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DEPARTMENT OF GENETICS[1]

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GENERAL STATEMENT

The study of heredity is proceeding ever toward more fundamental phenomena. In Galton's day it was a study of the family incidence of certain traits. The plant experimenters of a century ago were, like the late Mr. Burbank, concerned with the transfer of characteristics by hybridization, by the uniting of alien germ cells. As biological knowledge grew, the problem of the mechanism of heredity was transferred from the germ cells to the nuclei of the cells and especially to the chromosomes. While biological philosophers had long agreed that there must be a finer unit—the gene—it has been scientifically studied for only about the last twenty years.

Concerning the nature of the gene, diverse views exist. One view is that, though simple, it varies in size in different strains. When the gene is large a "strong" well-developed character arises; when small the character is more weakly expressed. On this view the mutations in a gene are purely quantitative. Another view regards the gene as made up of gene elements or "genomeres," which may or may not be chemically the same. Still another view is that the gene consists of a large molecule to which the same side-chain of molecular groups is attached several times. As between the quantitative theory of differing factors at the same locus and the various theories that call for a qualitative difference between these factors, the observations of Demerec throw the weight of evidence toward the qualitative theory, inasmuch as the various mutations play qualitatively distinct roles. From this point of view the gene is a compound molecule, the stripping off of whose molecular groups causes changes partly of a quantitative, partly of a qualitative, nature. The analogy of this behavior to that of certain better-studied organic molecules is somewhat close. It is thought most probable that each gene in the cell is a substance that directly or indirectly produces enzymes, each of which stimulates differential growth and development of a specific kind.

The foregoing considerations bear upon the problem of the size of the gene. Our former colleague, the late Dr. Belling, considered the small paired particles that can be seen strung along the length of the chromosome in its attenuated stage as such genes. They lie close to the limit of resolvability, when viewed by ordinary white light. The visible ones vary in size, and apparently still smaller ones can be seen by ultra-violet photography. They are of the order of one-fifth of a micron (or 8 millionths of an inch) in diameter, and smaller. Certain experimental work has led some geneticists to conclude that the real genes are about one-tenth of the diameter of Belling's "genes." Since the latter agree with theory in number, though not in size, it seems probable that the ultimate genes lie imbedded in the heart of Belling's genes—a view to which Belling had come shortly before his death.

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Scores of problems cluster around the gene. To state that it acts as a true catalyst does not carry us far, for each kind of gene plays a particular role in development, affecting the development of particular organs. The great problem is how, out of the apparently full equipment of genes, do just those that influence the specific nature of the cell become functional at the right time and place.

The investigation of the gene is of the highest importance not only for an understanding of how the body develops and becomes specialized or differentiated in its various parts, but also for an understanding of the nature of the ultimate living substance. When we understand the structure of the gene we shall know the essential difference between living and non-living matter. The geneticist should shortly be in a position to aid the chemist in getting at the ultimate nature of living matter and especially must both cooperate in the solution of the problem of the fundamental property of the living molecule, namely its capacity for dividing indefinitely with retention of all of its qualities. For upon this property depends all agriculture and animal husbandry—depends all life itself. Before the self-dividing molecule had been evolved, this was a lifeless world; unless it has been evolved in other planets, they are lifeless still. The living, dividing molecule, of which the gene is a special sort, is the great upbuilding agency in a universe that is running down. Its capacity for creation is due to the genes whose ability to increase living matter is limited only by the conditions imposed by the non-living world. For the genes create living matter out of the non-living material, while periodically that which they have created is returned to its source for new generations to feed upon. Indeed, it is not sufficient that the gene multiply, it must forever change and build up a new and different generation to keep pace with changing cosmic conditions, and, as opportunity arises, to meet those conditions more effectively. Of what makes the gene change we have a conception; but of what makes it divide we have no inkling; we only know division to be its unique and fundamental nature.

All the personnel of this Department cooperated in the Sixth International Congress of Genetics held at Ithaca last August, and with the Third International Congress of Eugenics held in New York City the same month. Especial mention may be made of the work of Laughlin in organizing and installing the Eugenics Exhibit at the American Museum of Natural History and of Demerec in getting together the Genetical Exhibit at Ithaca.

On Sunday, August 21, 1932, the foreign visitors to the Congresses were received at Cold Spring Harbor and shown the work of the Department. Neighbors invited guests to their near-by country homes for luncheon. The American Museum was host to delegates to both Congresses. During the months following the Congresses we had for a longer or shorter period as research guests Dr. Tage Kemp of Copenhagen, Dr. and Mrs. Timoféeff-Ressovsky of Berlin and Dr. Curt Stern of Dahlem.

The Institution has suffered severe losses by the death of persons long associated with this Department. Dr. John Belling, who was with us from 1920 to 1929 died in Berkeley, California, February 27, 1933. Personally shy and retiring, his scientific work was characterized by a boldness that would have been regarded as rashness had events not proved the accuracy of his

observations and the flawlessness of his deductions. His was an unusual combination of scientist, philosopher and poet. The impress of his genius will be felt on genetics for a generation to come.

Miss Julia I. Goodrich, who served for twenty-seven years as secretary of the Department, died on January 21, and George H. Claflin, for twenty years chief clerk, died May 13.

DETAILED REPORTS ON CURRENT INVESTIGATIONS

THE GENE

EXPERIMENTS ON MOLECULAR STRUCTURE

That development of the organism is controlled from the inside by means of definite particles of different kinds that play a differential role in development is a conception that is at least 100 years old. But in the past 25 years the pangenes of Darwin and the genes of Johansen have taken a more concrete form. They can now be counted, located, measured, differentiated. But of their more intimate nature or structure we have little knowledge. In this department it is especially Demerec whose work has led to the formulation of a working hypothesis of the nature of the gene. The genes are experimentally proved to be minute particles; probably single organic molecules—an assumption not, however, necessary to his concept. If genes are large organic molecules, they most probably consist of a number of interconnected molecular groups. This conclusion is supported by the facts of multiple allelomorphs—genes of differing but related qualities and occupying, in different biotypes, the same locus in the chromosome.

In the *miniature* locus of *Drosophila virilis* ten allelomorphs are known which can be arranged into a two dimensional series as follows:

mt-1	mt-3	mt-2	mt-5	mt-4	wild-type
	alpha		alpha		
	beta		beta		
	gamma		gamma		

Allelomorphs are arranged in the horizontal line at the top according to size of the wings, and in the vertical column according to the degree of stability (mt-3 and mt-5 allelomorphs being unstable). There is a much closer connection between the allelomorphs of any one vertical group than between the allelomorphs of the horizontal group, since a transformation of one allelomorph into another in the vertical group occurs rather frequently and such a transformation has never been observed for the allelomorphs of the horizontal groups. This evidence suggests that changes producing different allelomorphs are independent of each other and indicates that they might arise by changes in different groups of one gene molecule.

This hypothesis is being tested by Demerec who is studying the changes produced by X-rays in the white locus of *Drosophila melanogaster*. White eye may be obtained from the wild type (red eye) as well as from other allelomorphs of the white locus, such as eosin, apricot, cherry and blood. Now, if each of the 11 known allelomorphs of white is produced by a change occurring in a different group of the gene molecule, it is to be expected that

whites obtained from different allelomorphs will be different. The white derived from wild-type would involve a change in the group responsible for white: the white derived from eosin would have in addition to the change in the white group also a change in the group responsible for eosin, etc. A reversion, therefore, from white derived from the wild-type should be red, from white derived from eosin should be eosin, and from white derived from apricot should be apricot.

The testing of this hypothesis has not been easy. To secure reversion from white required a very large number of individuals subjected to a heavy dosage. The treated male was mated to an attached X female. The dosage used was 2500 and 3000 r-units and was so heavy that it caused a high degree of sterility among the treated flies. The results of this prolonged experiment are given in the following table:

Changes observed in the white locus of Drosophila melanogaster

Origin	Changes to white		Reversions from white		
	Number of		Number of		Appearance of reversions
	Males	Changes	Males	Reversions	
White stock	.....	.....	12,098	0	
Wild-type	3,910	5	33,638	0	
Apricot	2,446	4	10,495	2	1 apricot; 1 darker
Eosin	2,014	8	15,035	1	eosin
Cherry	783	2	4,918	0	
Blood	1,098	1	.....	.....	

Of the three reversions from white shown in the table, two have been tested so far and found not to be due to a change in the white locus but to changes in other loci, located in autosomes. This suggests that the white gene could more easily be induced to produce color by changes occurring in the gene complex (made up of associated genes) rather than in the principal gene itself. The data indicate, furthermore, that if the allelomorphs are due to changes in various groups of a gene molecule, the changes occurring in different groups might give a similar phenotypic effect. It is obvious that a method that induces sterility and requires 25,000 male offspring to afford 1 reversion from white will yield the sought answer only on prolonged search.

THE ROLE OF THE GENE IN VITAL FUNCTIONS

It has been found that a great majority of changes observed in known loci of *D. melanogaster* are lethal; also the loss of a small region of a chromosome (deficiency) has a lethal effect. These two observations suggest that a lethal in a known locus might be due to an elimination of the gene; *i.e.* a deficiency in a single locus has a lethal effect on the organism. Demerec has tested this conclusion. ' He used females of a race that frequently eliminates an X-chromosome in the somatic cells of females and mated them with X-rayed yellow males, a portion of whose sperm carries

lethals induced by X-ray treatment. In cells of any resulting females in which the X-chromosome has been eliminated, yellow spots will appear. But if the yellow-bearing chromosome carries a lethal factor, which prevents altogether the development of those cells with eliminated (X) chromosome, then yellow spots on such females will not appear. Actually there were less than half as many lethals among the females with spots as among the females without spots, since the latter carried cell-lethals. The results indicate that 56 per cent of all lethals are cell-lethals. The conclusion seems inescapable that a full complement of at least certain genes is essential for the life of the cell. From these facts Demerec draws an important conclusion. If a strain of organism possesses only a few genes not present in another strain, that fact would cause a high degree of sterility among the offspring produced by crossing these two strains. Even a difference in one locus of the type described by Patterson as "viability gene" would be sufficient to produce complete incompatibility between two lines, one possessing the gene and the other not possessing it. Such a difference would be sufficient for the formation of a new species.

UNSTABLE MINIATURE-5 GENE

As indicated above, unstable miniature-5 (which was described in Year Book No. 30 and which is an allelomorph in the miniature series, having a somewhat longer wing than miniature-3) shows 3 allelomorphic forms, alpha, beta and gamma. Modifying factors which stimulate the rate of change in miniature-3 affect similarly the rate of change in the miniature-5 gene.

EFFECT OF X-RAYS ON THE RATE OF CHANGE OF THE UNSTABLE MINIATURE-3 GENE

The material carrying miniature-3 alpha and gamma was X-rayed at different stages of larval development; dosage about 2000 r-units. The rate of change in the unstable miniature-3 gene was not significantly affected.

SPINDLE-FIBER ATTACHMENT OF THE X-CHROMOSOME OF DROSOPHILA VIRILIS

In completion of the work described in Year Book No. 30 (p. 48), Demerec shows that the percentage of equational non-disjunctions diminishes markedly toward the end of the chromosome that contains the bobbed gene, and draws the conclusion that the attachment of the spindle fiber (an important bit of the machinery of chromosomal division) is located in that region.

The loci studied, their location, and the percentage of equational non-disjunctions observed are as follows: scute, 3, 12/45=26.7 per cent; cross-veinless, 25.5, 14/45=31.1 per cent; miniature, 72.1, 17/45=37.8 per cent; small bristles, 138.8, 13/45=28.9 per cent; apricot, 137, 10/38=26.3 per cent; ragged, 159, 10/62=16.1 per cent and bobbed, 174, 1/24=4/2 per cent.

CHROMOSOME STUDIES

UNBALANCED HAPLOID

While the genes individually and collectively are the agents of the species that direct the development of the individual, it is not sufficient that they should be in the cell; it is essential that they be grouped in the nucleus in definite fashion so that they may be transmitted from mother to daughter

cells in an orderly way and so that they may come into functioning at the proper time and place. The chromosomes are, as has long been known, paired. The members of a pair have nearly the same genes arranged in the same order. In the maturing of the germ cells and in some somatic cells, like chromosomes pair, lying side by side, and with corresponding genes opposite each other. Thus, like poles are together, wherein the attraction between chromosomes differs from that between magnets.

From these text-book standards, Daturas show many instructive departures. In the first place instead of the typical 12 pairs of chromosomes (the diploid condition) some Daturas show only 12 single chromosomes (the haploid condition). Such haploids may grow, though not vigorously, and may flower, but ordinarily do not reproduce. This year Blakeslee has found two cases of a new type of chromosomal mutant; a haploid with 1 extra chromosome, making 13 in all. The first is probably a 1n + 7·7 type. The mother was a 2n + 7·7 and the modified haploid probably arose parthenogenetically with the secondary 7·7 chromosome extra. The chromosomal constitution was inferred from the somatic appearance of the plant and confirmed by cytological study. Though the plant is weak and may not survive to reproduce, it is important as revealing the greatest unbalance, 2 extra halves to 12 normal chromosomes, so far found in a Datura plant. The second case showed 13 chromosomes in pollen mother cells and in somatic tissue of the bud, but cells of the root tip showed a reversion to the 2n condition. Perhaps for this reason, as well as because of its lessened unbalance, in comparison with the first modified haploid, it is a relatively vigorous plant. It was the offspring of a 2n + 15·15 female parent which was heterozygous for the interchanged chromosomes 11·15 and 12·16 of Prime Type 20.

That chromosomal irregularities may occur in other species of Datura besides *stramonium* is demonstrated by our recent finding of tetraploids in both *D. ferox and D. pruinosa*, and a haploid in the latter.

PRIME TYPES (PT'S)

These are strains of *D. stramonium* with 2n chromosomes that differ not in the genes but in their arrangement in the chromosomes. The collection of prime types corresponds to a printer's font of type since it is a source of modified chromosomes with which it is possible to make up 2n + 1 tertiaries and compensating types, as well as pure-breeding chromosomal types. Whereas last year Blakeslee reported 57 prime types in 33 of which one or both of the modified chromosomes were known, this year he is able to report a total of 87 prime types in 55 of which one or both modified chromosomes have been determined. The kinds of chromosomal modifications involved are of three types. Nearly two-thirds have been due to segmental interchange, about one-fifth to simple translocation of gene groups and slightly over a tenth to interchange between "humps" attached to the ends of chromosomes. It is in the latter two types that bad pollen is most frequently found.

Prime types are used as chromosomal testers with which to identify the ends of chromosomes by noting their terminal attachments in meiosis. At

present Blakeslee has more than one prime type tester for each of the 12 chromosomes.

COMPENSATING TYPES

Compensating types, in which parts of two modified chromosomes compensate to form the equivalent of a single normal chromosome, are of value in locating genes and in retaining a single chromosome or chromosomal group during the process of back crossing. It is for this reason that we have been attempting through combining prime types to establish a complete series of compensating types which would compensate for each of the 12 chromosomes. So far we have succeeded in making up compensating types that will take care of all except 3 chromosomes.

SYNTHESIZED PURE-BREEDING TYPES

Whenever the cells of the plant carry, in addition to the normal (doubled) equipment of genes, an additional set of genes inhabiting a fragment of a chromosome firmly joined to another chromosome or chromosome fragment essential to the existence of the gametophyte, then, due to these excess genes, the plant is somatically different. If the chromosomes, including the extra inseparable fragment, are all paired, then a pure-breeding type has been synthesized. The prime types give the key to the process, inasmuch as they afford composite chromosomes, with firmly united fragments, and also others with free fragments which may compensate with one of the components of the composite. When, as is not always the case, the extra chromosomal material is transmitted by the pollen, a race may be established that will breed true.

During the year under review, a plant has been built up out of two prime types, of which one had a free ·24 fragment and the other a 23·14 chromosome. The abnormal chromosomes of this plant have the composition: $\left(\frac{\cdot 24}{23 \cdot 14}\right)_2$. It is homozygous for the extra ·14 half and consequently is expected to breed true. It is hoped to develop further such true-breeding types.

SPECIES IN NATURE

One of the main objectives of the Datura work is an understanding of the nature and origin of species as they occur in nature. The frequency of interchange of chromosomal fragments in *D. stramonium* and the relation of this phenomenon to the formation of new pure-breeding types has led to the hypothesis that segmental interchange has accompanied the changes responsible for the formation of species in the genus *Datura*.

Cryptic types (resulting from segmental interchange) have indeed been identified in all the species of the genus in which three or more races have been tested; namely, *D. stramonium, D. quercifolia, D. leichardtii, D. meteloides, D. innoxia* and *D. metel*. The conclusion is accordingly drawn that segmental interchange leading to intraspecific races with modified chromosomes has commonly occurred within the genus *Datura*. This subject is being further investigated.

Inter-specific chromosomal differences also are being studied. Here, a single race is chosen as standard for each species in terms of which differ-

ences between it and similar standard testers in other species can be interpreted. A report was made last year of the findings in three species of the stramonium group (*D. stramonium, D. ferox* and *D. quercifolia*). This year results were obtained with *D. leichardtii.* The tester race of this species, by interchange between the 1·2 and 17·18 chromosomes and between the 11·12 and 15·16 chromosomes, has (in comparison with our standard line 1 of *D. stramonium*) the modified chromosomes 1·18, 2·17, 11·16 and 12·15. The 1·18 and 2·17 chromosomes are similar in end arrangement to those of the "B" race of *D. stramonium.*

D. leichardtii will cross with the species *D. innoxia, D. meteloides* and *D. pruinosa,* all of which belong to the *meteloides* group. They apparently will not cross directly with *D. stramonium. D. leichardtii* which has been hybridized with *stramonium* is therefore used as a bridging form to which hybrids with these other species can be back crossed and ultimately related indirectly to our final standard Line 1 of *D. stramonium.* This method necessitates the use of tester races intermediate between *stramonium* and *leichardtii.* Such testers are being gradually established and through their use we hope before long to be able to report upon the chromosomal constitution of these other species.

One species of the *meteloides* group, *D. discolor,* has been found capable of crossing with *D. stramonium* when the former is used as a pollen parent. It should be possible, therefore, to make direct determination of the ends of its modified chromosomes by study of the chromosome connections in hybrids with the various testers of *D. stramonium.* Preliminary study by Dr. Bergner indicates that the chromosomes of *D. discolor* differ from those of *D. stramonium* by a number of interchanges. The leaf characters of the hybrids, however, do not differ widely from those of *D. stramonium.* It should be possible, therefore, to recognize compensating types among the hybrid offspring and, provided the hybrids have adequate pollen, it should be possible by continued back crosses to the appropriate compensating types to produce races with all *stramonium* chromosomes except for the chromosome or chromosomal group protected by the compensating types.

MUTATION IN DATURA

Genes, of which we reported a considerable number in the last Year Book, are in process of being located in particular chromosomes by a variety of methods. One of especial interest may be mentioned at this time. It causes a doubling of chromosomes at meiosis, through the formation of dyads instead of tetrads of pollengrains. A "dyad" plant when selfed gives rise to dyad tetraploids in which the somatic tissue is 4n and the pollen grains have 48 chromosomes. Among the offspring of a tetraploid dyad, Miss Satina, who has been studying the cytology of this type, has made a count of about 72 chromosomes in somatic tissue of a bud. The plant is of weak growth but apparently represents a hexaploid (6n).

The formation of new genes by spontaneous mutation has been rare in *Datura,* although gene mutation can be readily induced by radiation and possibly by other stimuli. A series was started this summer to test the possible influence of age of seed upon mutation rate following the recent report

of Navashin, that more chromosomal abnormalities were found in root tips of plants grown from old seed.

Among effects of radiation treatment, those showing in the pollen are perhaps the most frequent. They include both the results of single genes and of chromosomal abnormalities. Pollen abortion can be used to advantage, therefore, as an index of the mutation rate, especially since the majority of pollen genes show in the individual grains affected and thus give an advantage of a generation over recessive genes which cause changes in somatic tissue. Dr. Cartledge, who has charge of the work in pollen abortion, has found 4.5 per cent pollen abnormalities in about 500 plants from seed 10 to 5½ years old and only 0.5 per cent abnormalities in about 1000 controls which came from seed 3½ to 1 year old. The older seed had been stored in the second floor of the main building, in the basement of which, about 32 feet away, an X-ray machine has been in operation since the summer of 1928. The machine has been enclosed in a ⅛ inch sheet of lead since the spring of 1930. The higher rate of mutation in the old seed is undoubtedly significant. Whether stray radiation from the X-ray machine in a distant part of the same building could have been at all responsible for the increased mutation rate is being tested by new plantings.

SOMATIC MUTATION IN DROSOPHILA

That mutations occur in somatic cells giving rise to "mosaic" individuals such as are illustrated by variegated plants has long been known, and they have been intensively studied by Demerec in the flowers of the *Delphinium*. Mosaics have been described in *Drosophila* also. Their nature has been uncertain. Dr. Curt Stern, while a guest at this Department during the latter part of the year under review, has made experiments on this subject in *Drosophila*. He finds that the spots which differ in appearance and genetic constitution from the surrounding tissues are not to be explained by mutation in the somatic cells, but by the disappearance of chromosomal parts with their genes. The experiments that he has made lead him to the conclusion that this disappearance is brought about by an exchange of parts between homologous chromosomes and by a subsequent segregation of these chromosomes. "These processes are similar to the well-studied processes of chromosome behavior in germ cells, but had not been known to occur in body cells."

FACTOR INTERACTION IN DROSOPHILA VIRILIS

Collaborating with Demerec, Mr. G. A. Lebedeff has completed a series of experiments showing extensive changes in the phenotype due to interaction of various genes. He has studied particularly the recessive genes: ruffled (ru), which makes tips of dorso-central bristles and hairs adjacent to them to be curled forward and the abdomen telescoped; and shaggy (sh), which causes hairs of the abdomen to be irregular. Also the dominant genes: rounded (*R*), which produces truncate wings and in a few instances makes dorso-central bristles curled; clipped (*Cl*), which makes the posterior end of both wings cut off; and beaded (*Bd*), which makes the margin of the wings scalloped. The new types appearing as a result of interaction in crosses involving these genes are indicated in the accompanying diagram.

These studies indicate the important role played by genetic environment upon the phetotypic expression of the gene. In a particular environment the ruffled gene, for example, produces only curling of dorso-central bristles and adjacent hairs, while under other conditions the same gene may produce exaggerated curling of bristles and hairs, different types of vortex character and short spread and roofed wings.

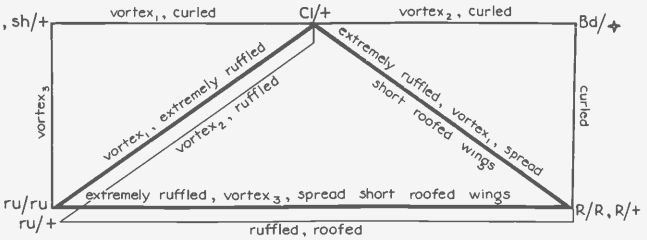

FIG. 1—New characteristics appearing in crosses involving five genes as the result of the interaction between these genes.

SOME NEW GENES IN DROSOPHILA VIRILIS

A dominant in the second chromosome, which causes all longitudinal wing veins to expand into deltas where they join the wing margin has been called delta (D). It is located 19.7 units from puffed and 37.75 from barbed. A new recessive in the third chromosome is intersex (ix) which, in the homozygous condition, changes females into intersexes. Another new gene, located in the third chromosome and a semidominant, when homozygous, kills about 75 per cent of males and about 50 per cent of the females; when heterozygous it does not affect females but kills about 15 per cent of the males.

COIL-SPRINGS AND CHROMOSOMES

It has been suggested that in basic structure, chromosomes have the form of coil-springs. Both cytologically and genetically, chromosomes have been shown to require certain mechanical behaviors which are called by such names as crossing-over, deficiency, duplication, non-disjunction, fragmentation, dislocation and reverse order. If, in shape, chromosomes are really coil-springs then certain chromosome-phenomena must tie-up in parallel fashion with the behavior of coil-springs; that is, chromosomes must follow certain analogous mechanical rules which govern coil-springs when, for example, "splitting the strand of the coil lengthwise and separating the resulting coils," or when "crossing-over." The mechanical and mathematical rules which govern coil-springs, when made to present phenomena parallel to those known in chromosomes, have been worked out by Laughlin, and coil-spring models built to show such mathematical and mechanical parallelism in eleven situations.

TRANSMISSION BY INOCULATED CELLS

LEUKEMIA IN MICE

Up to this point we have considered first the gene, as the ultimate regulator of development in the ancestral way. Next we have considered the chromosomes which constitute the mechanism for transmitting the entire equipment of genes. In another laboratory in this Department we are studying somatic cell mutations. Cytological studies indicate that these mutations are not chromosomal, so that we infer gene changes from the cell behavior. These are the specific changes in lymphoid tissue responsible for the disease lymphatic leukemia. This work is being carried on under the leadership of MacDowell in cooperation with the Department of Pathology of the College of Physicians and Surgeons, with the support of a grant from the Carnegie Corporation.

Critical evidence of the neoplastic nature of leukemia was reported a year ago by MacDowell and Potter in the demonstration that leukemic cells continue to divide indefinitely in a suitable host environment, and in the metabolic work of Victor which shows a similarity between leukemic tissues and recognized neoplasms. This is of importance because in man the high incidence of bacterial infection in leukemia has caused doubt as to its etiology and nature. As Dr. Victor of the Department of Pathology points out, the mouse material is uniquely valuable for bio-chemical studies relating to tissue respiration and fermentation because of the genetic control of cell type, clinical course, pathologic distribution and host resistance. This control, together with considerable increase in accuracy in weight determinations of tissues used, has made possible unusually uniform results. For example, Victor's determinations of oxygen consumption give standard deviations ranging from 3 per cent to 14 per cent of the means as contrasted with 45 per cent (Warburg) and 70 to 80 per cent (Jackson, Parker and Glover).

The determination made this year by Victor, assisted by Miss Margaret Prest, at the College of Physicians and Surgeons, confirmed previous findings that the metabolism of leukemic cells differs from that of normal cells and resembles that of malignant tumors (as reported by Warburg), in the consistently increased anaerobic glycolysis. The ratio of aerobic glycolysis to oxygen consumption rises from a normal of 0.4 to, respectively, 1.0, 1.4 and 0.9 in three transmission lines.

These results agree with the findings for sarcoma of Barron and many other investigators. However, evidence is completely lacking of an impairment in oxydative capacity which is required for Warburg's interpretation of malignancy. Indeed, oxygen consumption was significantly raised in some cases. While other investigators have neglected to use for comparison normal tissues of the same type as the malignant tissue, in this investigation lymph nodes have been used in all determinations. The normal nodes have been compared with nodes taken at a time after inoculation when the infiltration of leukemic cells has become so extensive as to obliterate all the normal architecture and transform the node into a mass of malignant cells. To determine this time, which varies with the line of cells and strain of hosts, Potter made special studies of the progress of infiltration in each of the combinations of lines and strains studied by Victor.

A distinction must be kept clearly in mind in what follows. The term *strain* is applied to the continuum of inbred mice descended from a common ancestor; the term *line* to the continuum of leukemic cells through whatever individual mice they may have been passed.

INFLUENCE OF HOST ON LEUKEMIC CELLS

For some time it has been known that mice of our strains C58 and StoLi differ in susceptibility to leukemic cells of both line I and line M-liv. Strain C58 has always been 100 per cent susceptible to these two lines. Strain StoLi on the other hand was 100 per cent resistant during the early history of these lines. In the year under review, however, the virulence of both lines had increased to the point of growing even in strain StoLi.

At this time Potter made a cytological study day by day of line I cells in strain StoLi comparable to that reported last year in the host strain C58. The size of the predominating cell was measured, and the path and rate of dissemination of the cells after inoculation, as well as the morphological characteristics of the cells, were determined. Potter found that during the first 72 hours after inoculation, the leukemic cells in strain StoLi developed at the same rate and reached a like stage of infiltration as in the hosts of strain C58. After 72 hours, either the infiltration persisted until death of the StoLi host or underwent regressive changes that led to recovery of the hosts. In the first case the interval between inoculation and death of hosts was only slightly longer than in hosts of strain C58. In the second case (recovery) the cells of the line apparently did not differentiate but died and were phagocytized by the host cells.

Victor reports that the normal lymph nodes of mice of these two host strains have the same metabolism and that in the hosts of one of these strains (C58) two lines of cells (I and M-liv) at this period gave the same metabolism. However, infiltrated with cells of line I, nodes of StoLi hosts compared with C58 hosts have higher oxygen consumption, decreased anaerobic glycolysis and irregularly decreased aerobic glycolysis. Infiltrated with line M-liv, nodes of StoLi hosts compared with C58 hosts have the same oxygen consumption and both aerobic and anaerobic glycolysis are very much diminished. These differences in metabolism of lines I and M-liv when grown in StoLi hosts are neither cumulative in continued transfers in StoLi hosts, nor are they indicative of any modification of the cells themselves, since in returning to hosts of C58 they show at once the same metabolism as cells of these lines grown throughout in C58 hosts.

Thus lines of cells that have the same metabolism under one set of conditions may have quite different responses to a change in these conditions. And further, different strains of uninoculated mice may show no metabolic difference, but infiltrations with the same line of leukemic cells may develop metabolic differences which depend upon the genetic constitution of the host. Such differences between hosts are related to the genetically controlled susceptibility to particular lines of leukemic cells, which susceptibility is, accordingly, not related to host metabolism. The metabolism of leukemic cells is not an absolute but an interaction between the constitution of the cell and the constitution of the host.

METABOLIC AND CYTOLOGICAL DIFFERENCES BETWEEN CELL-LINES OF LEUKEMIA

Studies are being made of various lines of inoculated leukemia to distinguish between specific secondary line differences and the essential features of malignancy; to develop fundamental relationships between physiological and morphological traits of cells and to approach the problem of the spontaneous occurrence of leukemia. The individuality of the different inoculation lines from different spontaneous cases has now become so impressive as to lead toward the conclusion that each case of spontaneous leukemia has its own individuality even though originating in the same genetically homogeneous strain of mice. As MacDowell points out, such differences correspond to the individuality that appears in other forms of cancer and has produced conflicting findings. Thus, on the single criterion of size, leukemic cells fall into a graded series from small to large. Clearly various types of lymphocytes carry malignancy.

The twelve lines of leukemic cells that Potter has now studied cytologically differ not only in the size of the predominating cell type but also in virulence (time required for massive dose to kill host), distribution and type of lesion, cultural requirements in host, nucleo-cytoplasmic ratio, distribution of chromatin, rate of cell division, rate of dissemination of cells, number and form of mitochondria, frequency distribution of cell size within a transfer, oxygen consumption, aerobic and anaerobic gylcolysis.

Frequency distributions of cell size give a more complete picture of leukemic differentiation than does the average size of the predominating cell type. All measurable cells (800 per determination) in fields of maximum infiltration are classified into four size groups and reduced to a percentage basis.

The three criteria of line differences in metabolism have been established this year by Victor, working with lines A, I, M-liv and MsplD, all in hosts of strain C58. The accompanying table shows the diversity between the four cell lines. Two of the lines differ significantly from normal in oxygen consumption, three in aerobic glycolysis and all four in anaerobic glycolysis. But each cell line shows a characteristic deviation from normal anaerobic glycolysis, *i.e.* 2.5, 7.0, 14.0, 9.5 units.

Cells	Oxygen consumption			Aerobic glycolysis			Anaerobic glycolysis		
	Mean	Diff. from normal		Mean	Diff. from normal		Mean	Diff. from normal	
Normal	5.45	.....	.....	2.13	.....	.....	5.78	.....	.....
Line A	6.40	0.95±	0.15	1.88	−0.25±	0.14	8.31	2.53±	0.44
I	5.47	.02±	.12	5.57	+3.44±	.62	12.76	6.98±	.57
M-liv	5.78	.33±	.23	8.40	+6.27±	.31	19.78	14.00±	.47
MsplD	6.68	1.23±	.19	6.15	+4.02±	.18	15.31	9.53±	.38

CHANGES IN CELL LINES

The preceding list of criteria offers a close check on the occurrence of changes in cell lines. Last year changes in virulence were reported; this

year changes in gross lesions, cell traits and metabolism have been observed. Knowledge of the nature and structural basis of these changes may be expected to throw light on the problem of the changes which transform a normal cell into a leukemic cell.

A series of eight sublines from one spontaneous case was started in January 1932 and carried on by the most uniform technique that could be devised from our previous experience. In all cases virulence increased during the course of transfer: (1) rapidly and continuously during the early transfers; (2) very slowly and continuously over many transfers after stabilization of the line; (3) abruptly, within one or two transfers, at any time. What is the inter-relation between these different types of change in virulence? Are they different manifestations of the same process? How are they related to changes of lymphocytes from normal to malignant?

Starting with the most abrupt change in virulence, the frequency distributions of cell size in the successive transfers were obtained. These showed a marked increase in the proportion of the next to largest cell class, which began gradually a few transfers before the sudden change in virulence and increased rapidly at the time of the sudden change. Thus a relationship was established between the shift in population of cells and the change in virulence of such a nature as to indicate a dependence, above certain thresholds, of virulence upon cell type. Similar studies on other periods of sudden change confirm this conclusion. Furthermore, the specific positive correlation of virulence and cell size indicated by comparison of different lines and by comparison of spontaneous cases and early transfers with late transfers is strikingly confirmed.

Since abrupt changes are unpredictable, Victor has made a metabolic study of each of the first eight transfers of a new line, during which continuous changes in virulence occurred as expected. None of the three criteria of metabolism showed changes that could indicate a casual connection with the changes in virulence, although anaerobic glycolysis showed a very slight though continuous rise. Further indication of the weakness of the relation between virulence and metabolism is given by a distinct metabolic difference between two lines of cells (I and M-liv) at a time when their virulence and morphological traits (except mitochondria) were alike. In spite of all this there does stand out a general tendency for the more virulent lines to show higher glycolysis.

A close correlation appears between aerobic glycolysis and the character of certain cell granules (called mitochondria) lying outside the nucleus. Their number and shape have been studied by Potter and Miss Findley in the lines whose metabolism was studied by Victor. At the same time lines I and M-liv were found to differ in metabolism, the mitochondria were the only other criterion that showed a difference. Further, the metabolic differences that each of these lines showed when growing in hosts of strain StoLi were accompanied by changes in the number of mitochondria within each line. That mitochondria are related to carbohydrate metabolism has long been suspected, but hitherto not clearly demonstrated.

The interpretation of changes in cell lines that has seemed most plausible is that the process of transfer acts as a constant selective mechanism work-

ing toward greater adaptation. That different lines of cells proliferate more extensively in some organs than in others suggested that within a spontaneous case leukemic cells from one organ might be genetically different from those in some other organ. A test of such diversity of cells was attempted by using cells from different tissues of the same spontaneous case as the start for different transmission lines, to be carried by successive transfers of the same type of tissue originally used. The early transfers in all lines gave remarkably similar results, but differences shortly appeared in distribution of lesions, metabolism and in cell morphology. In no case was there any indication that the cells taken from different parts of the spontaneous case had any special relation to the type of tissue used, nor was such a relationship developed during the course of transfers. Frequent control transfers with cells from spleen checked this conclusion. Although variations of leukemic cells according to the part of the body were not found, the interpretation that the changes observed are dependent upon a selective action working on a mixed population of cells still stands. It receives support from cytological studies indicating that differential rates of cell division at periods of rapid change are associated with changes in composition of populations of leukemic cells.

ORGAN-SECRETIONS AS AGENTS IN GENETICS AND DEVELOPMENT

The leading work in this field of genetics has been done, in this Department, by Riddle and his associates, Bates, Cauthen, Dykshorn and Lahr. Researches have been made primarily on the pituitary gland and secondarily on the thyroid and germ glands.

A THIRD HORMONE OF THE ANTERIOR PITUITARY GLAND

Last year was reported the isolation of a hormone from the pituitary gland that provides the immediate stimulus to milk secretion in mammals and to crop-gland development in pigeons. During the present year efforts have been concentrated upon an extension of our knowledge of this and other anterior pituitary hormones. In the period under consideration there appeared the full publication of Riddle, Bates and Dykshorn. Their results were summarized as follows:

"A new anterior pituitary hormone, called prolactin, was shown to be neither prolan nor the growth nor the gonad (and thyroid) stimulating hormone of the anterior hypophysis. It caused (*a*) secretion of milk from the prepared mammary glands of normal and castrate guinea-pigs of both sexes, of normal and castrate female rabbits, of hypophysectomized rats, and of normal and castrate female monkeys; (*b*) growth with secretion in the crop-glands of doves and pigeons of both sexes, including one without hypophysis and 5 castrates.

"Prolactin was prepared by alkaline (also acid) extraction of bovine or sheep anterior lobes, removal of an inert precipitate at pH 7.5–8.0, followed by precipitation and washing of the prolactin fraction at pH 5.0. Prolactin so prepared gives no stimulation of the immature bird testis. Various treatments cited by others as destroying the growth hormone did not destroy prolactin.

"The fraction soluble at pH 5.0 contained the gonad-stimulating (sex-maturity) hormone. When either this latter fraction, the 'aqueous pyridine and water-soluble' fraction of Fevold, *et al.*, the thyreotropic fraction of Collip, or commercial antuitrin was injected, the testes of immature doves were enlarged 3 to 10 times within 4 to 10 days with little or no enlargement of the crop-glands. Prolan (antuitrin S, and fresh preparations) had no effect upon either gonads or crop-glands of doves or pigeons.

"Growth hormone preparations of Lee and Schaffer, Collip, and Van Dyke gave only traces of crop-gland stimulation and very rarely a lactation response. An Evans growth preparation and antuitrin G strongly stimulated the crop-gland. All growth preparations tested, except that of Collip, Selye and Thomson, strongly stimulated the testis of the immature dove.

"Numerous tests proved that pure gonad-stimulating and growth hormone stimulated neither the crop-gland nor lactation; and other tests demonstrated that these two responses are induced by the same hormone—prolactin.

"Prolactin induced secretion of milk beginning about the fourth day in guinea-pigs and after 2 to 3 days in rabbits. Daily injections of prolactin into doves or pigeons increased the weight of the crop-glands up to 7 days, when the maximum was attained.

"Prolactin at pH 7.5 to 8.5 heated for one hour at 100° C. showed little loss of potency. Sodium chloride increased the rate of destruction."

It seems probable that non-physiological or pathological effects or responses which are not specific to any anterior pituitary hormone are induced by the simultaneous administration of two or more potent principles which never normally coexist in such high concentration in the blood. Thus Riddle had noted some years ago that marked enlargement of the liver regularly results from the injection of impure pituitary extracts into doves and pigeons. The same phenomenon, and also glycosuria, has been observed in mammals also. The studies of this year have supplied evidence that this response is an induced pathological state. This combined effect calls for further and serious study. It is hoped that the work on prolactin will be of aid in the general, formidable task of purifying and determining the interactions of the various anterior pituitary hormones.

During the year a method for the quantitative assay of prolactin, based upon crop-gland response, has been developed by Bates. It has been found that as little as 0.2 of a milligram of our present preparations gives a positive biological test. For some months much time has been spent in isolating and assaying on animals the considerable amounts of prolactin currently used in clinical tests of this hormone. Such tests, made by others, have shown the effectiveness and usefulness of this hormone in medicine. In this practical application the stability of the hormone is of importance and this feature has been studied by Bates.

Incidentally, it has been found that prolactin exerts a depressant action on the adult testis of birds and it is possible that it will be found to be connected with—and serve well to clarify—the process of "luteinization" in the ovaries of mammals.

AN ANTERIOR PITUITARY HORMONE THAT STIMULATES THE THYROID GLAND

It is known that one or another of the hormones produced by the anterior pituitary gland is essential to the normal functioning of the thyroid gland, and that when this hormone is supplied in excessive amount the thyroid enlarges and increases the rate of heat production in the body. We have studied the capacity of the different anterior pituitary hormones (or extracts) to effect those two thyroid responses in ring doves.

In the study on thyroid enlargement it was found that usually, but perhaps not always, those pituitary extracts which cause growth in the gonads also cause enlargement of the thyroids. Further, that neither the growth hormone nor prolactin has any specific capacity to produce this hyperplasia of the thyroid. A publication on this subject by Riddle, Bates and Dykshorn was summarized as follows:

"For the first time it is shown that two anterior pituitary hormones—prolactin and the growth principle—do not cause the thyroid hypertrophy which characteristically follows the injection of various pituitary extracts. Hyperplasia of the normally developed thyroid following pituitary administration is a specific response to the gonad-stimulating hormone, or to another pituitary derivative having very similar solubilities. Good gonad-stimulating preparations do not invariably induce an increase in thyroid weight in doves and pigeons."

A parallel study of the effects of the various anterior pituitary hormones on the rate of heat production (basal metabolism) is now under way, with the aid of Dr. Bates, Mrs. Smith and Mr. Lahr. This aspect of the pituitary problem assumes further importance because Dr. P. E. Smith, of Columbia University, has supplied evidence that there are two anterior lobe hormones which affect thyroid activity—one accelerating and one depressing it.

ACTION OF PITUITARY HORMONES AND PROLAN ON MATURE GERM GLANDS

Riddle, Bates and Lahr have made three contributions to this subject. First, prolactin seems to have a specific inhibiting or depressant action on the mature testes of doves and pigeons. This effect of the prolactin perhaps explains the lack of desire of the male bird to copulate during incubation, for evidence has been found that the secretion of prolactin—which is to result in crop-milk formation at the end of the brooding cycle—really begins as soon as the parent birds begin to incubate the eggs.

Second, the injection of good extracts of the gonad-stimulating hormone into adult males results in increased weight of the normal testis and has a powerful stimulating effect on the adult ovaries of doves and pigeons. At the same time body weight is reduced. This weight reduction is considered a secondary action of the hormone, since it causes increased activity of the thyroid, hence an increase of metabolism and a tendency toward emaciation.

Third, prolan—obtained from the urine of pregnant women—is believed by some to be a mixture of two substances, both derived from the anterior pituitary; one is believed to promote true gonadal growth while the other induces "luteinization" of the ovaries. By the use of available samples of prolan and other preparations of our own we find a slightly adverse effect

upon the adult testis of doves and pigeons. Prolan has, however, no capacity to enlarge the thyroids in our animals; and, wholly unlike prolactin, which markedly represses the testis, it has no capacity to stimulate the crop-glands nor to induce lactation. Our results give little or no support to the conclusion that the "luteinizing substance" obtained from pregnant urine is a pituitary derivative.

BASAL METABOLISM OF DOVES AND PIGEONS

Riddle's studies on basal metabolism, done in collaboration with Dr. F. G. Benedict, director of the Nutrition Laboratory, and with the assistance of Mrs. Guinevere C. Smith, are largely concerned with a variation that is associated with race, sex, hybridity and reproductive stage. This year studies have been made upon variation in metabolism associated with age and the free-flying state. Riddle's study of effect of advanced age supplements certain work that Dr. Benedict is doing on man and rat. Studies on adolescent pigeons (tipplers) will be valuable for comparison with results obtained from birds in which ovulation has already set in. In the free-flying studies, Homer pigeons are used, which have been carried to varying distances from the laboratory so as to force them to undertake prolonged flights.

The reproductive cycle in doves and pigeons involves a cycle of marked changes in behavior, endocrine status and body weight. Of these "broodiness," in which the male takes full part, is one of the most striking. Riddle, Smith and Benedict have concluded a study of the changes in metabolism of ring doves after they have been incubating eggs during 10 to 14 days. Though evidence was found that this period of unusual inactivity is accompanied by a 10 per cent decrease in the metabolism of males, no change was found in that of the female. But this result was obtained only when the birds were measured at an environmental temperature of 20° C. When measurements were made at 30° C.—the socalled "zone of thermal neutrality"—irreconcilable results were obtained. Since other evidence indicates the validity of the results obtained at 20°, the validity may be questioned, at least for birds, of measurements made as in current practice, at the zone of thermal neutrality, when the object of the measurement is to disclose the influence of one or another factor on the current basal metabolism.

Again, Riddle with the assistance of Miss Pela Braucher, having found that his birds gained weight during the incubation period, and having formulated the hypothesis that this result is associated with a decrease in the basal metabolism of the incubating pair, is now undertaking, with Mr. Cauthen and Mrs. Smith, a general study of the relative rates of food consumption during the various stages of the reproductive cycle.

HISTOLOGICAL CHANGES IN THE OTHER ENDOCRINE GLANDS RUNNING PARALLEL TO THOSE OF THE ANTERIOR PITUITARY GLAND

In this important part of our program Dr. Riddle is being assisted by Mr. Lahr, who has sectioned and studied a very large number of ovaries, testes, mammaries, etc.

A PROTOZOAN DISEASE IN PIGEONS

Our ability to satisfactorily carry out genetical endocrine studies on doves and pigeons depends upon the health of the stock. Many deaths occur, due to a parasitic worm that inhabits the alimentary tract and which belongs to the genus *Capillaria*. With the aid of Mr. Cauthen this parasite has been brought under control. But a Protozoan, *Trichomonas columbœ*, that lives in the upper alimentary tract and forms fatal cysts there and even gets into the liver, pancreas, lung and heart, has been the subject of special attention but has not yet been brought under control.

TRANSMISSION BY SEX CELLS

GENETICS OF CLADOCERA

Banta, who has been associated with us during summers, has continued his researches on the genetics of Cladocera. Continued studies of dwarf strains demonstrate that dwarfness is due to slow rate of growth and development, perhaps governed by a single recessive factor which, in addition to what is apparently another single recessive factor, causes a cessation of pre-adult growth and the onset of reproduction while the animals are still below normal adult size.

Accumulation of Recessive Mutations During Long-Continued Parthenogenesis

This process, which has been abundantly and strikingly demonstrated in *Daphnia longispina*, has been worked out in other species of Cladocera by Miss Thelma R. Wood and Mr. George A. Smith. They inbred (by sexual reproduction, of course) *Moina macrocopa* which had passed through 1090 generations of parthenogenesis and compared the resulting recombinants (sexually produced offspring) with parthenogenetically produced offspring from the mother alone. There was more sterility, greater variability in reproductive capacity, in longevity and in other physiological characteristics among the recombinants than among simultaneously reared clonal sisters. Apparently recessive mutations similar to those detected in *D. longispina* occur in *M. macrocopa* also.

The Hatching of Sexual Eggs of Cladocera

As previously reported, Miss Wood found that a considerable portion of winter eggs of *Moina macrocopa* hatch without a latent period. Since these would frequently hatch when conditions were not just right for survival, it seems that they would be selected against. Now, Miss Wood has found that many of the eggs of *Daphnia longispina* also will hatch a week or so after being laid and without having been dried. Viability of the sexual eggs, as revealed by their hatchability, is decreased by dry storage prolonged for a period exceeding 3 or 4 months and becomes very low after 9 to 12 months. Storage in water without disturbance or renewal of evaporated water is less deleterious.

Developmental Norms for Daphnia

As a useful step in genetical studies, Miss Wood has been making determinations of developmental norms for *Daphnia*. Sizes are determined at different instars. It appears that body length at time of birth is about

0.65 mm., at the 6th instar (after the first young are produced) is about 1.72 mm. This increase is made during 120 hours. In terms of the first instar the ratios of the first six instars are, respectively, about 1, 1.23, 1.59, 2.03, 2.43 and 2.66. There is a progressive diminution in percentage increment of these ratios; while the duration of the instars increases progressively in the proportions of 1, 1.01, 1.14, 1.44 and 2.33. It has been discovered that instead of the usual 4 instars before adulthood is reached there may be 5 and occasionally as many as 7. More rarely there are only 3.

Studies on Effects of Concentration of Medium and Number of Animals on Rate of Development

Under Banta's direction, Miss Maurita McPherson some time ago made experiments designed to test Robertson's allelocatalytic theory of growth, which grew out of Robertson's discovery that several unicellular organisms in a drop will reproduce faster than only one. Miss McPherson found that by varying (1) the concentration of the culture medium and (2) using differing numbers in equal amounts of culture medium, she could govern the rate of development of *Moina macrocopa*. With series consisting of 1, 3, 6 and 9 animals in the same concentration (and same amounts) of culture medium the single animals developed more quickly than the plurals when the medium had less than optimum concentration; but when the concentration was above optimum the groups of animals developed more rapidly than the single ones. This study has been extended by Mr. George A. Smith, using (like Robertson) a Protozoan, *Paramecium caudatum*, and by various methods he has found results very similar to those from *Moina*. Single *Paramecia* in weaker media have, in general, a greater fission rate than plurals; in concentrated medium plural animals have a higher fission rate than singles. It may be concluded then that Robertson and his supporters probably utilized culture media stronger than optimum for a single animal and consequently his plural animals reproduced more rapidly than singles. On the other hand those investigators who failed to confirm Robertson's results may readily have used a less concentrated medium which permitted the isolated animals to have as rapid as, or a more rapid rate of fission than, plural animals in the same amounts of the same medium. That is, it is possible to obtain results (1) similar to those of Robertson, or (2) similar to those obtained by Robertson's opponents by varying the experimental set-ups.

Genetics of the Thoroughbred Horse

After years of intensive compilation and analysis of data on the racing capacity of the running horse, made possible largely through the monetary contributions of Mr. W. J. Salmon, Laughlin is now engaged in working up his findings for publication.

The Measurement of Racing Capacity

A necessary preliminary to the study of inheritance of racing capacity is the quantitative expression of that capacity. Laughlin has devoted much time to the devising of an appropriate "yard stick" for this purpose. This he has successfully accomplished. The formula for measuring the racing

capacity of the individual horse depends upon the measure of quality of performance in each of his several races. In turn the formula for the quality of performance is a mathematical expression in which the speed-performance of the particular horse in the particular race is a function, simultaneously, of sex, age, weight-carried and distance-run, other factors being constant. Separate formulas have been computed for colts, geldings and fillies. The formula for colts together with a set of mathematical models of the formula are given in the accompanying figure.

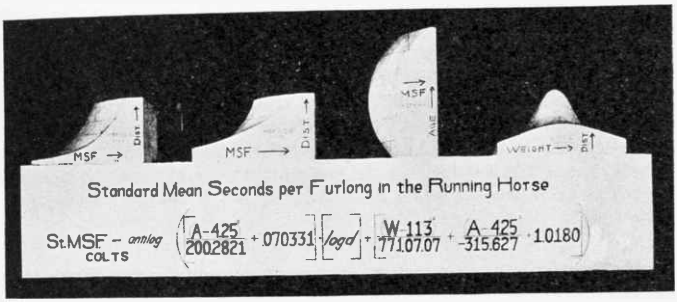

FIG. 2—Formula for standard means seconds per furlong in colts and a set of mathematical models of the formula.

In the formula, St.MSF stands for Standard Mean Seconds per Furlong, that is, for the mathematically smoothed best record which American "horse-flesh" has achieved for the particular complex of sex, age, weight-carried and distance-run. In this formula "A" stands for age in years, "D" for distance-run, "W" for weight in pounds carried on the back. How good a horse is, that is, the measure of his racing capacity, depends upon how nearly, in his several races, he approaches the St.MSF for the same set of conditions. For example, for colts 3.75 years old, the left-hand model shows, on the front face, the relation between the number of seconds required by the "standard colt" to go a furlong and the distance run in the race. It shows that the longer the race the slower the rate (more seconds per furlong). Sections cut parallel to the front face vary in form with increasing weight-carried. Thus, "seconds per furlong" diminishes as weight-carried increases to a certain point and, thereafter, speed is retarded.

Practical work tables have been completed for the values of these formulas for every practical complex of these several constituent factors. As working material the racing-capacity measures have been worked out for a few more than 10,000 of the best Thoroughbred horses in England, United States, France and a few other countries.

INHERITANCE OF RACING CAPACITY

Laughlin has made further analysis of this topic, has worked out an "operative formula" and has made a mathematical model for the formula; of which the three dimensions are: (1) the futurity index (or the prediction

basis); (2) the thing predicted (or offspring-racing-capacity within a 5-pound range); and (3) the vertical coordinate, or probability. Thus, if a foal is born with a futurity index, or hereditary promise, of 120.39 the probability of racing-capacity-range for this foal, if it is raised to maturity and races under average American conditions, is 0.121 for the class 110 to 115; and 0.104 for the class 115 to 120. In higher and lower racing-capacity classes the probability becomes smaller and smaller, until at 60 to 65 the probability is 0.013, and at 130 to 135 it is 0.012, the total probability by capacity-class for the same prediction-basis being 1.000.

Laughlin emphasizes the point that he has still to continue the search for the genetic elements ("specific stresses") for each of the near antecedent bloodkin, which, entering into the prediction index, will give the best prediction. He calls attention to the fact that racing capacity, far from being based upon a single Mendelian unit, or upon the additive and segregable resultant of a few such units, is the developmental end product of the interaction—accelerative, cancellative, creative, additive—of a host of Mendelian units—perhaps hundreds. Still the end-product, racing capacity, is a thing which is definitely measurable in the individual and which definitely runs-in-the-family.

THE GENERAL FORMULA OF HEREDITY

As an outgrowth of the operative formula for the inheritance of racing capacity in the Thoroughbred horse, Laughlin has worked out a general formula of heredity. This gives the probability (K) that a random-selected offspring with a given prediction-basis (M) (derived from the quality in antecedent near-kin) shall fall within (R) the selected class-range of offspring. Since many complex traits are not analyzable or predictable in terms of definitely numbered genes, he believes that this general formula will be useful in many physical and medical investigations. It may be generalized as K=f (M, R). In actual use for specific formula-finding, it is demonstrated that the correct numerical values for each of eleven constants will suffice to fit quite closely the general formula to any extensive group of accurately observed inheritance-data.

THE MEASURE OF EVOLUTION

Laughlin concludes that the foregoing general formula of heredity is available for analyzing problems in evolution; particularly it may be used (*a*) to predict evolution in a very slight character-change from one generation to another, (*b*) to determine the trend or direction of evolution, (*c*) to locate its current goal or (better) its target, (*d*) to mark its progress, per generation, toward its present target, and (*e*) to describe the constitutional nature of the population of which the particular sample is truly representative. Laughlin points out that the measure of evolution consists not in comparing the mean of the parental group with the mean of their offspring, but the mean of the parental group with the point of no regression.

Instead of assuming the mean of the breed, the mean of the parents and the mean of the offspring to be the same, it is found more useful to plot the prediction diagonal, *i.e.*, the line which connects points of equal value for parents and for offspring, and then to plot against this line for each

parental prediction class the mean of the offspring of that class. Through the series of points marking such means of offspring-classes a curve is then fitted and the point computed at which the prediction diagonal and the smoothed curve of the offspring-class centers cross. This crossing point is the point of no regression; it is the point of the true genetic mean; the point toward which the breed, represented by its particular sample of breeding-stock, actually tends to move from the particular parental generation to the immediate offspring of that generation. If, for example, only a highly selected sample, say "the cream of the breed," is dealt with, the general formula detects a genetic mean; whereas without the technique of this formula the actual point of no biological regression, being outside the mean of immediate consideration, would be difficult to locate.

The foregoing principles are illustrated by the data obtained from a group of 54 Thoroughbred foals produced during the years 1924 to 1928 and raced between 1926 to 1931. The mean hereditary promise, or futurity index, of these 54 foals was 116.08, while the mean racing capacity was 97.76. These data are substantially above the point of no regression. Using them in the way described, it is found that the genetic mean of this particular sample of Thoroughbred racing stock is located geometrically at 64.38. This analysis shows why highly selected breeding stock of any breed must be subjected continuously to the most radical selection if extreme standards are to be kept up. The "cream of the breed" regardless of their individual quality, unless their genetic mean can be kept up, constitutes a highly artificial "individual-selection-group," and not a subspecies or a superior strain. This finding is in general keeping with the experience of breeders who strive for highly specialized and extreme values of any type.

On the other hand, random-selected good stock, but below the genetic mean, if given fair opportunity, will, like their superiors, tend to gravitate toward the genetic mean, but this time such gravitation is an improvement rather than a loss. Thus the genetic mean is not to be confused with the somatic mean of parents and offspring.

In further application of the general formula of heredity, Laughlin makes use of the data of Galton's study on inheritance of stature in British families. The mean stature of the 928 children (commuted to the male basis) is 68.09 inches, and the average mid-parental stature is 68.66 inches. The genetic mean derived from these data is 68.54 inches. Thus it appears that in the families measured by Galton not only were the mid-parents taller than the children by something more than a half inch, but the genetic mean of the particular breeding-stock was not quite so great as the mean of the breeding-stock itself. It is logical to conclude that for this particular sample of breeding-stock for this particular generation the stature was degenerating about one eighth of an inch.

On the other hand a similar analysis of a large number of American children and parents indicate a genetic mean at around 74 inches for men and 69 for women, so that if this particular sample be considered as a segregated population of breeding-stock, the two generations studied show a decided evolutionary trend toward substantially taller stature.

Laughlin also applies his general method of determining the genetic mean to Osborn's studies on skull-length in Titanotheres. During approxi-

mately 15 million years this skull-length had increased from 31.3 centimeters to 80.0 centimeters. Laughlin concludes that from generation to generation Titanothere skull-length was moving toward a genetic mean of 120 to 130 centimeters—a giantism probably far beyond the physiologically fatal limit. At the earlier rate, this attainment of this extreme skull-length would have required 20 or 30 million years more. The genetic constitution which moved successive offspring toward such a goal may have been one of the major causes for the disappearance of the Titanotheres.

Laughlin suggests that his mathematical considerations lead to the conclusion that evolution is the resultant of the interaction of the genetic constitution on the selective forces, internal and external, which operate during the turn-over of individuals from one generation to another. Considered as a breeding movement, evolution is the trend of the somatic mean toward the genetic mean; the internal immediate or driving force of evolution is the difference between these two means.

HUMAN GENETICS

Racial Difference Between Indians, Negroes and Dutch

This study is being developed by Steggerda along the lines laid down in last year's report. On August 25th he and Mrs. Steggerda started for the Southwest and made their headquarters at Santa Fe, New Mexico. They worked at the following schools: Rehoboth, Crown Point, Fort Defiance, Ganado, Tuba City. At these points on the Navaho Indian Reservation a total of 382 children was measured. Considerable time was spent in securing birth records of the children, and it is probable that much of the data can not be used because of incompleteness in this essential item. This work is largely preliminary; the genetical, familial studies will develop later.

The month of November was spent in Holland, Michigan, continuing the genetical growth studies on children of Dutch descent. The number of children in the growing series now measured twice is 232.

On January 17, 1933, Dr. and Mrs. Steggerda left for Yucatan, for the third year of study of the genetics and growth of the Maya. At present there are 92 boys and 78 girls whose development is being traced, at the villages of Pisté, Chan Kom and Xocempich. March and early April were spent in a reconnoitering trip in Guatemala and Southern Mexico. A number of Indians were measured at the principal stopping places on this trip.

During the latter part of April and part of May, a series of measurements of growing children was begun at Tuskegee Institute and vicinity. This study was facilitated by the cooperation of the principal, R. R. Moton, LL.D., and Mrs. Louise M. Atkins of the faculty. The series comprises about 108 children, whom it is proposed to measure in successive years.

Special Studies at Yucatan

The difficulty of determining the age of children in a country where birth records are not scrupulously kept is considerable. There are, of course, some records. Then, as family pedigrees are worked out and each pregnancy becomes accounted for, the age of each child can often be estimated fairly closely. The time of starting to attend school helps. Physiological age of

girls can be known with precision, since it is the custom for girls to cease going to school at the first day of the onset of the menses. For boys the development of terminal hairs will aid in determining physiological age. Incidentally, it may be mentioned that marriage of girls takes place frequently within a year or two after puberty sets in, and they become mothers at 15, 16 and 17 years. Infantile deaths are very common, even where the mother is quite matured.

The necessity of knowing intimately the family has led Steggerda to make a census of the entire little village of Pisté. This village is the nearest settlement to the excavations being made at Chichen Itzá. Most of the workers at these excavations come from Pisté and as they receive silver for their labors the village is one of the wealthiest of its size in the peninsula. In about 80 houses there was a total of 153 adults and 150 children. There was a record of 87 children who had died. The corn, which constitutes perhaps the principal article of diet of the inhabitants, is grown on some 6000 mecates, or something less than 600 acres. There were 65 horses available for the 85 men. In addition there were 46 cows, 262 pigs, nearly 1000 chickens, and 100 dogs (mostly used for hunting). A few goats and bees constitute the remainder of the domestic animals.

The size of the village depends in part upon the capacity of the soil to feed the population. It is well known that a corn field, or milpa, is planted in Yucatan for two successive years only, on account of rapid loss in yield. Seeking the reason for this loss in yield (which may be a factor in the desertion of ancient Maya cities), Steggerda has collected samples of soil from a new milpa and also one in its second year. These were analyzed for us by the Division of Soil Fertility, U. S. Department of Agriculture, in Washington (Oswald Schreiner, Chief) and a report made showing a marked loss of nitrogen and other organic constituents in the soil. The report concludes:

"The analyses of the two samples, submitted from new and old milpas, would seem to indicate that the differences are due to oxidation of the organic matter owing to high temperature and aeration. The exchangeable bases, especially the calcium, which were previously held, could then be leached rapidly by the presumably high rainfall. It seems entirely improbable that the relative exhaustion indicated by the analyses is due to the direct removal by a few years of cropping."

Dental Studies

At the request of Dr. Weston A. Price of Cleveland, Ohio, Steggerda gathered 30 small vials of saliva from 30 Pisté men. It is hoped that these will be a contribution toward an explanation for the excellent teeth of the rural Maya. A comparison of the full-blooded Indians of the Chichen Itzá region with Jamaica Negroes on one hand and Smith College students on the other indicates that the teeth of the Maya are comparatively resistant. This is opposed to the conclusions of Dr. Williams.

Comparison of Stature of Carvings With Stature of Living Mayas

Steggerda was interested to see whether the carved human figures on the colonnade in front of the Temple of the Warriors are full-size delineations

of the Maya inhabitants of that time. Statures were obtained from 197 carvings, showing a mean of about 121 centimeters and a range between the shortest and the tallest of 25 centimeters. This range is the same as is found upon the living men, but the stature is about 34 centimeters (10 inches) less than the average of present Maya men (155 centimeters). Steggerda believes the purer the blood of the Maya the smaller their stature. He does not, however, feel justified in concluding that the carvings really represent full-size warriors of the day when these carvings were made.

Comparative Studies on Papillary Patterns

Steggerda has been associated with Dr. Harold Cummins of Tulane University in a study of interracial differences in the patterns of the balls of the fingers (finger prints). By grading arches 0, loops 1, and whorls 2 the total value of the finger patterns of the individual ranges from 0 to 20. The higher the value, the more whorls in evidence. Racial comparison shows that the Eskimos lead in the number of whorls, with Indians, Jews, European-Americans and Dutch in descending frequency. Pattern size and pattern form also are quantitatively expressed and racial comparisons made.

Comparative Human Auxology

The studies in child development at Letchworth Village have been continued with the hearty cooperation of Dr. C. S. Little and Dr. Eugene W. Martz. All individuals of the series have been seen at six-months intervals. All measurements made on the 40 or more individuals, who have been repeatedly measured for six or more years, have been plotted so as to reveal the course of physical development. Two studies have been published.

Growth of the Human Foot—The length of the foot has a growth that is more or less parallel with that of the body, except that during childhood it may grow faster for a period than the height of the body as a whole. The length of the foot is about 15 per cent of stature in the adult, slightly more in men, less in women. In boys the ratio tends to increase until preadolescence, when it reaches a maximum of about 16 per cent, then it decreases. Thus, the foot length tends to anticipate the adolescent spurt. The foot length in relation to lower leg is greatest in the negroes and least in the Mongoloid Dwarfs. The foot length is about 66 per cent of the lower leg length in the adult male. In infancy the foot is relatively much longer (80 per cent, or more of the lower leg) and falls steadily until the adult proportions are reached. The relatively long foot is an anthropoid condition, suitable for grasping limbs of trees, but not for swift running or walking.

The area of the foot grows steadily with age, but rather more rapidly from 8 to 10 years than from 10 to 11. As the adolescent spurt starts in, growth in the foot area becomes faster again and slows up as the adult stage is reached. The foot area of the Negro boys is markedly larger than that of the Nordics. In relation to stature, the foot area increases regularly from 6 to 16 years; that is to say, it is more closely related to the cubic stature, or weight, than to mere height. The area of the foot, age being held constant, has a correlation of about 0.66 with stature and with weight, and the correlation between area of foot and hand, at a particular age, is about 0.67. As the boy

grows the heel elongates more rapidly than the foot as a whole, and assumes a constantly larger angle with the ground, thus increasing the height of the instep.

The mutations that have lead to the human foot are the end of a series of mutations that have been going on for a long time in the Primate series and have been found advantageous for survival. The human foot has permitted the upright position and preserved the hands and the brain for higher functions.

The Crural Index—The crural index is the ratio of the length of the lower leg to that of the thigh, the latter taken as 100. The crural index tends to increase during fetal life and, indeed, into childhood. From an index of about 75, in the first half of fetal life, it rises to around 90 at about 11 or 12 years and then falls to about 86 in adult whites. Thus the change in ratio results from the slower growth of the thigh, as compared with the lower leg, during the period of increase of the crural index; followed by a slowing up of the tibia and more rapid growth of the femur. Relative to the leg as a whole the thigh first decreases, then increases and vice versa in the lower leg. One may say that the tibia grows faster than the femur in early postfetal life in accordance with the prevailing longer tibia in quadrupedal mammals. In humans, as in the lower Primates, the femur is the larger at the start, showing the precocity of a larger organ and one nearer the trunk. Thereafter the tibia tends to assert itself to assume its role as approximately equivalent to the femur in locomotion; the role that it plays in most mammals, including the lower Primates. Finally, during adolescence, the relatively long femur begins to show itself and the crural index diminishes. The high index is associated with leaping and romping, while the small index is associated more with rapid walking and running. Lamarck's view that function has determined structure receives no evidence from modern genetics; rather the changes in the form of the leg precede and determine how the leg shall be used. The mutation comes first, and function accords with it.

Growth Standards—With the aid of Miss Lillian B. Frink an attempt has been made to secure anthropometric and other observational data upon the parents, brothers and sisters, uncles and aunts, and first cousins of the children who are being followed at Letchworth Village. More or less complete data have been obtained about 110 families.

In order to be able to compare with children between the ages of 6 to 18, the physical proportions of their grown parents and brothers and sisters, of varied ages, it became necessary to establish standards for the different dimensions and proportions for both sexes at all ages, from birth to maturity. The desired standard could not be obtained from the literature on the subject, inasmuch as the results of such detailed measuring have nowhere been published. Using then our own data, we have prepared such standards. The comparison with the standard has to be made somewhat indirectly, namely, by expressing the deviation from the standard in terms of the so-called "standard deviation." Treated in this way, marked deviations from the standard show themselves frequently as family characteristics.

This method rests upon the assumption that the proportions of the individual make their appearance at an early stage of development, that one

may expect a somewhat similar deviation from its standard of a girl of five years and her father of thirty-five years. Preliminary examination of the subject shows that there is some warrant for this expectation, though of course it does not hold rigidly. The whole matter requires further examination. The perfection of the standard also requires additional data for certain of the ages.

Heredity of Mental Traits

Banker has completed his investigations into family likeness in scholastic achievement, based upon the school records in the Huntington school of different members of the same family. This study was made on some thirty or forty families.

Complications appeared owing, in part, to the different methods of grading students as employed by different generations of teachers. This difficulty was fairly well met by a special device, as explained in earlier Year Books. By extension of these methods, Banker has made it possible to compare achievements of the same individual all the way from the primary school to college and universities. His researches have led him into a somewhat pessimistic attitude in regard to the possibility of determining the genetic mental constitution of an individual from his scholastic records. Nevertheless, some of his studies have revealed a similarity of high grades in particular studies obtained by close relatives. This result is not uniform enough to be very convincing of the genetical factors present.

Banker also stresses the insufficiency for genetic analysis of methods as yet devised for measuring mental traits, or the genetical factors that determine such traits.

The Inheritance of Sporadic Goiter

While Dr. Tage Kemp was a guest of this Department during the autumn of 1932, he made an investigation of a family on Long Island showing sporadic goiter. His study of the distribution of goiter in this family, together with a consideration of its distribution in other published pedigrees, leads him to the conclusion that the most reasonable interpretation is that hereditary sporadic goiter depends upon a dominant gene that is located in an X-chromosome and causes not only the development of goiter but also non-disjunction of the two X-chromosomes in the female. Besides this sex-linkage it is reasonable to suppose that sex limitation also occurs. If we assume, as in *Drosophila*, that in this type of non-disjunction exceptions from the general rule appear in such a way that the non-disjunction of the 2 X-chromosomes does not occur, then there might arise occasional goitrous families in which normal females have normal daughters and males which are conductors or are goitrous themselves. Such occasional goitrous males have been recorded in families of sporadic goiter.

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PERSONS ENGAGED IN VARIOUS ACTIVITIES DURING THE YEAR ENDING OCTOBER 31, 1933

INGER M. ANDERSON (MRS.), Secretary
AMOS G. AVERY, Associate
ANNETTE BACON, Assistant
HOWARD J. BANKER, Investigator (Retired)
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ROBERT W. BATES, Investigator
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A. F. BLAKESLEE, Assistant Director
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MARIE BUCURIS (MRS.), Janitress
EDWARD BURNS, Farmer
ETHEL P. BURTCH (MRS.). Switchboard Operator and Stenographer
CATHERINE CARLEY, Computer
GEORGE E. CAUTHEN, Assistant
†G. H. CLAFLIN, Chief Clerk
CHAS. B. DAVENPORT, Director (Retired)
M. DEMEREC, Investigator
WILLIAM DRAGER, Assistant
†SIMON W. DYKSHORN, Assistant
MABEL L. EARLE, Editor and Library Abstractor
WILLIAM FAGAN. Animal Caretaker
MARGARET FINDLEY, Assistant
LILLIAN B. FRINK, Assistant
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ALICE HELLMER, Assistant
PAUL HOLM, Caretaker
MARY J. HOLMES. Stenographer
ETHYL I. HUNT (MRS.), Stenographer
J. N. JOHNSON, Carpenter
MARGARET KAYLOR, Assistant
ALICE GOULD LAANES (MRS.), Curator of Archives
THEOPHIL LAANES, Assistant
DAVID B. LACKMAN, Assistant
E. L. LAHR, Assistant
HARRY H. LAUGHLIN, Assistant Director
G. A. LEBEDEFF, Associate
GEORGE MACARTHUR, Supt. Buildings and Grounds
E. C. MACDOWELL, Investigator
MARGARET MARTIN, Indexer
FLOYD ANDREAS MATSON, Stenographer
J. D. MCGLOHON, Chief Clerk
ELIZABETH DEG. MCKEE, Histologist and Artist
RUTH MILLAR, Assistant
MERRITT J. MURRAY, Assistant
MIRIAM E. NORTH, Librarian
LESLIE E. PECKHAM, Clerk
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JAMES S. POTTER, Investigator
OSCAR RIDDLE, Investigator
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JAMES P. SCHOOLEY, Assistant
JENNIE O. SCHULTZ, Assistant
DOMENICO SEPE, Garden Hand
HARRIET L. SMART (MRS.), Assistant
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MORRIS STEGGERDA, Investigator
MARTHA J. TAYLOR, Assistant
HARRY WHITE, Painter
MADELEINE S. WILKINS (MRS.), Assistant

TEMPORARY, SUMMER 1933

A. M. BANTA, Investigator
JAMES BANTA, Assistant
STANLEY BROOKS, Assistant
LELAND A. BROWN, Investigator
J. T. BUCHHOLZ, Investigator
J. LINCOLN CARTLEDGE, Investigator
PRISCILLA CHINN, Assistant
EDITH ANN COULTER, Assistant
MERLE P. EKAS, Assistant
RUTH E. HENDERSON, Assistant
HELEN HOUGHTALING, Assistant
ROSCOE D. HUGHES, Assistant
RALPH KAMENOFF, Investigator
RUDOLF KOSTER, Assistant
MARION MEURLIN, Assistant
LOIS I. PLATT, Assistant
CURT STERN, Investigator
THELMA R. WOOD, Associate

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