

1941

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Recommended Citation

Stiles, Karl A. (1941) "Recent Advances in Human Genetics - Paper Presented at the Fifty-Fifth Annual Meeting," *Proceedings of the Iowa Academy of Science*: Vol. 48: No. 1, Article 9.
Available at: <https://scholarworks.uni.edu/pias/vol48/iss1/9>

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RECENT ADVANCES IN HUMAN GENETICS

KARL A. STILES

Advances in human genetics are taking place on several fronts; and despite the diversity of attacks on the problems involved, the author of this paper will limit himself to a few areas in which he and his students have either done some research or have a special interest.

Every year some advances are being made in our knowledge of the inheritance of physical traits and an attempt will be made to briefly indicate some of the achievements and problems encountered in this field of study. The writer has been making a number of studies of the inheritance of physical traits. One unpublished study has to do with abnormalities of the hands and feet. Although in some members of the family the abnormal hands and feet resemble a skeletal defect which has been termed "lobster-claw", yet there are many variants which certainly could not be so classified. In fact, a careful review of the literature on hereditary malformations does not reveal a case exactly like this one. It was possible to study seven generations of this family; the skeletal anomaly first appeared in the third generation, and it can be postulated that the mutation arose in this generation. One of the interesting features of this study is the wide range of variation showing in the hands which have long thumbs, no thumbs, crooked thumbs, no fingernails, cleft fingernails, small fingernails and missing fingers. The feet do not show quite as much variation as the hands, the feet being more nearly alike.

In the five generations of forty-three people through which this trait was traced, only fifteen exhibit a deformity. Because this character appears regularly in those judged to be heterozygous for the defect it appears to be inherited as a dominant trait.

Pitted ear is another human physical trait which has recently been the subject of a great deal of research. This is a relatively rare human anomaly in which there is a pit of greater or lesser size in the skin in the proximal end of the upper part of the helix. The investigation of this character involved a study of three different families, designated as families A, B, and C, but not known to be related. The pedigrees of these three different families show that 24 individuals exhibit pitted ear. This trait is usually unilateral in its expression in all these families and appears about as often in one ear as in the other. This lack of

bilateral symmetry for an inherited trait remains one of the unsolved problems of biology, although attempts have been made to explain the inheritance of such an asymmetrical condition on both genetical and environmental grounds. It may well be that both of these forces influence this type of development.

The pedigrees of pitted ear indicate that the inheritance of this trait cannot be as simply explained as the malformed hands and feet just discussed. Pitted ear has been reported in the literature inherited as a simple dominant trait, and the first two pedigrees which we studied both lent themselves to this interpretation; however, the pedigree of family A, which proved to be the most extensive and instructive of all, does not permit of such a simple mode of inheritance. In simple dominance it is characteristic for the trait to appear in every generation but that is not true in the case of this family. Therefore, it is concluded that pitted ear is inherited as an irregular dominant rather than as a simple dominant.

As the studies of human heredity have progressed in the author's laboratory all of those assisting in the investigations have been impressed with the number of physical traits which seem to be inherited in a very complex manner. Earlier reports of the inheritance of human traits usually concluded by stating that the inheritance was of a relatively simple nature. It is suspected that there has been a strong tendency among those interested in human heredity to report only those characters which can be explained easily by known genetical laws. As one goes through the literature on human traits he can scarcely avoid being impressed by the large number of traits which are considered to have a simple type of inheritance. While it is doubtless true that some human characters do appear to be so simply inherited, it can well be suspected that if all cases had been reported, there would have been anything but complete uniformity in the mode of inheritance.

In view of the fact that the problems of human heredity do not often lend themselves to the experimental approach so readily available to other investigators of genetical problems, it is believed that our knowledge of human genetics will be most rapidly advanced, not by reporting isolated cases that can be easily analyzed, but rather by reporting all possible types of heredity whether they lend themselves to a simple explanation or not. It is encouraging to report that there is evidence that this is being done at the present time more than ever before.

Recognition of the fact that physiological characters are as much inherited as those of a physical nature has led to the development of a whole new field termed physiological genetics. When it is fully realized that the differences in chemistry found among men may be the result of hereditary differences, a new significance to the importance of human genetics is indicated.

Differences in the senses, such as taste and smell; mental characters; tendencies to develop non-infective diseases as well as susceptibility to infective diseases are all examples of physiological traits known to be hereditary. Many diseases known to medicine have a definite hereditary background. Keeler has listed eighty-two of these diseases. As a result of the accumulation of facts in this genetical area, a new branch of genetics called medical genetics is rapidly developing. The medical school of Ohio State University has a course in medical genetics; Duke medical school, only this last winter, organized a similar course; and the University of Minnesota Medical School now lists genetics as a required pre-medical subject. A book on medical genetics by Dr. L. H. Snyder of Ohio State University will be off the press in a few weeks; Dr. Clyde E. Keeler of the Wistar Institute has also written a book on medical genetics which is still in manuscript form; and Dr. M. D. Schwitzer of Cornell Medical College has been working for several years on a monograph of medical genetics. Within the last few months, the University of Michigan has established a department of human heredity for the purpose of studying the inheritance of physical defects and tendencies to disease in human beings. The new department will be closely associated with the medical school. Although one or two laboratories of this kind have been established in Europe, none has hitherto been founded in this country.

This activity in the field of medical genetics has been mentioned to emphasize its rapidly growing importance. Just to indicate one line of investigation in this field tuberculosis will be quickly considered. Studies by Wright and Lewis (1921) on inheritance factors in guinea pigs as well as those more recently by Lurie (1938) on the rabbit indicate that certain stocks are inherently more susceptible to infection than others. This is precisely what one would expect on apriori grounds, for if animals inherit different kinds of chemistry, and one type of chemistry provides an unfavorable soil for the growth of the tuberculosis organism whereas another provides a favorable soil, we have the basis for susceptible and non susceptible stocks.

In man, Pearl (1936) reports studies on the frequency of tuberculosis in a total of 564 matings producing 2,480 offspring. His investigations show that when both parents have tuberculosis the child is about 4.3 times as likely to develop tuberculosis as when neither parent is affected. When one parent is affected the child is about 1.6 times as likely to have it as when neither parent is tuberculous. One might conclude that these differences were the result of environmental factors but Pearl concludes from his analysis that in the cases investigated the differences in heredity are the only factors which play a significant role in the result.

The author and one of his students, Thomas Stewart, have just completed a study of the susceptibility of a human family to tuberculosis. While we do not wish to be as dogmatic in our statement of the case for heredity as some have been; nevertheless Mr. Stewart and the writer conclude from their study that while one may not be justified in proposing any exact analysis of the mode of inheritance, the high incidence of the disease, the consistency of the place of infection, and the acuteness of the infection make it seem highly probable that in this family, the natural constitutional qualities (diathesis) have been of considerable importance in determining the development of the disease and its character after an infection occurs.

Many facts from the various studies now being reported of the role of heredity in disease point to one thing, namely, that heredity plays a very important part in the development of various infectious diseases.

Medical genetics in relation to mental deficiency is making progress. Some of the recent studies in relation to mental deficiencies include studies of specific organic deficiencies, familial deficiencies, and genetic deficiencies in relation to mental illness. These human deficiencies will be considered in the order named.

Specific organic deficiencies may always or only occasionally be associated with mental deficiency. Genetic deficiencies occasionally found associated with or existing independently of mental deficiency may equally be manifestations of an organic defect and might thus also be included in the general field of human deficiency. A very extensive study of inherited biochemical deficiencies found associated with mental defect has been made by Jervis (1937, 1937a) who lists among these deficiencies phenylpyruvic oligophrenia, a type of mental defect in which the patient shows serious subnormal mentality. In the two hundred cases

studied by Jervis two-thirds of the patients were at the idiot and one-third at the imbecile levels. The biochemical basis for phenylpyruvic oligophrenia is an inborn failure of the body to oxidize phenylpyruvic acid which appears to be determined by an autosomal recessive gene (Jervis, 1939, 1939a). Other biochemical deficiencies are amaurotic idiocy (Tay-Sachs' Disease), which is caused by a genetically determined inability of the body to oxidize the lipid sphingomelin; certain inherited degenerative basal ganglion lesions; glycogenosis, an inherited inability to properly metabolize carbohydrates; and tubero-sclerosis, in which a genetic factor is probably operative.

Sachs (1936), Davidenkov (1940), Murphy (1940), and others have contributed studies of genetic deficiencies especially in relation to the areas of general medicine, neurology, and mental defect. In many, if not all instances, genetic deficiencies may be thought of as being responsible for establishing the organic basis for a large percentage of the mental or behavior deficiencies in man.

Familial deficiencies are inherited deficiencies which are found in certain family groups in which no constitutional features showing disease have been determined. The prominent clinical features of the familial group are seen in general physical, mental and social inadequacies of the group as a whole. The deficiencies appearing within the group may be an expression of a generalized deficiency of the individual, or of such specific types of defect as may appear within any human group. The problem of familial deficiencies is of great social significance since such deficiencies probably represent a large percentage of the defectives produced by the borderline and subcultural groups.

In the field of mental deficiency it has been customary on the basis of etiology to classify all cases into primary and secondary deficiency. Secondary deficiency including all cases known to have resulted from toxic or traumatic conditions, primary deficiency, those for whom the etiology is of hereditary or unknown origin.

Tredgold (1937) summarizing the studies of several authorities as to the frequency of primary defectives, has indicated that estimates of incidence of primary deficiency are, on the average, 70% to 90%. Mayerson (1936) and others have reported that genetics plays an important role in this group. Penrose (1934) has observed that genetic factors operated in 91% of his cases and that environmental factors were present in 71%. These figures indi-

cate that there is an overlap of hereditary and environmental factors. Penrose (1938) has reported that disease conditions associated with hereditary mental defect have been best demonstrated in idiots and imbeciles and that less is known about genetic factors in higher grades. However, it must be recognized that in all grades of defect heredity may play a part, but the degree of the influence of the hereditary factors may be different in various grades. He points out that the defects in idiots and imbeciles are often recessively determined or are due to a new mutation. Thus he explains why these groups have not so generally been considered the result of bad heredity as the higher grades of mental defectives, who, like normal persons, owe their mental grade to the interaction of dominant additive genes.

Recent studies of the genetics of mental illnesses extends the area of human deficiency well into the problems of mental illness. Duncan, Penrose and Turnbull (1936) have called attention to the frequency of mental subnormality in the manic-depressive illnesses, the similarity of symptoms, the course and prognosis of these disorders in normal and subnormal groups, and the tendency to emotional instability exhibited by many defectives, all suggesting a close association between the two conditions. They state that in some cases a manic-depressive psychosis may be a manifestation of mental defect. However, they indicate that the defect in the manic may represent an impairment in the generating mechanisms of emotion, even in the terms of over production of emotion and lack of governing factors. At least in the manic-depressive the defect lies primarily in instability of mood.

Slater has postulated a specific dominant factor in the manic-depressive states and Rosanoff (1935) has indicated that there is a hereditary basis for most of the manic-depressive psychoses.

A great deal of evidence that schizophrenia is frequently associated with genetic factors is presented by Kallman (1938) who states that "the probable incidence of schizophrenia among the offspring of schizophrenics is nineteen times greater than in the general population. Even the grandchildren, nephews and nieces are, in their turn, about five times as likely as the normal average person to become schizoid." Pollock, Malzberg and Fuller (1940) also agree that genetic factors play a definite part in the etiology of both manic-depressive and schizophrenic psychoses.

Therefore, defective heredity which is one form of human deficiency, provides a biological basis for more closely relating the

field of mental deficiency to many aspects of the medical and social sciences.

A paper on recent advances in human genetics would not be complete without something being said about the inheritance of blood groups. Some emphasis, it will be noted, has been placed on the inheritance of various types of chemistry in man, and one of the most striking evidences of this is the blood groups. It is rather common knowledge that the blood of the human body based on its chemical reactions is classified into different groups. It is generally known that the reason for typing blood before a blood transfusion is to make certain that incompatible bloods are not mixed.

As an indication of Germany efficiency, it has been pointed out that the Nazi troops which invaded France were so organized that all the men of each unit belonged to the same blood group, so that blood transfusions could be made on the battlefield without the delay of blood tests. And it has recently been reported that the United States Marines are being divided into platoons according to their blood types.

Dr. Landsteiner first discovered in 1900 the simple O, A, B, and AB blood groups; following that the M, then N, and MN, and blood reactions were found by Landsteiner and Levine in 1928. Recently Landsteiner and Levine have added sub-groups A_1 and A_2 which have been used in medico-legal cases. There is also the possibility that an A_3 sub-group may exist. And studies are in progress which may reveal further subgroups.

The blood groups have undisputed value in such matters as the identification of criminals, and the accidental exchange of babies in hospitals. However, a new application of medico-genetic knowledge is the employment of blood group tests as evidence of non-paternity in cases of illegitimacy. It is possible through a knowledge of the inheritance of blood groups to scientifically prove in many cases that the supposed father involved in an illegitimacy case could not be the father of the child in question.

In 4818 cases recorded from all countries in recent years since the addition of the M-N tests, there have been 834 exclusions (17.3%). Since if all accused men were innocent there would be about 33% exclusion, this would indicate that of the accused fathers only half were the true fathers. The procedure of permitting the woman in the case to name the father doubtless results in considerable injustice. Blood tests can help to correct this, and the fear of being charged with perjury should tend to

lessen the number of false accusations. There are more than 1000 cases of illegitimacy in New York City alone which come before the Court each year.

Ohio, Wisconsin, New Jersey, and New York states now have laws requiring that the results of blood-group tests be accepted in their courts as evidence in cases of illegitimacy. However, in the other states of the American Union in which the exonerating results of blood tests are not required by statute to be accepted as evidence in cases of illegitimacy, the acceptance of such tests as evidence is naturally at the direction of the local judges hearing the particular cases.

Because it is believed that medico-genetic knowledge should be applied to human well being wherever possible, it is sincerely hoped that the State of Iowa will soon have a statute requiring the acceptance of blood-group tests in cases of illegitimacy. There is good reason for believing that it is only a matter of time before every state in the union will have such a law and the writer would like to see Iowa a leader rather than a follower in this new application of genetics to social welfare.

The author wishes to express his sincere appreciation to Doctor Edward J. Humphreys, Director of Research, Letchworth Village, Thiells, New York, for the use of material on the inheritance of mental deficiencies.

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