MENDELISM IN MAN

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When, some thirty-two years ago, MENDEL's laws were rediscovered and his work became famous, one of the first questions that arose was whether the laws of MENDEL were applicable to man. For it was at once seen that if the prediction of an average result could be replaced by a definite statement of the consequences of a particular mating a great step would be gained. The question was answered differently by different investigators, and, it will be recalled, a bitter controversy arose in England between KARL PEARSON, as biometrician, on the one hand, and WILLIAM BATESON, as Mendelian, on the other.

The first demonstration of the application of MENDEL's laws to man was made by the late W. C. FARABEE, then a student of W. E. CASTLE. Very soon papers multiplied, and it became known that the inheritances of eye color, skin color, hair form and many diseases of the skin, eye, etc., clearly showed segregation and were based, in some cases, on simple Mendelian factors. It is because of this avalanche of facts that PEARSON has ameliorated his opposition to Mendelism.

Students of heredity in man soon began to run into difficulties due to evident complications in the laws of human inheritance; there seemed indeed a certain justification for PEARSON's opposition to the universal applicability of Mendelian laws to human heredity.

The difficulties in testing Mendelian theories in man are very great and have been often enumerated. There is, first, the great time which elapses between generations, in consequence of which it is difficult to get precise first-hand information concerning even as few as three generations. The best way of meeting this difficulty is, it has long seemed to me, to have established one or more repositories of human records where these will be preserved through the generations. It was with the aim of securing some such preservation that the EUGENICS RECORD OFFICE was established by Mrs. E. H. HARRIMAN. However, since this office carries data concerning less than two in a thousand of the population of the United States, it falls short of meeting the need of a general repository. For selectively bred cattle, hogs, dogs and especially race horses there are rather complete herd books and stud books; there are grave difficulties (chiefly financial) in the way of creating any such pedigreed list of man. But for genetics far more is needed than a pedigreed list, namely, a quantitative statement of the traits and performance of each individual, and this requirement means immensely increased time, expense, and bulk.

The second difficulty lies in the small sizes of fraternities, since it is almost impossible to apply Mendelian formulae where there are only one to three children. Tied up with the difficulty introduced by small families is the considerable error introduced by selection of families. If one is collating the incidence of a trait in fraternities of offspring when neither parent shows the trait, one naturally is forced to select just those fraternities that reveal the trait. All those fraternities are omitted that might have shown a member with the trait had the fraternity been large enough, but in which it is (by chance) absent, owing to the small number in the fraternity. By these omissions the proportion of persons showing the trait in the sum of the fraternities is too high.

The errors due to the small size of families and to selection of only those families showing the trait can be, in part, corrected by the use of WEINBERG's method, or some other similar methods; but by applying these methods one diminishes greatly the number of available fraternities.

Another difficulty lies in the circumstance that many human traits depend upon multiple factors. This is, doubtless, true of hair color and hair form. It holds true in the range of skin colors found in man. Only recently I have been working upon two apparently unrelated traits, namely, tendency to goiter and a type of hardness of hearing called otosclerosis, and have found that in each the facts are best in accord with the hypothesis of two genes, one sex-linked and one autosomal. If, as seems not impossible, a trait is due to three or more genes, it will be very difficult if not virtually impracticable with our present methods and with the difficulties inherent in human pedigrees to determine the fact definitively.

While in Drosophila the number of traits depending upon multiple factors is proportionately small, in man such characters seem to be predominant. It is perhaps hardly to be wondered at, since man himself is so complicated in his development and, just because he lies at the end of a long period of evolution, has accumulated a large number of mutations. Also, it is probable that through his capacity for adjustment to conditions of life, even under bodily and environmental handicaps, more of these mutations have been preserved than would be the case in a species that was less plastic and adaptable. As medical skill and state care of defectives advance it is probable that more and more of these mutations will be heaped up in the population. The same gene will have a chance to undergo further genetical change so that we may expect many an allelomorphic series, such as we have in hair color, to arise and many genes to cooperate in a summation result which we call a human trait.

Another difficulty grows out of the principle, applicable in the realm of diseases and defects, that clinical entities are not necessarily genetical entities. This is now familiar enough to experimental geneticists in other fields. Thus there are perhaps one hundred genetical types of albinism in corn. In MACDOWELL'S mouse colony there are, or have been, at least three types of circular movements allied to the whirling of the Japanese dancing mouse. In man, myopia, in some pedigrees, shows a sex-linked factor; in others that factor seems to be absent. Other examples are illustrated in WAARDENBURG'S recent book on the inheritance of eye defects.

Still another difficulty grows out of the sensitiveness to environmental changes shown by many human characters in their development. This is probably, in part, due to the circumstance that human development is so prolonged, continuing for years, as contrasted with the development of the Drosophila or Daphnia which takes place in less than a week. This interaction of heredity and environment is well illustrated in the case of goiter where a hereditary insufficiency in the development of the thyroid gland may pass unnoticed in an environment rich in iodine. It first becomes apparent when the iodine in the water or food falls below a certain minimum.

Though, as often stated, man is perhaps the worst species in which to work out the laws of genetics, yet it is of great importance to mankind that the principles established in other organisms should be tested in man. Also there are certain traits, especially mental ones, whose inheritance can be better studied in man than in any other species, partly because of our familiarity with his physiological and psychological variations and the opportunity to get his cooperation in their measurement. It is, indeed, possible to study inheritance of wildness in rats. But the picture of hyperkinesis in man is infinitely richer in detail—the joviality, the generosity, the briskness, the impulsive actions, the erotic tendency, the flow of speech and other familiar traits give us many criteria of the hyperkinetic state and suggest its complex nature.

On the other hand, in his instincts and special capacities man is hardly superior to dogs as an object of investigation in heredity. This is not because his instincts and capacities are not as varied but because, for the most part, mankind has not mated so as to produce strains characterized by such special instincts. Dogs are so mated. However, in some cases matings of similar instincts occur, as between naval families whose social interrelations are such that the young men and women of these families are brought early into contact. Similarly, there is selective mating among biologists, partly because of the existence of summer marine laboratories like those at Woods Hole

and Cold Spring Harbor where the young people associate in informal and intimate fashion. Despite the unassorted mating obvious in most cases there is a good deal of social stratification. Thus we have the scholastic stratification, seen in the matings inside of college communities, the stratification among politicians and statesmen, who sojourn long with their families at the legislative capital, the stratification of artists who tend to live in colonies, the stratification of the deaf who can converse only with other deaf who know the sign language, the stratification of exiled missionaries, the stratification of the farm communities and the stratification, in this country, of the valley communities with their high incidence of feeble-mindedness. These stratifications, or castes, if you will, afford an opportunity for the study of selective matings, even in a species whose matings seem at first glance so uncontrolled as man's.

While the slow development of man increases the interval between generations it gives opportunity for prolonged testing and analysis of mental and emotional traits. The school is, indeed, a place of revelation of instincts, tastes, and special capacities, both mental and physical. The physical and scholastic achievement records of our schools are such as to afford material for the study of inheritance of mental capacity.

In one other respect the study of man offers advantages for Mendelian analysis, and that is in the frequency of twins, especially monozygotic twins; for about one quarter of one percent of human births is a birth of monozygotic twins. Now it is clear that in no other animal can we know in such detail and so quantitatively the physical, mental and temperamental qualities as in man, and, accordingly, human twins can be compared with a detail not possible in other animals. By analysis of twins we can distinguish between traits whose development is more influenced by environmental changes and those in which environment plays a smaller part. The opportunities for genetic analysis in twins are almost limitless.

Finally, reference may be made to a characteristic of heredity in the higher vertebrates which, on the one hand, complicates their Mendelian analysis, and, on the other, adds a certain interest to its study. This is intervention of the endocrine glands between the genes and the full development of the trait.

For example, the study of the heredity of dwarfism becomes the study of the inheritance of an insufficiency in the anterior pituitary gland. The heredity of fleshy body build with male genital dystrophy becomes that of a defect of another anterior pituitary hormone. The study of hereditary goiter becomes that of the heredity of thyroid functioning, and so on. It becomes daily clearer that the endocrines form an important link between the genes

and the finished body. Because of the responsiveness of the endocrine glands to environmental conditions they play an important rôle in adjustment to environment.

This interaction of heredity and environment is well illustrated in the case of goiter. Goiter is commonly said to be due to insufficiency of iodine in the water or food. But this cannot be the whole story, since in one and the same valley where goiter is endemic certain families will be quite immune. Also, on the sea coast where iodine is abundant, sporadic families will be found which have always lived in the locality and yet suffer from goiter. Evidently the symptoms of goiter begin to appear where a certain degree of thryoid effectiveness meets a certain degree of noxiousness of environment. Thus, if the thyroid be inefficient, then, despite a good environment, it will fail; the environment becomes more noxious, through reduction in iodine content, and a larger proportion of thyroids will prove to be inadequate; as the iodine content falls to its minimum the incidence of goiter in the population becomes a maximum. In general a developmental trait requires for its expression at least a minimum of the specific internal impulse combined with at least a minimum of supporting environmental conditions. As either of these factors increases the expression becomes more marked.

Thus the studies of the past three decades in human heredity have, by the application of Mendelian principles, been given a very practical slant such as would never have accrued from the purely statistical studies based on masses.

What of the future? Are we in a position to predict the directions that the studies in human heredity will henceforth pursue? Let us try to forecast a few.

First, efforts to complete the investigation of the inheritance of human traits must be made. Expensive as they are, they are of such practical importance for the future of mankind that they must not be neglected.

Second, in human traits as in the case of those of other organisms we should no longer be satisfied with factorial analysis but should try to get a clearer insight into the way the genes do their work by tracing the ontogenetic development of each trait. This is the point of view that HAECKER long ago emphasized. KRISTINE BONNEVIE has shown how it may be carried out by her fine researches on the development of the papillary ridges of the finger tips. Some students of the comparative embryology of human races, for example, A. H. SCHULTZ, reveal how early and in what fashion the differential characters between Negroes and Europeans show themselves in ontogeny. CHESLEY and KAMENOFF, students of DUNN, are getting most interesting results from a study of the ontogenetic history of the

crooked-tailed mice; this is outside the human group of studies to be sure but illustrates the method and the interpretations to which it leads.

Third, since with humans it is rarely possible to get the earliest stages of embryos that we are certain are going to develop a particular trait, while with the rapidly growing mammals this is often possible, it seems desirable to carry along with human genetical researches strains of mice or rats. There are a large number of morphological and physiological characters that are common to mice and men of which the ontogenesis of the genes can be much more satisfactorily worked out upon the animal.

Fourth, since we now know that aberrations in the chromosomal complex are responsible for irregularities of development in both plants and animals, it is reasonable to look for them in man also. Herein may lie the cause of some profound defects that are clearly familial but the method of whose inheritance is not easily revealed. It would seem that, if anywhere, we should find such chromosomal irregularities in the group of feeble-minded. Some years ago I was able to assist PAINTER to get some perfectly fresh testicular material of a mongoloid dwarf. But, PAINTER tells me, this material revealed no obvious chromosomal irregularities. However, this negative result should not discourage us from continuing the search for possible chromosomal irregularities in genetically complex defects. Such chromosomal irregularities have, indeed, been found in cancer cells; they are, consequently, not foreign to human tissues, nor, probably, to human gametes.

To sum up: Mendelian studies in man offer an alluring field for future investigation, not, indeed, for the determination of fundamental laws of genetics but for the application of the laws to that species upon whom all progress in science depends and upon whom the social order that makes scientific work possible and even congenial rests. A more precise knowledge of the inheritance of traits will contribute toward an insight into the consequences of particular mate selections and of race crossing. Despite the difficulties inherent in genetical work with this species continued research is justified on man if for no other reason than that in no other can an investigation so well be made in the mental field as in the study of twins and perhaps in the endocrine field, opening up a new method of study of the way the genes do their work. In the future more stress will be laid on the internal control of development by the genes, with the aid of experimental mammalian material. Also the explanation of some irregularly inheritable traits will be sought in chromosome irregularities. Thus the solution of problems in human genetics will require in the future the aid of the embryologist and the cytologist.