Information was also obtained regarding differences in after-tastes. Following a salad of Globe Artichokes, about three-fifths of the people found the drinking water tasted sweet, while to two-fifths no change in the taste of the water was detected.

IMMIGRATION RESEARCHES

Laughlin has prepared a report for the Special Committee on Immigration and Alien Insane to the Chamber of Commerce of the State of New York, John B. Trevor, Chairman. The report is entitled "Immigration-Control—an analysis of the standards, procedure, spirit and results in current immigration control, pointing out the defects which prevent the effective enforcement of American immigration policy, and indicating the constructive work needed for such enforcement."

This report gives the results of a new survey and analysis of the racial stock of the inmates of 246 prisons and reformatories maintained by the Federal government and the several states. This population was studied on the assumption that such inmates constitute, on the whole, in the prisons of today undesirable human breeding stock. Of these, thousands of aliens are legally deportable upon discharge; but it appears the law relating to deportation is inadequately enforced, owing partly to a failure to recognize the importance for the future of this country of good breeding stock. Laughlin enunciates the principle: "That nation, state or local community which produces a defective or inadequate person of any sort shall be responsible for the care of such individual." Such responsibility calls not only for international but for interstate and intercommunity deportation as well. Laughlin points out that in the act of selecting immigrants, the state can exercise its most effective eugenical influence. Immigration, if properly controlled, can be made to improve the human seed-stock of the American nation, or it can be permitted to destroy the receiving nation. As a pure science, eugenics seeks to analyze the forces at work that tend to improve or impair the inborn qualities of a population. It is only one step further for the American people to apply such demonstrated principles, if they desire to control the future population in number, race and quality.

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PERSONS ENGAGED IN VARIOUS ACTIVITIES DURING THE YEAR ENDING OCTOBER 31, 1934

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