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Progress and Prospects in Human Genetics

A Preface to this Journal

I. FUNCTIONS OF THE AMERICAN SOCIETY OF HUMAN GENETICS

IN December, 1947 an informal gathering was held during the meetings of the American Association for the Advancement of Science at Chicago, at which the participants—some 150 scientists, representing various lines of work—decided to form the American Society of Human Genetics. The two major purposes of this organization were to be the furtherance of sound research in this subject and the publication of a journal dealing with such research. The Society was officially organized at the September, 1948 meeting of the American Association for the Advancement of Science in Washington, D. C. The first meeting for the reading of papers will be held in New York City next December and those desiring to take part should write to the Secretary of the Society, Dr. Herluf H. Strandskov, Department of Zoölogy, University of Chicago.

In a sense, the establishment of this society and journal has been long overdue, since most of the basic principles of "modern" genetics, applicable to living things in general, have been known for over a third of a century. Moreover, it has long been evident that the specifically human problems of genetics constitute such an immense and complex group of fields, and require for their successful prosecution such a combination of the knowledge of specialists in the respective human subjects with a thorough working understanding of genetic principles, that societies devoted mainly to general genetics are inadequate for dealing with this material. However, an unfortunate compartmentalism has for many years hindered persons in medicine and in the other specifically human disciplines from attaining the necessary knowledge of genetics and, *mutatis mutandis*, has hindered geneticists from mastering the more special human subjects. Although this situation has prevailed for over a generation, we believe that the time is now ripe for a fertile liaison, and it is the purpose of the present society and journal to subserve it.

Included in the ranks of our present group there are many persons of genetic competence who are primarily medical men, of varied specialties, there are some genetically qualified anthropologists, psychologists and students of social sciences, and there is a good share of persons whose main field is genetics itself but who have acquired a considerable interest in and knowledge of one or more of the specifically human subjects. Our board of directors and our editorial staff have been chosen so as to represent all these groups. We hope therefore

to be able to avoid that dilettantism which has in the past characterized so many attempts to study human heredity.

II. ERRORS TO BE AVOIDED

It happens that the prolonged delay in setting up the present working association has one very fortunate aspect. This derives from the fact that, until very recent years, the subject of human heredity was buffeted about by pressure groups from the extreme political right and left, who sought to impose their social preconceptions in the form of a spurious "nature-nurture controversy", in which the methods of objective science were largely forgotten. The development of a more scientifically minded group of students of the subject has required the influence of basic genetics, working over many years. And in recent years, this sounder attitude has been reinforced by the lessons of the terrible mistakes made by the political protagonists of fascism and of communism, respectively, when they gained the power to translate their biological prejudices into action.

Reactionaries who assumed that practically all social ills were results of inferior hereditary endowment on the part of the classes and peoples having an economically lower status had been prominently represented in the old-style eugenics movement, and this movement in turn played a major role in the motivation of the earlier studies on human heredity. These eugenists usually assumed naively (1) that the characteristics manifested by the economically more advanced groups (or thought by members of those groups to be so manifested) were superior ones and those of the contrasted groups inferior, and (2) that the characteristics, whether physical or mental, manifested (or thought by biased observers to be manifested) by any person or group were in the great majority of cases valid signs of corresponding differences in the underlying genetic endowment. In these self-flattering rationalizations, the influence of environment on the supposed differences was neglected or minimized.

This kind of wishful thinking, indulged in by members of a dominant group, was long ago formulated on a racial basis by Compte de Gobineau. It flourished increasingly in the "eugenics" of such racist propagandists as Lothrop Stoddard, Madison Grant, and Fritz Lenz. Finally, blossoming out into the Nazism of Hitler, it led to such excesses as to involve itself and a considerable portion of the world in ruin. Although in this process its fallacies became widely exposed, it is by no means all dead and buried yet, but represents a continuing peril, to be vigilantly guarded against by all serious students of human genetics.

Equally irrational is the view that, after evolution had finally arrived at the stage of man, all hereditary differences became unimportant, that genetic "equality" of individuals as well as of all groups is an established fact, and that, as regards the innate basis of human mental traits at least, there are no

significant qualitative or quantitative differences which can markedly influence the nature of the developed product. Here, environment is supposed to be the practically absolute dictator.

The atrocities to which the latter kind of "retreat from reason" can lead in the hands of unscrupulous authorities have been made clear in recent months by the officially admitted liquidation of all genetics, and of much of science in related fields, within the Soviet Union and its satellite countries. Setting up in the gap thus left open the archaic doctrines of direct adaptability of the germ plasm and the inheritance of acquired characters, these would-be environmentalists have however got themselves into a self-contradictory and awkward position. For, on their view, the effect of environment, being inherited, is necessarily cumulative from generation to generation, and so the less privileged classes and peoples would after all these centuries have become innately inferior. Some proponents of the view, when questioned about the matter, have reluctantly admitted this, saying that several generations would be required to overcome this supposed inborn handicap, although, in time, better conditions of living would automatically improve the stock. The Presidium of the Academy of Sciences of the U.S.S.R., however, in an official announcement, has attempted to sidestep the embarrassing discussion by saying that "to apply biological laws to human beings is to lower them to the level of beasts." According to this escape, only social laws operate in determining human nature, at whatever level.

Such are the dangers attached to a subject which lies so close to the interests of men, and to the scene of political, economic and ideological conflicts. It then becomes the more necessary for the scientists engaged in it to dissociate themselves from those powerful currents in which reason is swayed by passion, to resist the incursion into their field of prejudice, of whatever origin, to hold fast to the hard-won results of painstaking experiments, observations and calculations, to maintain objectivity of method, independence of thought, searchingness of analysis and freedom of criticism, no matter what "authority" may thereby be challenged. Fortunately for most Western scientists there are still, in their countries, considerable opportunities for pursuing such a course. It is, however, their obligation, along with that of all other men of good will, to aid actively in that concerted effort which experience has proved to be necessary for the continued maintenance of their opportunities for intellectual integrity. But all this serves to clear the ground for their specific tasks.

III. THE RELATION BETWEEN HEREDITY AND ENVIRONMENT

Let there be no mistake about the nature of these tasks in the subject of human genetics. Consider first the "nature-nurture controversy". The developed organism is more nearly a product than a sum (though actually a group

of far more complicated functions) of the sets of factors which constitute heredity and environment. This is illustrated by the fact that, with either set of factors effectively at zero, the resultant too, the organism, becomes zero. By suitable variation of either set of factors, moreover, the product can, conceivably, be affected to a virtually unlimited extent. In this sense it is illegitimate to ask, which is more important—heredity or environment? Yet in given situations, when dealing with particular characteristics, the actually existing differences of environment may be more or may be less effective than those of heredity in altering the observed outcome. There is no general solution, for the specific results will vary enormously according to the nature of the characters, the nature and range of the environmental conditions, and of the genotypes in question. Yet these specific findings are often highly important. They can be attained not through *a-priori*-based argument, but only through observations and measurements made under suitably controlled conditions.

It is perhaps necessary to labor the point that no fallacies in genetics are more absurd than the two complementary assumptions, made by so many laymen: (1) that, because a certain ailment or other characteristic is found to be inherited, we must regard it fatalistically, and set it down as something impossible to influence by environmental means, and (2) that because a certain characteristic is found to be acquired as a result of the action of environment, it is not also subject to hereditary influences. True, there are some traits, such as eye color or blood type, which are much subject to hereditary differences and, ordinarily, very little to environmental ones, although special conditions can be found which affect even these. And there are others, represented by the acquisition of a highly infectious disease, or a given language, or the breaking of a bone, which are to a paramount degree determined from without, though even here hereditary predispositions sometimes play a role. But the great majority of respects in which organisms differ fall between these two extremes. That this is true of most characters, both "physical" and mental, in human beings has been shown clearly by comparative studies on one-egg and two-egg twins. This elegant mode of attack, which so largely compensates us for our inability to obtain pure lines of human beings, is capable of yielding far more information on these questions than it has so far. In this kind of material, moreover, there is opportunity for a certain amount of experimentation, to determine the effectiveness of particular types of changes in environment.

The ascertainment of the extent to which the ordinarily observed differences in a given character are genetically or environmentally based is only the beginning of the serious investigator's job. For, whatever the answer may be for the differences as ordinarily found in his particular population, under the circumstances there prevailing, it may be quite different for another population, and/or under other conditions. His final aim therefore should be not

merely an over-all statistical description, but an analysis of the mode of operation of each significant factor. Only this will give security to his predictions for combinations of circumstances not already met with, and will bring his conclusions to the point where they are likely to have useful applications in practice. It is true that, owing to the immense complexity of the organism, and of its conditions of life, this job is in an ultimate sense almost an endless one. Yet this does not prevent the attainment of most important and useful information along the way, as the analysis, in its interwoven genetic and developmental aspects, reaches ever deeper levels.

The above point of view, so self-evident nowadays to those initiated in genetics, was not established readily or rapidly. It involves the whole distinction between phenotype and genotype. This had its start when Weismann called attention to the continuity of the germ plasm, and its distinction from the soma. It developed further as a result of the findings of cytologists, Mendelians, mutationists, and "pure line" workers like Johanssen, showing the relative stability of the hereditary material and the independence of its transmission from ordinary environmental influences, while at the same time experimental embryologists and physiologists were demonstrating the responsiveness and adaptability of the somatic structures and processes. And as genetics and the other fundamental biological and medical sciences have developed, our view of these matters has become increasingly concrete and detailed.

IV. EARLIER HISTORY OF HUMAN GENETICS

As the foregoing account has indicated, human genetics has been extremely dependent, for the correctness and usefulness of its interpretations, and for guidance as to significant directions and methods of research, on the progress of the sciences basic to it, and more particularly upon general genetics. It must always keep a firm foothold on this base. For, important though its special problems are for mankind, most of the fundamental principles of genetics, which are as it were its tools, have first to be worked out in pilot experiments on lower, more controllable organisms.

It is true that Francis Galton attempted to found a science of heredity and variation through a statistical study of the characteristics of human parents and their offspring. Thus he set up his so-called "law of ancestral inheritance" and the "theory of regression". However, the Mendelian studies on lower forms showed how misleading these findings were, when taken as guides to what happens in the individual organism. Even though the "law" itself is in the main correct if taken descriptively, it turns out to be a complicated resultant of the action of the Mendelian processes working in large populations, in combination with the action of environmental influences on the development of the same characters, in ways which the statistical study of heredity as employed by

Galton and his gifted but too stubborn follower Karl Pearson could never by itself have revealed. Basic knowledge was not yet ripe for a science of human genetics in Galton's time.

But though a science of heredity was not thereby established, something else did emerge. For the mathematics of statistics became in the process a full fledged and highly useful set of methods, applicable to problems in economics, psychology, physics, and various other fields. In human heredity these mathematical tools are in some lines quite indispensible, when taken in conjunction with the interpretations which general genetics, based on Mendelism, affords. Through the modern refinements of its operations, that inability to control individual crosses which so hampers the drawing of exact genetic conclusions is often in considerable measure circumvented nowadays by statistical mathematics. And, in some degree, it is almost universally necessary for helping to determine just how sure a given conclusion may be, or how wide is the margin of error of a calculation, whether in genetics or elsewhere.

With the coming of Mendelism, those students of human heredity who were scientifically more progressive began interpreting the inheritance of individual traits, as shown in pedigrees, on a Mendelian basis. The foremost pioneer in this work was Davenport, who deserves especial credit because he had been trained to look at heredity from the Galtonian angle. He organized such researches on a considerable scale, while others, in Germany and England especially, followed suit, and innumerable cases were amassed and fitted into the supposedly simple Mendelian scheme.

Unfortunately, the concepts of multiple gene action on the same character, and of environmental interaction in the result, which general genetics had only begun to demonstrate, were as yet insufficiently appreciated by these early workers with human pedigrees, even though Davenport himself did adduce sound evidence for multiple gene differences in skin color. Moreover, these enthusiasts usually failed to recognize differences in the degree and quality of the condition studied, forcing it into rigid presence-and-absence categories to correspond with their oversimplified conception of the genetic and developmental basis. And in deciding its presence or absence in each individual they commonly accepted the verdict of untrained observers, no matter how technical an adequate diagnosis of some of the clinically peculiar conditions might be. Finally, their cases were often selected for conformity with the schemes they were to follow, or at least for showing numerous "positive" individuals, and the effects of this selection of material were not allowed for. All this patent forcing of the data, and, still more so, of the interpretations, led many critically minded persons to look askance at both the specific and general claims made. Even more so did the fact that these precarious conclusions were often used in support of sweeping recommendations for eugenic measures, and that many

of the studies were indeed little more than accessories, made to put forward the preconceived eugenic notions of the writers.

Quite obviously the cart had been put before the horse, to the detriment of both. It would be helpful, for those now intending to work in this field, to examine some of these early reports critically, as object lessons of what procedures to avoid. Unfortunately there is still a good deal of material of this kind published, but now it exists chiefly in scattered form, in medical and biological journals primarily devoted to other objectives than genetics.

V. TRENDS IN SOME OF THE MODERN WORK

Since the days when literature of the above type set the standard in human genetics, there has been an enormous improvement. Thus, the *Annals of Eugenics*, passing from Karl Pearson into the hands of R. A. Fisher and L. S. Penrose, has set a very high standard for work of a statistical kind in which those processes of Mendelian recombination, linkage, multiple gene action, environmental interaction and mutation frequency established by general genetics are used as the elementary operations in the computations. Likewise the gathering and interpretation of pedigrees dealing with particular traits has been handled in a truly scientific manner in such work as that of the great Medicogenetical Institute which, with its 200 or more participating physicians, flourished under Levit in Moscow from 1929 to 1936, when it was liquidated. Much good work of a similar nature has been carried out, though with more modestly organized plans, in this country, the Scandinavian countries, Great Britain, Switzerland and Holland, as well as (if we make the right selections) in Germany and Japan.

In the modern work with pedigrees, the recognition of grades of "expressivity" and of "penetrance" of a gene (to use the terms of Timoféef, first applied in human heredity by Oscar Vogt) and of the "conditional" as well as vacillating nature of dominance (Levit) has helped considerably. So has the finding of special techniques for recognizing the presence of given genes when their conspicuous effect is absent, as in Mohr's X-ray identification of hidden carriers of brachyphalangy, Levit's blood-sugar determinations of unexpressed diabetics, Valentine and Neel's diagnosis of heterozygous thalassemics, the use of "brain waves" for spotting latent epileptics, Vogt and Patzig's finding of nervous symptoms disclosing subliminal cases of hereditary chorea, etc. This approach can be vastly extended, to great advantage for both medical diagnosis and prophylaxis. It is evident that success in the working out of such matters requires, on the one hand, high genetic competence, both for the provisional interpretations of pedigrees that guide the choice of individuals to be examined, and for the later assessments of results, and, on the other hand, detailed knowledge of the condition in question and of the techniques that

might be used in examining it. This means either a combination of the two disciplines in the same person, or effective collaboration between an up-to-date geneticist and an investigator who has made a special study of the particular field in question.

VI. "PHYSIOLOGICAL GENETICS" IN MAN

Surely the most striking illustration of the value of advanced techniques in the tracking down of genes is provided by the findings on the inheritance of antigens, as seen especially in the Rh and other series found in human blood. Although such work is still in its early stages (if we consider the much greater multiplicity of antigenic differences already demonstrated in the blood of cattle) it has already done more than perhaps all other work in human heredity combined to bring home to medical men the reality of the processes of inheritance dealt with by geneticists, and their relevance to problems of medical diagnosis, therapeutics and prophylaxis. One of the chief aims of human genetics must be to get the recognition of as many genes as possible on to a similarly definite basis.

The rapid rise in our knowledge of proteins and other biological substances, and of their interactions, should open many rich veins of genetic investigation to parallel that of the blood antigens. At the same time, as has been so well demonstrated in the studies on molds and bacteria, the intensive biochemical investigation of hereditary deviants is of great aid, reciprocally, in advancng our knowledge of the biochemical materials and reactions concerned themselves. As illustrations of such leads in our human material, we may mention such hereditary abnormalities of metabolism as are found in alcaptonuria and phenylpyruvic amentia, which surely represent but an insignificant fraction of the hundreds of chemical variants that must exist in man.

But it is not only on a biochemical level that the exact study of mutants, in comparison with the standard form, throws light on the processes occurring in the organism. The same is true in the study of physiological and pathological reactions in general, and in the study of development, including the processes of regeneration and of aging. Each mutant which distinctly affects development or physiology represents a research problem in itself, which is likely to be as profitable, and often much more so, for the elucidation of normal functioning, than a laboratory experiment in which the given part or character is investigated by means of surgery or medication. In fact, the unravelling of the whole great complex of biochemical, developmental, and physiological processes which constitute the organism must in time proceed more and more through the study of these very delicate experiments which nature provides ready-made for us, when presenting us with changes in the individual genes lying at the basis of the formation and of the workings of all somatic parts. And as in other fields

it cannot be otherwise in this, that increasing knowledge will carry in its train increasing possibilities of control.

Man is so closely related to the other vertebrates, particularly the mammals, that much of this genetic dissection of development and physiology can be carried out most profitably through pilot work on laboratory forms. Excellent examples are the intensive studies of Landauer on "rumpless" fowl, of Dunn and his associates on caudal abnormalities of mice, of Grüneberg and of Bonnevie on the developmental physiology of changes in the circulatory system of mice. It is likely that many results of this kind carry their lessons with regard to corresponding processes in humans and will later be found to be represented by homologous human cases. It is therefore worthwhile, on occasion, for a journal of this kind to consider them. On the other hand, men are examined intensively in so much greater numbers than any animal, that the human material itself will often present the pilot findings, which can later be followed out in more controlled fashion in animals.

VII. QUANTITATIVE INHERITANCE

The genes referred to in most of the above discussion are such as to give sharply recognizable differences. It should however be remembered that most of the gene differences prevalent in populations, distinguishing individuals phenotypically, only affect, at least as the end product of their action, the quantity of some character or characters. Usually the effect is also modified by the action of environmental conditions and of an undetermined but often large number of other, coacting gene differences, not readily distinguishable from them. We are thereby confronted with problems of multiple gene inheritance. For their study, in the absence of definitive signs of the individual genes, an approach combining the principles of Mendelian inheritance with the methods of statistics adapted to the latter are necessary. Through these means, although the genetic composition of the individuals themselves remains largely undetermined, nevertheless considerable progress can be made towards predicting in a general way the probable results to be expected from given types of crosses.

One of the objectives in such work must be the obtaining of evidence concerning the relative frequencies, in the population, of gene differences having different degrees of effect on the given character—i.e., a frequency-magnitude of effect distribution. Other objectives are to gain evidence as to degrees and direction of dominance shown by the gene differences of different magnitude, and as to the extent to which the effects may be treated as simply (logarithmically) cumulative or, contrariwise, as embodying more specialized types of interaction with each other and with environmental effects. Nor can the answers for one type of character, such as stature, or for one population, such as

West Europeans, be carried over without verification to another character, such as head-shape, or to another population, such as Eskimos.

Now it might be thought that in prosecuting such studies we are passing over from characters of medical interest to those which concern more purely the physical anthropologist. However, there is no fundamental distinction between gene differences of the more extreme and usually rarer kind and those of the less extreme and usually commoner kind; they grade imperceptibly into each other. Although the primary gene effect is probably in the vast majority of cases a qualitative chemical one, studies on lower forms show that it usually expresses itself through its quantitative influence upon some chemical process concerned with development or physiology, even when the final outcome again appears as a qualitative difference. And so the cumulative action of a number of minor differences that happen to work in the same direction may be as great as, and very similar to, the action of one "large mutation". To know how often to expect effects of different degrees, then, from given types of matings, we should know the frequency distribution of the gene differences of different magnitudes. *Vice versa*, the latter may to a certain extent be estimated from data concerning the former. But as yet there has been little attack upon these difficult problems. Their very formulation shows us, however, that there is no sharp category of "abnormal" versus "normal" variants. And medicine and even psychology, along with anthropology, will increasingly have to take the so-called "normal variations" into consideration in their judgments concerning diagnosis, prophylaxis and treatment.

VIII. GENETICS IN RELATION TO MENTAL PROCESSES

A few additional words are perhaps called for concerning the role of human genetics in relation to fields dealing with mental processes. Here more than anywhere else strong rancor was aroused by the sharp cleavage into hereditarians and environmentalists, and there are still many vehement proponents of these opposite extremes to be found, chiefly among persons not well grounded in modern genetics. It is germane in this connection to remind ourselves that the brain is an organ constructed for the achievement of maximum plasticity in response,[1] and that its reactions are therefore influenced in a far more thoroughgoing way by environmental differences than are those of any other organ. When it is recalled, in addition, that a vast store of environmental influences is handed down in families, and in whole groups, through unconscious as well as overt tradition, and through the transmission of the material means of existence, and, further, that all these factors are themselves subject to the most profound and marked continuing differences, it is seen how ultra-cautious the

[1] Paraphrased from a passage (p. 433) in the author's study of a case of identical twins reared apart (Muller, 1925).

investigator must be before ascribing any apparently inherited behavioral characteristics to the genes. In fact, these considerations are enough to make it quite illegitimate to make any deductions regarding genetic differences for mental traits, on the basis of comparisons between individuals or groups whose cultural or material background have been consistently different.

Despite the above stricture, however, innately determined features of the brain are of the utmost complexity and they must, like the minutiae of all other organs, be subject to genetic variations of innumerable kinds. These variations are bound to affect brain functioning in manifold ways not yet understood, contrary to the assumptions of those who claim that the genetic variations which can significantly influence behavior are confined to alterations in the production of hormones and in the form and functioning of other parts of the body than the brain itself. It is biologically certain then that there must be many important individual differences in behavior caused by genetic changes which directly affect the central nervous system. The discovery of these differences, the unravelling of their genetic bases, and of the manner in which they interact with influences emanating from the environment (using this term in the broadest sense, to include also the social environment) constitutes a tremendous field of research for psychologists, psychiatrists and all concerned with mental processes.

The disentangling of genetic from environmental effects on behavior, or at least the comparison of their nature and magnitude under given conditions, is not, as might at first sight seem to be the case, an impossible task. For some very valuable data along these lines have already been obtained, through those special techniques which provide us with relatively constant environment while the genotype varies and, conversely, with a relativcly constant genotype while the environment varies. Included among such techniques are, *par excellence*, comparisons of the amounts of difference between the members of one-egg and of two-egg pairs of twins. This attack has been broadened by the inclusion of cases of one-egg twins whose members were reared apart, or purposely subjected to different treatments. Further light on the subject has been obtained by the parallel investigation of ordinary sibs, of foster children, and of persons of different genetic background brought up in the same institution. All these results agree in ascribing very important roles to *both* the hereditary and environmental factors involved, in the case of the great majority of the mental traits studied. These are, however, but token investigations of the kind, compared with what yet remains to be done. Furthermore, since they prove that many of the more extreme mental differences between members of the same family must be largely genetic in their basis, it becomes justifiable to some extent to use the pedigree method of investigation also, although not so indiscriminately and incautiously as in most of the earlier work. And it goes

without saying that, in such studies, the precautions and skills of the professional psychologist or psychiatrist must be brought to bear.

IX. GENE FREQUENCY STUDIES

Passing beyond the more usual interests of the physician or psychologist in the individual man we come to the problems of the underlying biological basis of the health, vigor, capacities and properties of varied kinds genetically inherent in entire interbreeding groups of people, of the factors that brought them to their present state, and of those that are working to alter them still further.

In these studies on the genetics of populations it is of course the more definitely recognizable genes which usually serve as the more useful indicators. The work on antigen frequencies just opening up is an illustration of investigations of this type that promise to be most informative for the physical anthropologist in tracing the historical interconnections and migrations of peoples, and the conclusions on these matters will in turn be highly important for the cultural anthropologist. Of greater general biological as well as medical interest, however, will be data on the frequencies of lethal genes and of those producing various grades of detrimental effect, and on the amount of concordance in the nature of these genes in different populations.

These frequencies are known, from considerations of general genetics, to be in the main, for a given mutation rate, reflections of the nature of the breeding system: such as the amount of inbreeding, the kind of exogamy or endogamy practiced, the amount of migration, the population size, the extent of subdivision into smaller populations and their size and degree of isolation. The rigor and type of selection presents further variables of great importance here. Theoretically, if we had quantitative values for these factors and also knew the basic mutation rates of the genes concerned, we could calculate the results to be expected. Conversely, having the end results and having general values for all but one of the above sets of factors—for instance, the mutation rate—we could then arrive at an approximate estimate of the latter. Such solutions would in turn enable us to forecast how the values would change in response to alterations in the system of breeding or of selection. And, in time, actual evolutionary implications would emerge.

As it is the mutation rate which furnishes the primary pressure for the apparition of all the observed "abnormalities" their numbers will, other things being constant, be directly proportional to this mutation rate. It may, in most cases, be taken as a fixed base of reference, and a knowledge of it is one of the prime desiderata for our calculations of populational composition. Fortunately, a good deal of significant information can be obtained about mutation rates without use of the elaborate breeding methods employed in experimental organisms. For example, the simple relation that, for dominant genes which are not lethal to the fetus but render their bearers incapable of reproduction,

the frequency of individuals manifesting the disorder is exactly double the mutation frequency, allows us to derive the mutation frequency of all of these genes which can be definitely recognized. This has been done, with consistent results, in some cases approaching these conditions. However, we must make the qualification that there has as yet been no proof that just one gene locus was involved in the case of any of these abnormalities, rather than a group of scattered loci whose mutations produced similar phenotypic effects, as in the case of the *minute bristle* condition in Drosophila.

Similar considerations apply for any gene of which a fairly good estimate of the reproductive capacity of the individual exhibiting it may be made, as in the case of highly detrimental conditions like hemophilia. For in such cases, the amount of reappearance of the mutant in the population, caused by its own reproduction, can be allowed for, and then it is again possible to determine the mutation frequency of the gene from the frequency with which the given character is present in the population. It is thus evident that, both for mutation rate studies in themselves and, through them, for conclusions regarding population genetics, it is imperative to have more exact data on the actually existing frequencies of the various ascertainable hereditary ailments. At the same time, estimates should be sought of the amount of detriment which these ailments entail in reproduction.

The influence on the mutation rate of various factors, such as radiation, aging, or chemicals, is hardly a subject that can be investigated profitably in human material. It is a matter of great ultimate importance for human beings however, and so it is necessary, in the interests of our knowledge of human genetic processes, to conduct such studies on related, i.e., mammalian material. Such material must also be used for obtaining frequency distributions of the relative numbers of mutations of different types, since in man the types of mutations suitable for mutation frequency studies are as we have seen so much more limited. If then our results with different experimental organisms turn out to be in satisfactory agreement, we may fairly infer that a similar situation exists in man, and base our calculations accordingly. Of course there is no reason, even now, to doubt that such generally acting mutagens as high-energy radiation and mustard gas are effective in man, and, in the case of radiation, that the effect is proportional to dose. The question however is, what is the order of magnitude of the effect for a given dose. This we must know, before we can forecast quantitatively to just what extent the techniques that are being used will be reflected in the well-being of future generations.

X. THE MAPPING OF THE HUMAN GERM PLASM

So-called "formal genetics", of the type carried on extensively on Drosophila and maize in the early days—the making of maps of the chrososomes, would seem an almost utopian objective for human material. Yet a fair number of

loci have already been approximately mapped along the sex chromosomes of man. And, with special statistical aids applicable to the data from small families in which the original gene arrangements were unknown, probable cases of linkage, involving crossing-over, have been discovered in other chromosomes. The recent findings of so many identifiable hereditary antigens will greatly facilitate such work and it is not unlikely that, if the number of definitely recognizable characters increases rapidly, there will, even in our generation, be a real opportunity for the construction of genetic maps. In these, the landmarks formed by the good "marker" genes should in turn facilitate the finding and locating of genes that would otherwise be harder to follow.

There is probably little of immediate practical value soon to be derived from such studies. However, it should be beneath the dignity of man to be content to remain forever ignorant of such basic facts of his own structure. Moreover, as more and more information of this sort is gained, it should eventually be of use in allowing us to follow the transmission of chromosomes and chromosome parts and so even to deduce, to some extent, the pathways of inheritance of those genes whose effects, for whatever reason, could not individually have been spotted by themselves. Thus, if a recessive lethal had been known to be closely linked with a given antigen, and the antigen was found to be received by a given offspring, it could be taken as highly probable that the lethal had been received as well.[2]

With chromosome mapping there also goes the possibility of studying such genetically observable aspects of chromosome behavior as crossing over, nondisjunction and structural change. These too must some day become objects of genetic research, even in human beings. Long before such genetic data can become available, however, there is bound to be a great increase in cytological knowledge, and it is unnecessary at this stage of genetics to have to explain in what numerous ways cytology can aid in interpreting the results of breeding. From the work of Winiwarter and of Painter on human chromosomes as seen under the microscope to the recent work of Schultz & St. Lawrence (1949) is a long stride, and this achievement gives promise of providing cytological maps long before the corresponding genetic ones are available. Moreover, we must not forget that, through still newer techniques of observation, the resolution may be still further increased. And, with the use of tissue culture methods, even experimental cytology of various kinds becomes possible with human material, as was demonstrated by Shiwago in his *in vitro* studies of the chromosomes in human epidermal cells and leucocytes.

[2] The eventual applicability of this type of inference in human inheritance was pointed out by Altenburg and the author (1920) in their account of the inheritance of *truncate wing* in Drosophila—the first case in which the methods of "markers", as it is now called, was used in the analysis of a multiple gene situation (see pp. 51–52 and 59 of that article).

XI. POLICIES OF THIS JOURNAL

It is hoped that the above very rambling discussion will at least show how very multitudinous and far reaching the subject of human genetics is, and how requisite it is that the work in it be carried out by persons highly proficient in the particular field concerned. They should at the same time be well versed in general genetics, in its modern form, or, failing this, work in close collaboration with persons who are primarily geneticists. Here we are faced with the deplorable situation that, with relatively few exceptions, genetics is neither a required subject for medical men, psychologists, anthropologists nor students of the social sciences, nor even taught in medical schools themselves. For this reason this great world of problems, so intriguing yet so difficult and so little explored, must for the present be left to a body of trained personnel which is quite inadequate in numbers. If however they emphasize quality rather than quantity of work in their attack, their results will in time convince the less initiated of the importance and richness of the subject in relation to all branches of medicine and of human biology.

The recognition consequent upon these advances will gradually lead to measures for the better training of the younger generation, and as a result the cadres involved, and the volume of their work, will in time become greatly augmented. Thus we may confidently look forward to a day, not many decades hence, when, in place of one journal to cover the whole vast group of subjects herein comprised, there will be a considerable group of periodicals, each devoted to its own special field. Until that day comes, however, the present journal must remain so diffuse in its range that only a portion of its articles will be intelligible to any individual reader. If we insisted on a general intelligibility, we should have to sacrifice that technical quality and significance for which we stand to the interests of a shallow popularization which could best be carried on by other organs. At the same time, however, it should be the duty of the journal also to include some more general articles, which interpret one field of work for the benefit of specialists in other fields, and to make even its more technical articles as generally understandable as is consistent with a high level of scientific contributions.

For those insufficiently versed in general genetics who would read this journal it would not be feasible for our authors continually to go out of their way to explain established principles and operations. They should avoid, however, the older-style treatments which, instead of stressing methods, precautions and general principles, attempt to present compendia of the voluminous material piled up by uncritical pedigree collectors. Similarly, in so far as the more specialized medical and other human fields are involved, we must assume a general familiarity with any such subject on the part of the reader of any article dealing with it. We would remind those who have hitherto regarded genetics as "too

technical" that there are various excellent introductory text books of general genetics, such as those of Altenburg (1946), Sinnott and Dunn (1939), and Snyder (1946), to mention but three, a reading of any one of which should be sufficient to put them abreast of the genetic terms and concepts used in the pages to follow. If they prefer, they could turn instead, or in addition, to some introductory volumes dealing more specifically with human heredity, such as those provided by Roberts (1940) or by Crew (1947).

The question will be asked, what attitude will our society and our journal take towards the presentation of eugenic topics? We must answer, first, that our primary purpose is research in human genetics, the laying of a firm basis of methodology and of factual knowledge. This knowledge is as much an end in itself as any other knowledge—or even more so, if we admit that "the proper study of mankind is man".

However, we recognize also that this knowledge *may* and—if mankind continues to advance—*will* eventually be put to use, and this realization certainly acts to strengthen our motivations in the prosecution of these studies. Now, one series of uses of the knowledge (also sufficient as an end in itself), is the far greater degree of control over our present somatic constitutions and reactions, through improvements in medical methods and in general ways of life, which must follow in the train of such knowledge. This bettered control would be an inevitable consequence, first, of that deeper insight into normal mechanisms which is to be gained through "physiological genetics" (including here also its psychological side), and second, of the increased ability to detect detrimental deviations while they are still latent, to guard against their development, and to treat them if they have occurred. Conversely, latent qualities of a desirable nature could be better spotted and made use of. In all these way genetics comes to the service of organisms without interfering with the genetic bases underlying them.

All the above is not to say that these are the only ways in which genetics can be applied. There remains, not least, the question of the guidance of reproduction away from genetically less favorable and in the direction of more favorable paths, in other words, the question of eugenics. As we have pointed out above, this whole subject has fallen into disrepute because it has been so perverted by unscientific propagandists and cranks, with hastily conceived remedies which they desired to foist upon the community as substitutes for social measures with which they did not agree. We do not wish this kind of eugenics. Neither would it serve the advancement of human genetics to have our society and journal become organs of agitation. It is to the detriment of research for it to have to use the same channels as those for propaganda, even if that propaganda is of a desirable kind.

At the same time, we must be careful not to be panicked into throwing away the wheat with the chaff. It is the present writer's considered opinion that eugenics, in the better sense of the term, "the social direction of human

evolution," is a most profound and important subject and that it will in due time be worked on seriously, not in a spirit of ill-considered partisanship and prejudice, but in one of scientific objectivity combined with social consciousness. Moreover, the effective recognition of either especially detrimental or especially valuable genes is by no means so impossible as some objectors have claimed—if it were, no natural or artificial selection could ever have succeeded. But the heat and the misunderstandings of present political controversy, and the prejudices rampant in all existing societies, make very bad soil for the development of sound eugenic policies at the present time.

For the above reason we can as scientists best pave the way for a proper approach to such applications by devoting our main present energies to the building up of an ever more thorough understanding of the genetic basis of mankind, of its transmission, its variations, its modes of expression when in combination with different environmental factors, and the changes which it undergoes in populations that are subject to different systems of breeding, selective conditions, mutagenic influences, etc. As these topics are dealt with, it should not be held amiss if the investigator utilizes the occasion to draw lessons concerning the effect of this or that situation on the human genotype, and concerning possible means of avoiding ill effects or gaining advantages for it. In this way, gradually, the basis may be laid for a calmer, more detatched and scientific consideration of these topics than has heretofore been possible.

It is to be hoped that, by the time this ripening has occurred, the racial and class biases so rampant in most societies today will in considerable measure have been smoothed out. This will allow attention in the subject of human heredity to be drawn away from those conspicuous but superficial group differences which for most people now loom so important, and facilitate the more intensive study of the genetic differences within populations. For present information gives good ground for the conclusion that these individual differences, on the whole, concern far more important characteristics, and are, on the average, of much greater magnitude, than the differences between the averages of present racial or economic groups. This realization should make possible a far more unbiased treatment of the whole matter, one in which unthinking group pressures have been reduced to a minimum. Meanwhile, let us bend our main efforts to the increase of basic knowledge.

Whatever may be the reader's opinions on the subject of eugenics, we invite him to participate in the building up of this journal, if only he is willing and able to join in the development of the factual and methodological basis of human genetic study. Medicine in all its branches is overflowing with genetic problems open to investigation, and many of them can be tackled in the course of the day's work, without the practitioner going far out of his way. Ophthalmology, pediatrics, orthopedics, immunology, dermatology, neurology—what field concerned with medicine or, for that matter, with the so-called normal man, can be named in which interesting and important deviations of a familial nature

are not to be found? These must be studied, however, not with the slip-shod casualness characteristic of the earlier reports, if they are to serve as stepping stones to a more integrated knowledge of the foundations of the organism. The investigations should be carried out with the aid of the best awareness of modern genetic principles and possibilities, and with the best statistical tools that are available. In this way we will come at last to know ourselves.

Although we hope our own *Journal* will serve as a center in North America for the bringing together of such studies, we believe it to be desirable for those American journals which from time to time carry articles on human genetics to continue to do so. The cleavage of subjects should not be absolute, and it is well for those whose center of interest is somewhat different from ours to have these opportunities of remaining aware of our own field. The numerous scattered articles of more or less genetic interest which appear in medical journals are on the whole well placed there. They will make it easier for the specialized genetic journals of the respective fields to take shape when the time is ripe. The journals dealing with general and experimental genetics, and more particularly *Genetics* and the *Journal of Heredity*, which have published many valuable papers on human material, will, it is hoped, continue to invite such papers. We also wish to acknowledge our appreciation of the important work on human genetics published abroad in such periodicals as the *Annals of Eugenics*, *Archiv der Julius Klaus-Stiftung*, *Genetica*, *Hereditas*, *Heredity*, and the *Journal of Genetics*. Most particularly we send our greetings to our older brother, *Acta Genetica et Statistica Medica*, whose first number appeared a year ago. This journal is under the able editorship of three leading geneticists who are at the same time medical men, Gunnar Dahlberg, Head of the State Institute for Human Genetics at Uppsala, editor-in-chief, Tage Kemp, Director of the University Institute of Human Genetics at Copenhagen, and Otto L. Mohr, Rector of Oslo University. It is devoted to the same purpose as ours, and should be followed with especial interest by our readers.

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