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SYMPOSIUM ON CONGENITAL METABOLIC DISEASE*

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GENETIC ASPECTS OF CONGENITAL METABOLIC DISEASE

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Most of the conditions to be considered in this symposium share one feature: their genetic origin. It could be profitable then to outline some of the principles of gene action and of the characteristics of genetic disease which will apply equally to all of the disorders to be reviewed.

To begin, a definition of gene action is offered. This must be an empirical one since it is not known, with any precision, what a gene is. However, it is known that the genetic material provides the most basic mechanism for homeostasis, ensuring that offspring will exhibit the characteristics of the parent, whether the offspring be daughter cells or human beings. This is accomplished by means of control over the formation and design of the vital molecules of the organism; those molecules which in their turn control its intricate and interrelated metabolic functions. It is for the most part these metabolic functions which we attempt to measure in the elucidation of gene action in disease, and it will be seen in the ensuing discussions that only rarely is one able to make any direct assessment of the physicochemical properties of these molecules which bear a specific relationship to the gene.

Much more commonly, a measurement is made of some form of activity of such substances, and a stepwise elucidation may be accomplished of the secondary effects which are consequent upon alterations in reaction rates or reaction failure. It is, in general, these secondary, tertiary, or consequential effects which are most easily measured, and which are the overt expressions of the disease. The principle illustrated here is, what a gene is said to do, depends upon which function we measure.

How does one make a diagnosis of single-

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gene etiology of any characteristic? Most commonly the family history is examined seeking aggregations of affected individuals. Sometimes one finds parent and child combinations, or even people who show the characteristic under study in several generations, or in other situations one finds normal parents, but two or more affected persons in a sibship. If the distribution is of the former type, we say the gene is dominant, if of the latter, it is recessive.

A dominant gene is one which expresses itself in the heterozygote, while a recessive one can do so only in the homozygote. But expresses itself how? Here again everything depends upon which measurement is made. Current thinking indicates that if we knew how to make some measurement directly related to the gene action, no gene would show dominance. This is known to be true of the genes governing the blood-group antigens and the hemoglobin variants, but is not true of the genes whose measurable functions are less proximal to their primary actions.

This may be illustrated by referring to some work carried out on the pathogenesis of familial, nonhemolytic jaundice. These patients become jaundiced immediately after birth and remain so as long as they live. There is no hemolysis or liver damage. All the bilirubin in the plasma of these patients is indirect, and since bilirubin is excreted as a glucuronic acid conjugate, it was supposed that their defect might be in the capability to make such a conjugate.[1] This was tested in two such patients and many of their relatives, through determining their capacity to make another type of glucuronic acid conjugate, using sodium salicylate as the test substance. It was found that the ability of the jaundiced children to carry out this function, when compared with suitable controls, was very poor. Their parents, and some of their sibs also showed some impairment, but this was not so severe as in the fully affected patients.[2]

If these families are considered with reference to jaundice alone, it is found that all the affected persons are in one generation, and this, together with the observation of consanguineous parents, suggests the segregation of a recessive gene. But when the distribution of affected persons is considered in regard to ability to make glucuronic acid conjugates, there are persons in three generations who show some degree of alteration. Therefore it was reasonable to think of the gene as one which shows incomplete dominance; that is, a greater degree of expression in the homozygote, and a lesser degree in the heterozygote.

This matter of examining the relations may indeed be important, if one would make a genetic diagnosis at all. This point may be illustrated by referring to some work on an enzymatic defect in which the erythrocytes of certain individuals are unusually susceptible to hemolysis, when exposed to a number of substances: Primaquine, phenylhydrazine, the metabolites of naphthalene, nitrofurazone, vitamin K, some factor in fava beans, and others.[3-5] All of these substances have been known to cause hemolytic anemia. In these erythrocytes there is reduced activity of glucose-6-phosphate dehydrogenase, an enzyme which provides reduced triphosphopyridine nucleotide (TPN), a substance which acts as a substrate in the reversible oxidation and reduction of glutathione.[6] In the absence of reduced TPN, the reduced glutathione in the erythrocyte decreases markedly in the presence of the agents mentioned, and hemolysis ensues.

In-vitro testing methods have been devised so that individuals who exhibit this defect and who have never had hemolytic anemia may be detected.[3,6] Studies using such methods have shown that this is an heritable disorder associated with a sex-linked, incompletely dominant gene.[5]

The family distributions would be, of course, entirely different depending upon whether based on hemolytic anemia or the results of the in-vitro tests. Indeed, if hemolytic anemia is the criterion used, there might be but one affected person in the family, and no genetic etiology is suggested. The principle illustrated here is

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that the kind of family distribution seen, and the phenomenon of dominance, depend upon what measurements are made, and whether they are made or not.

It is well known that all examples of any genetic disorder are not exactly alike. Genes function, not in a vacuum, but in a cell, that is as a part of the metabolic system of the cell. As such, they are subject to the effects of other genes as well as of the external environment. Now since the total genetic composition of all individuals is unique, it should not be expected that any two persons possessing the same gene will be quite alike. This is then, one source of variation. There are others.

Variations may be due to the fact that representatives of the genetic material capable of occupying a particular site in the chromosome, and responsible for a particular process, may differ and produce different effects. For example the genes controlling the production of hemoglobins A, S, and D are all hemoglobin genes, and all exist at the same locus, but the clinical differences associated with various combinations of these genes in individuals are well known. Such a multiplicity of genes controlling one function and producing measurable differences are well known in microbiology, and doubtless there are many more such gene sets in human populations than are now recognized.

Finally, variations between apparently similar cases may result from the presence of wholly dissimilar genes controlling dissimilar biochemical functions. For example, it is known that there are three blocks in the biosynthesis of thyroid hormone, all of which cause a similar picture of goitrous cretinism.[7] Despite the superficial likenesses between all the cases, it is quite unlikely that entirely different metabolic steps could be controlled by genes at the same locus. The point illustrated here is that biochemical differences, though sometimes slight, are usually the reflection of genetic differences, and attempts to seek these out and to place the defect in its proper category are necessary so that treatment, if any, may be appropriate.

Much has been made of consanguinity in genetic disease, especially in those disorders due to recessive genes. The fact that the incidence of consanguineous matings among the parents of patients with such disorders is greater than that found in the general population is a property of the infrequency of the genes involved. That is, first cousins are far more likely to share a rare gene than are randomly mated couples, assuming that one of their common grandparents possessed it. The number of consanguineous matings to be expected among the parents of a group of patients with a disorder due to a recessive gene can be calculated if one knows the frequency of the gene and the incidence of marriage of related couples in the general population. It is clear that the frequency of first-cousin marriage to be found among the parents of patients varies inversely with the disease incidence, and directly with that for the population at large. Recent estimates of the incidence of first-cousin matings in the general population are about one-tenth those made before the late war. This means that such matings can be expected in the disorders under question with less frequency than formerly. When found, however, the phenomenon remains a valuable indication of genetic etiology.

In summary, the distribution of genes in families or in a population are governed by calculable probabilities. The apparent inconsistencies, variations, and the phenomenon of dominance are not due to a capricious nature, but rather to the remarkable capabilities of an organism to adapt itself to a metabolic aberration, to variations in the genetic material itself, and to our relative inability to make appropriate measurements.

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PHENYLPYRUVIC OLIGOPHRENIA

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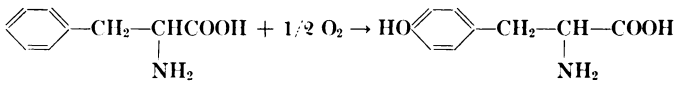
PHENYLPYRUVIC OLIGOPHRENIA is an inherited disease characterized by mental deficiency and urinary excretion of phenylpyruvic acid.* Patients with this disorder are unable to carry out a particular enzymatic step in the metabolism of phenylalanine; this reaction is the conversion of phenylalanine to tyrosine:



Phenylalanine Tyrosine

These individuals therefore appear to be human mutants, analogous to mutants such as those which have been induced in Neurospora crassa and Escherichia coli. However, in contrast to the enzymatic defect in certain mutant microorganisms, which is often recognizable in terms of a specific nutritional requirement, the metabolic block in phenylpyruvic oligophrenia is associated with a relatively complex picture.

Phenylpyruvic oligophrenia is a recessive trait; it has been estimated that the gene is carried by approximately 0.5 to 1% of the population. Although most patients with this disease exhibit markedly reduced mental capacity, a few show only moderate retardation. A high percentage of patients with phenylketonuria have fair skin, blue eyes and blond hair. About 25% of patients with phenylpyruvic oligophrenia have experienced seizures, and many of these patients have been reported to show abnormal electroencephalograms. Several necropsies have revealed evidence of abnormal myelination; on the other hand, other postmortem studies have been described as essentially negative.

Patients with phenylpyruvic oligophrenia may excrete as much as 1 to 2 gm each of phenylpyruvic acid[2, 6–8] and phenyllactic acid[2, 9, 10] per day; these compounds are not usually detectable in normal urine (Fig. 1). Urinary excretion of phenylalanine, normally no more than about 30 mg/day, may be as high as 1 gm/day in phenylpyruvic oligophrenia.[2, 6, 11] Phenylacetylglutamine,

* Phenylpyruvic oligophrenia (phenylketonuria) was first described by Følling in 1934.[1] Since this time, more than 300 cases have been reported in the literature. Reviews have appeared describing the incidence,[2, 3] genetic considerations,[2, 3] physical and mental findings,[2–5] and pathologic studies.[2, 3]

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