FREQUENCY OF GENETIC POLYMORPHISM:
IMPLICATIONS FOR MENTAL DISEASE

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The total number of genes occurring in the cells of higher animal organisms, such as man, is not accurately known. The figure most often quoted is 50,000, but this is no more than a slightly educated guess. The total amount of DNA contained in the nucleus would account for something like one hundred times that number of genes, but a large amount of the DNA, probably most of it, does not carry genetic information.

The function of most genes, as far as is known, is to determine the specific structure of the various proteins; these proteins are mainly enzymes and the structural proteins making up the supporting materials of membranes, microtubules, etc. Other genes, perhaps a few, perhaps a great many, are involved in regulating the activity of those mentioned above; still others determine the structure of various ribonucleic acids that are a part of the machinery of protein assembly.

A change in a gene (mutation) may have one or more of the following effects on the gene product:

1. No change (synonymous mutation)
2. Altered structure but normal activity
3. Altered activity (more, less, none)
4. Altered amount of protein (more, less, none)

Mutants have been a major tool of the geneticist ever since the inception of the science with Mendel. Until recently, mutations were studied by analysis of their effects on the organism, called
phenotypic effects. The phenotype is the outward manifestation of the gene. Thus, such phenotypic traits could be studied as eye color, shape of the wing, etc. In man, many of the phenotypic effects of most interest and considerable study have been those that produce disease. All such mutants obviously must affect activity or function of the gene products, since they produce phenotypic effects.

A major feature of any species is genetic variability. Within any species, such as Homo sapiens, there is a high degree of genetic homogeneity: all men look very much alike and are easily distinguishable from any other species. On the other hand, there is much obvious difference. Geneticists have long wondered and long been trying to find out whether most of the genes within a species are mostly alike or mostly different. Methods available until recently have not been very useful for answering the question, but the general supposition has been that most genes in man, or in any single species, are mostly alike. A subquestion of the general question has been, how many "deleterious" (hereditary disease-transmitting) genes does a population, and a single individual, carry? It has been estimated that each individual carries about a half-dozen deleterious genes, designated the "genetic load." When an individual mates with a person carrying one of the same defective genes (assuming the genes are recessive), one-fourth of the offspring will be homozygous and will have the disease. Alternatively, if the deleterious gene is dominant and has complete penetrance, every person carrying it will have the disease, and one-half of his offspring will also have it.

As to the amount of genetic variation in the individual and in the population that is not deleterious, transmitting the so-called neutral or partially neutral traits such as hair color, body size, etc., little useful information for accurate estimate has been available in the past.

METHODS AND RESULTS

Recently developed methods (Hunter and Markert 1957) have made such an estimate feasible. These methods are based on direct examination of the gene products, the proteins. They utilize the fact that very minor alterations in protein structure, that is, substitution of a single amino acid by a different one, are frequently detectable by gel electrophoresis (Shaw 1965). This class of mutants must retain at least some of the activity of the enzyme or they could not be detected on the gel. Rapid screening of a relatively large number of individuals and of different enzymes is now possible, using an aqueous extract of a tissue, such as erythrocytes. A small sample (about 10μl) is applied to the electrophoretic medium, usually a starch gel. Following electrophoresis by application of a direct current through the gel for periods of time ranging from one to