GENETICS IN RELATION TO MENTAL DISORDERS.*

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DESPITE the precarious vulnerability of genetic theories to partisan distortion and abuse, a report on the progress of genetics in relation to mental disorders merits introduction on a fairly optimistic keynote. It seems that in quest of a better understanding of human behaviour deviations we have finally arrived at the threshold of the age of biology as a focal discipline. There are many indications that in searching for adequate methods of biological analysis, one of the key positions of science is held by *human genetics*.

Built on the earlier pioneer work of British biologists, the knowledge of human heredity has steadily advanced in recent years. Much of this advancement was due to the methodic investigations carried on in the laboratories of this country. The progress extended to many of the medical problems of genetics, especially to those concerning mental deviations. As a psychiatrist who has long been interested in the genetic principles of human personality disorders, I fully appreciate the opportunity to be with you at this conference.

In an unbiased analysis of the potential effects of genic elements in the causation of psychopathological manifestations, one may safely proceed on the premise that basically uniform patterns in the organization or disorganization of *mental capacities* are controlled by heredity in the same manner as are those underlying the normal or abnormal developments of physical traits. From a psychogenetic standpoint, the capacity for maintaining a state of mental health is a complex biological phenomenon and not merely the equivalent of the providential absence of emotional strain exerted by the prevalence of social imperfections in the structure of modern society. At all times this capacity constitutes an integral part and central driving force of human personality development. Its existential effectiveness rests upon the individual ability to conduct a multitude of psychosomatic functions with a relative degree of vital efficiency.

Despite the rather dogmatic claims of some modern evolutionists, the *biological process of personality integration* never ceases to be subject to the laws of organic existence and structural growth. No aspect of this developmental process can be assumed to occur either by chance or by instinct. Differences in terminology do not alter the fact that the possession of instinctive energies at birth depends on the capacity for maintaining organic life, which must have begun to function before it lends itself to interpretation as to its psychological meanings and social consequences. Beyond question there would be no vital energy in any infant unless it had been produced by the operation of a complicated genetic process. It is equally certain that there is no evidence either for a self-perpetuating form of human culture that could exist in a biological

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vacuum or for any evolutionary differentiation of behavioural responses without the organic means of expressing behaviour.

For the purposes of descriptive convenience it is perfectly legitimate, of course, to distinguish between instinctual generality and acquired specificity of human behaviour, or between the separate effects of organic and social inheritance, or between specialized fixity and adjustive plasticity of mental traits. Psychologically oriented biologists may also be correct in stressing that behavioural plasticity of the human mind represents the most typical and uniquely human characteristic. There are no intransigent objections to such a generalized formulation, even if one may find it difficult to concede that "social organizations on the human level are built on the principle that an individual is able to alter his behaviour to fit any situation, whether previously experienced or new" (as has recently been claimed by the same group of writers). In fact, human personality development is so intricate a process that it permits description of the multiformity of its existential expressions on many organizational levels of appearance in the organic world.

Genetically, however, there are definite limitations to the candid or disguised tendency to think of behavioural responses of man pre-eminently in terms of *culture-personality problems* "emancipated from dependence upon inherited biological dispositions." Regardless of the degree of evolutionary emancipation achieved, mental behaviour of any kind remains a structural function of the organic nervous system. The ability to be mentally adjusted as well as the ability to react to "unadjustable" circumstances with a true psychosis must be regarded as a unique expression of the attainment of human status in the evolutionary development of man's mental equipment and cultural setting. These abilities depend basically on the common denominator of hereditary potentialities, since it can be shown without difficulty that similar mental reactions of a normal or psychopathological variety are produced by similar environmental circumstances only in a certain number of the persons exposed to them. One may say that both the tendency to become vulnerable to the destructive effect of a schizophrenic or manic-depressive psychosis and the capacity for maintaining a mentally adjusted life, despite biological and cultural imperfections, are interdependent indications of the genetically controlled inability of man to attain superhuman status emancipated from the bondage of organic inheritance (at least, till the end of the academic summer season 1947).

This statement does not mean, of course, that a person is "born" a schizophrenic or a manic-depressive, or that all carriers of either gene constellation will actually develop the trait as a matter of fate. From a genetic standpoint, the term "hereditary" applies to any mental disorder that would not originate without the presence of a certain gene combination. The implication is that some persons *have* the genetic capacity for reacting to precipitating stimuli with either a schizophrenic or a manic-depressive type of psychosis, while others *have not*. Whether or not a real psychosis will be developed by such a "predisposed" person usually depends on an intricate interplay of constitutional and environmental factors.

The effect of *environmental agents* may be instrumental in bringing such a

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psychotic state to the foreground, but it should not be assumed that the suppression of an unexpressed or only mildly expressed genotype must necessarily be due to the action of purely environmental influences. Very frequently protection by other genetic background factors in a person distinguished by a strong constitution may be more important than the accidental absence of deleterious elements in the environment. In any case, there is no known constellation of plainly environmental circumstances that would produce a true schizophrenic or manic-depressive psychosis in persons who do not have a specific predisposition for either condition.

The *specific nature of the respective genes* is indicated by the observation that the incidence of schizophrenia is increased in the twin partners and other blood relatives of schizophrenic twin index cases, and that of manic-depressive psychosis in the consanguinity of manic-depressive index cases. No twin pair has as yet been found with a schizophrenic psychosis in one member and with a manic-depressive psychosis in the other, if a consistent system of classification is used. Another truism is that even of those blood relatives of a schizophrenic or manic-depressive patient who share exactly the same environment with a psychotic brother or sister or parent, only a limited number develop a psychosis. The others seem sufficiently protected against a schizophrenia- or depression-producing environment by the fortuitous absence of a specific genetic predisposition.

The statistical evidence in support of the *genetic etiology of schizophrenia* centres around the well-established fact that the disease occurs much more frequently in families which include a known case of schizophrenia (called an index case or proband in family studies) than it does in the general population, that is, in any group of persons who are not distinguished by blood relationship to such an index case. The average expectancy of schizophrenia in a general population without a pronounced tendency to inbreeding is less than 1 per cent. —0·85 per cent. to be exact.

However, the children of one schizophrenic parent have a probability of developing the disease nineteen times that of the general population. The grandchildren and the nephews and nieces are about five times more likely to show a recurrence of schizophrenia than is the average person. The schizophrenia rate of the parents of schizophrenics approximates 10 per cent. The expectancy for brothers and sisters as well as for the fraternal twin partners of schizophrenics is somewhere around 14 per cent., while that for half-siblings is about 7 per cent., and that for step-siblings, 1·8 per cent. The highest morbidity rates are found among the children of two schizophrenic parents, who have about 80 times the average expectancy, and among the identical twin partners of schizophrenic index cases, who show an expectancy rate of 85 per cent.

This distribution of schizophrenia rates indicates clearly that the chance of developing a schizophrenic psychosis increases in direct proportion to the degree of blood relationship to a schizophrenic index case—a rather convincing proof of the operation of heredity. It may be added that the morbidity rates quoted were obtained in two surveys with a total of over 1,800 schizophrenic index cases, of which 794 were born as twins, while the others were single-born.

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The families of the index cases studied included a total number of about 20,000 consanguineous persons, who were uniformly classified according to their mental, social and genealogical conditions.

Regarding the morbidity rate of 85 per cent. for the monozygotic partners of schizophrenic twin index cases, it may be borne in mind that the figure expresses the chance of developing schizophrenia in a comparable environment for any adult person that is genetically identical with a schizophrenic index case, but is not distinguished by the fact of having been selected as the child of such an index case. The latter qualification needs particular emphasis, since it apparently explains the difference found between the schizophrenia rates for the two identifiable groups of potential homozygotes of the schizophrenic genotype, that is, the children of two schizophrenic parents and the monozygotic co-twins of schizophrenic index cases. These two groups differ considerably in their morbidity rates, which amount to about 65 and 85 per cent. respectively. It is only by an analysis of this difference that a satisfactory estimate can be obtained of the extent of biased sampling in a morbidity study dealing with children of schizophrenic index cases. In order to provide such a sample, schizophrenics must have had a chance of getting married and of having offspring.

It has been shown by various fertility studies that the total reproductive rate of schizophrenic index cases is not more than about half that of a comparable general population. It is also known that the decrease in fertility is especially pronounced in the deteriorating types of schizophrenia. The consequence is that milder schizophrenic cases have a better chance of reproducing a schizophrenic child than have the more severe cases. If the children of one schizophrenic parent will often be the offspring of patients with lessened severity of their symptoms, the children of two schizophrenic parents may be expected to represent an even greater selection of potential schizophrenics in the direction of a more highly resistant constitution. Such a selective process does not operate in persons who have only the distinction of being the monozygotic twin partners of schizophrenic twin index cases. From the standpoint of disease expectancy, therefore, it is preferable for a potential schizophrenic to have two schizophrenic parents rather than one identical schizophrenic twin.

Statistically no less conclusive is the finding that all the observed variations in the schizophrenia rate are correlated with *different degrees of consanguinity* to a schizophrenic index case, but not with similarity or dissimilarity in the respective *environments* of the twin partners and other siblings of schizophrenics. About one-quarter of one-egg twin pairs show concordance as to schizophrenia without similar environment, while close to one-half of two-egg twin pairs remain discordant, even if the two twins have been exposed to precisely the same environment. This observation excludes the possibility of explaining the difference in morbidity between one-egg and two-egg co-twins on non-genetic grounds, that is, by a simple correlation between closeness of blood relationship and increasing similarity in environment.

The hypothesis of *recessive inheritance* in relation to the unit genotype of schizophrenia is borne out by the taint distribution in schizophrenic index

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families, showing transmission in the collateral rather than in the direct line of descent, and by an excess of consanguineous marriages among the parents of schizophrenic index cases. In two of our surveys about 5 per cent. of the index cases originated from consanguineous parental matings. Preferential support for a dominant type of inheritance was probably motivated in part by an endeavour to justify a compulsory sterilization program for schizophrenic patients. Considering the common occurrence of schizophrenia and the noticeable effect of inbreeding in certain population groups, it seems safer all around to assume that a true schizophrenic psychosis of any variety can be developed only by a homozygous carrier of the predisposition. Schizoid personality types may be either homozygotes with effective resistance to the expression of the genotype, or heterozygotes with strongly reduced resistance.

According to many observations in schizophrenic twin pairs and other sibship groups, the *variations in the clinical appearance* of the single-recessive unit factor for schizophrenia range from the mildest to the most destructive forms of the disease. The clinical variations include the episodic syndromes of a simple or catatonic variety as well as the chronic and strictly progressive forms of paranoid or hebephrenic colouring. Therapeutically it is especially important that the expression of the genotype may be fully suppressed under certain conditions. Such frustrated homozygotes may be either schizoid in personality or completely normal in outward appearance.

These differences in the phenotypical expressions of the genotype appear to be controlled by a *constitutional defence mechanism*, which is probably non-specific genetically, and certainly multi-factorial in that portion which is determined by heredity. There is a wide range of graded variations in the ability to resist the development, or to counteract the progression, of a schizophrenic psychosis. This ability has been shown by the results of biometric studies to be correlated somehow with the morphological development of mesodermal elements. The most useful correlative indicators of the constitutional capacity for mobilizing effective mesodermal defence reactions still consist in the measurements of the athletic component of physique and in the ability to maintain a stabilized level of body weight.

Our material of monozygotic twin pairs abounds with cases in which both members developed *similar types of schizophrenia* at practically the same age and with the same outcome of the disease. In such pairs no significant differences occur in regard to physical characteristics indicative of constitutional development. As a rule, the strongest resistance to schizophrenic deterioration is found in index cases with high athletic and low asthenic components of physique. The tendency to extreme deterioration corresponds to a high asthenic component, which is inversely related to the athletic component.

The situation is quite different in that relatively small group of monozygotic twin pairs whose behaviour to schizophrenia reveals some significant *dissimilarity*. If one twin remains completely free of schizophrenic symptoms, or breaks down much later than the co-twin, or shows a far more benign type of psychosis, there is always a difference between the twins in regard to physical strength and body weight from early childhood, the difference being consistently in favour of the more resistant twin. Apparently, any factor affecting either

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the general constitutional equilibrium or the stability of body weight has the tendency to reduce resistance to the expressivity of schizophrenic phenomena. For obvious reasons the same agents may be expected to impede the adequacy and permanency of a spontaneously or therapeutically established remission. The list of damaging factors observed most frequently in our monozygotic twin pairs includes unusual physical or emotional strain, pregnancy, acute infections, and a too drastic form of reducing diet. Similar principles prevail in the concordant sets of dizygotic twin pairs.

On the other hand, if all one-egg and two-egg twin partners are compared in regard to similarity or dissimilarity in constitutional characteristics and the clinical course of the disease, the difference between the two twin groups approximates the ratio of 1 : 55. It would be rather difficult to obtain more conclusive evidence for the operation of a graded and, therefore, apparently multifactorially determined constitutional defence mechanism in schizophrenia.

In view of this marked variability in the expression of the schizophrenic genotype it may be concluded that the disorder, although plainly based on a specific predisposition, can be both *prevented and cured*. Therapeutically the most effective procedure would consist in a true duplication of the biological defence reactions of a strong constitution protecting a homozygous carrier of the schizophrenic genotype from developing any or a progressive psychosis. Since it is a clearly established fact that some schizophrenic processes either are arrested spontaneously or remain undeveloped completely, it is equally certain that whatever takes place in the mobilization of the constitutional defence mechanisms of such persons can be identified morphologically and somehow duplicated biochemically. The realization that our understanding of the gene actions of constitutional modifiers is still very incomplete should merely be an incentive to more concentrated attacks on the complex biological problems involved.

In schizophrenia as well as in other inherited disorders the rationale of any treatment depends on the etiology of a disease. If it is evident that the development of a certain type of mental deviation cannot be explained without a specific dysfunction produced by genically controlled elements, a more profound knowledge of these agents is bound to lead to improved methods of treatment rather than to a fatalistic state of therapeutic inactivity. The persistently presumed analogy of inheritance and incurability is merely a reflection of deep-seated general preconceptions and rationalizations which still prevail in relation to the implications of heredity. Unfortunately, even many intelligent and academically trained people have been unable so far to acquire complete immunity from one of the most obdurate taboos of modern civilization.

Generally speaking, there is no inherited disorder which is incurable merely because it is hereditary. With respect to *symptomatic* therapy, the contingencies of inheritability and curability are virtually unrelated, and certainly not exclusive of each other. A depression may clear up spontaneously, or respond to shock treatment regardless of whether it has been predominantly reactive or endogenous in nature. An encephalitic personality deviation acquired in childhood may remain incurable, while a eunuchoid condition will

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lend itself to active hormonal therapy despite its possibly genetic origin. The effect of anticonvulsant drugs is considered independent of the etiologic type of epilepsy treated, and no one will claim that the knowledge of the genetic basis of schizophrenia has interfered either with the discovery of shock treatment or with any aspect of its clinical application. By analogy there is not the slightest genetic reason militating against the development of some new compound that would correct certain biochemical deficiencies in manic-depressive psychosis or amaurotic idiocy.

In fact, as far as the prospects for a *causally directed* treatment of such disorders are concerned, a better understanding of their respective genetic background factors is certain to be of immediate therapeutic value. Since we cannot expect to find a cure for a clearly inherited condition through the simple device of minimizing the effect of heredity in regard to human mental capacities, it is essential to determine how the underlying dysfunction is transmitted, reproduced and brought into play.

In general, one may say that therapeutic action against an inherited disorder is possible either by modifying—perhaps through substitution—the biochemical dysfunction which is the primary effect of the underlying main gene (Beadle), or by changing its expression through methodical stimulation of secondary modifiers and, if possible, through carefully directed management of vital environmental factors. For all of these purposes we have to know, however, how a morbid genotype is chemically constructed, under which conditions it will be able to be fully expressed, and to what extent its expressions may be controlled by constitutional resistance factors.

Apart from animal experiments, the only experimental method available for such investigations is the *twin study method*. At the present state of knowledge, the most urgent need is for the organization of long-range studies of monozygotic twin partners who are still discordant as to the earliest stages of certain types of mental disorder. It should be generally known by now that such twin pairs are of incalculable value for scientific investigation, that their occurrence is rare, and that the failure of any physician to arrange without delay for their thorough examination would represent a rather serious offence of omission. For obvious reasons, the magnitude of the task demands centralization of such twin studies in a few specially equipped institutions. It seems safe to predict, however, that important therapeutic problems of psychiatry will be near their final solution, if it can be determined why some monozygotic co-twins of psychotic twin patients develop no psychosis although they live under comparable environmental conditions ; or why they do break down with a milder psychosis at some other time ; or why one twin may show a more favourable type of response to the same method of therapeutic stimulation than the other twin. In all future twin studies the emphasis should be on the *cause* of such differences, rather than on establishing the fact itself that significant dissimilarities of constitutional resistance occur in similar genotypes.

It is very likely that there are " easier and quicker opportunities for satisfying the investigator by achievement " (Little). There can be no doubt, however, that properly organized genetic studies will provide the sound foundation of experimental fact upon which psychiatry can surely rely. It is also

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beyond question that man's educability cannot be put to a more vital purpose than to that of discovering the basic truth about the biological phenomena which control his mental health and the emotional stability of future generations.

REFERENCES.

(1) BEADLE, G. W. (1944–1945), " The Genetic Control of Biochemical Reactions," The Harvey Lectures, Series XL.
(2) DOBZHANSKY, TH., and ASHLEY MONTAGU, M. F. (1947), " Natural Selection and the Mental Capacities of Mankind," *Science*, **105**, 2736.
(3) FRASER-ROBERTS, J. A. (1940), *An Introduction to Medical Genetics*. London: Oxford University Press.
(4) HUNT, J. MCV. (1944), *Personality and the Behavior Disorders*. New York: Ronald Press Co.
(5) HOSKINS, R. G. (1946), *The Biology of Schizophrenia*. New York: W. W. Norton & Co.
(6) KALLMANN, F. J. (1938), *The Genetics of Schizophrenia*. New York: J. J. Augustin.
(7) *Idem* (1946), " The Genetic Theory of Schizophrenia," *Am. J. Psychiat.*, **103**, 3.
(8) *Idem* (1947), " Heredity and Constitution in Relation to the Treatment of Mental Disorders," section of the Symposium of the Am. Psychopath. Ass. on *Failures in Psychiatric Treatment*, edited by P. Hoch. New York: Grune & Stratton.
(9) MULLER, H. J., LITTLE, C. C., and SNYDER, L. H. (1947), *Genetics, Medicine and Man*. Ithaca, New York: Cornell University Press.

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