GENETICS AND PUBLIC HEALTH

Medical practice has genetic effects of several kinds. By decreasing the severity of hereditary disease, it allows the responsible genes to increase in frequency. Through genetic counseling, it increases or decreases the frequencies of some genes. Through diagnostic and therapeutic radiation, and possibly some forms of chemotherapy, it induces mutations.

There is general agreement among human geneticists that, in our present state of comparative ignorance, genetic counseling should not be dominated by consideration of long-term effects on the population. However, physicians and other counselors should be familiar with the probable effects of increased or relaxed selection against an hereditary disease.

In all cases, a stable equilibrium is reached when the number of genes eliminated by death or reproductive failure equals the number arising by mutation. For a rare dominant, this will happen when the frequency of the disease equals twice the ratio of the mutation rate to the selective disadvantage (The factor of 2 enters because either homologous chromosome may carry the mutant). Thus a disease dependent on a dominant gene with a mutation rate of 1 per 100,000 genes per generation and a net fertility of 90% of normal has a frequency of $2(10^{-5}/.1)$, or 2 per 10,000 persons. We see that:

1. If the mutation rate were permanently doubled, the disease would become twice as frequent, approaching this equilibrium in a few generations.

2. If the net fertility were increased to 95% of normal, the disease would become twice as frequent.

3. If the net fertility were reduced to zero by abstention from reproduction, the frequency would be reduced to twice the mutation rate, or 2 per 100,000 persons.

4. The more harmful the gene, the less effective increased selection would be, because a larger proportion of cases would be due to fresh mutations.

A disease due to a rare sex-linked gene responds to altered selection or mutation almost like a rare dominant, but the equilibrium frequency of the disease in males is 3 times the ratio of the mutation rate to the selective disadvantage, providing the mutation rate is the same in egg and sperm. (The factor of 3 enters because recessive sex-linked genes are exposed to elimination only in males, which have 1/3 of the X chromosomes).

In the case of a rare, completely recessive autosomal gene, equilibrium is reached when the frequency of the disease equals the ratio of the mutation rate to the selective disadvantage. If the frequency of the disease is altered, return to the equilibrium frequency is very slow, because most of the genes are protected in heterozygous carriers. Since the gene frequency is approximately the square root of the disease frequency, only a very small proportion of the genes in the population are due to fresh mutation. For example, with a mutation rate of 1 per 100,000 genes and complete lethality of homozygotes, the disease frequency would be 1 per 100,000 persons and the gene frequency 3 per thousand, which is 300 times greater than the mutation rate. In the long run the same principles hold as for dominant genes, but the immediate effects of increased mutation or altered selection on homozygotes are very small.

For an incompletely recessive gene, the equilibrium frequencies are almost completely determined by the selection on the heterozygote, even if this is very small. For example, if the lethal recessive gene considered above reduced the fitness of the heterozygote by only 1%, the theory for a dominant gene would apply and the gene frequency would be .001, giving a disease frequency of only 1 per million. If heterozygotes could be detected, and would voluntarily reduce their fertility to 90% of normal, the frequency

of the recessive disease would be only 1 per 100,000,000 instead of 1 per 100,000 as calculated for the completely recessive gene. Thus a recessive disease can be eliminated by a small reduction in fertility of heterozygous carriers.

Some physicians and geneticists have expressed concern about the ultimate effects of relaxing selection against an hereditary disease. This concern is based on the fact that at equilibrium the frequency of a dominant or recessive disease is proportional to the ratio of the mutation rate, say u, to the selective disadvantage, s. Therefore the total damage to the population is the sum of (u/s)s, or simply the sum of the mutation rates, and we see that the damage done by a deleterious gene is in the long run independent of how deleterious the gene is. To put this another way, on the average every deleterious gene leads to one genetic death, whether the disease it produces is mild or severe. Therefore, unless each medical advance in the treatment of hereditary disease is accompanied by some slight voluntary reduction in the fertility of carriers, the ultimate effect will be an increasing dependence of the population on medical care, with no reduction in the damage due to genetic disease. Of course the severity of the disease in individual cases would be reduced, but the number of people affected correspondingly increased.

These considerations no longer apply if the disease is completely cured. However, an equilibrium will finally be established between opposing mutation rates, and a large proportion of the population will require the necessary therapy, as diabetics today require insulin or people with myopia require glasses.

Most geneticists regard these prospects with some alarm and believe that ultimately some voluntary reduction in the fertility of certain types of genetic carriers should be encouraged. The above example shows that even a very small fertility reduction is sufficient to lessen the present

frequency of hereditary disease, even if great advances in medical care normalize the survival of affected persons. There is general agreement that it would be premature to encourage such changes in fertility until human genetics has progressed farther.