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MOLECULAR DISEASE

by Linus Pauling

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I like people. I like animals, too—whales and quails, dinosaurs and dodos; I am sorry that I shall never see a living dinosaur or dodo. I like trees; I hope that the giant redwoods will not all be cut down. I like micro-organisms. I like crystals—minerals, such as calcite, rhodochrocite, pyrite, sunyite, lazulite. I do not like to think about the tons of beautiful crystals of galena, azurite, and malachite being mined and smelted to make the lead and copper used in unnecessarily great amounts in our expanding technological civilization.

I believe that Dr. Albert Schweitzer did not go far enough in formulating his principle of reverence for life. We need to have reverence for the whole world, both animate and inanimate.

But I like human beings especially, and I am unhappy that the pool of human germ plasm, which determines the nature of the human race, is deteriorating. The collection of molecules of deoxyribosenucleic acid that will make the next generation of human beings what it will be is not so good as that which determined our character; there are more bad molecules in the collection. The defective genes are now not being eliminated from the pool of human germ plasm so rapidly as in the past, because we have made medical progress and have developed feelings of compassion such as to make it possible for us to permit the individuals who carry the bad genes to have more progeny than in the past. Moreover, defective genes are being manufactured at a greater rate than in the past, because there are new mutagenic agents operating in the world of today.

A good example of a hereditary disease is chondrodystrophy, which causes dwarfism. The gene for chondrodystrophy is dominant. One child in 12,000 who is born suffers from this disease, as a result of his possession of a newly mutated gene. About 80 percent of them die in the first year after birth. It is likely that the incidence of chondrodystrophy is increasing, as a result of the action of the new mutagenic agents in the modern world.

I estimate that in 80 percent of the cases of mental disease there is a strong hereditary factor. There is, of course, also in many cases a significant environmental factor. The hereditary nature of a human being may sometimes be such that he can withstand great environmental stress, whereas for other human beings the hereditary character is such that even the minimum amount of environmental stress is enough to cause serious mental disease. About half the hospital beds in the United States are occupied by mental patients. About ten percent of the American people spend some time during their lives in a mental hospital. I believe that, as more is learned about the molecular basis of mental disease, it will be possible to decrease significantly its incidence.

Sickle-cell anemia was the first disease to be recognized as involving an abnormality of a molecule. A dozen years ago it was thought that all human beings manufacture the same kind of hemoglobin. Then it was discovered that the hemoglobin molecules in the red cells of patients with sickle-cell anemia are different from those in other human beings. The molecule of sickle-cell-anemia hemoglobin has an electric charge differing by two units from that of a molecule of normal adult human hemoglobin.

It was found that the parents of the patients with this disease manufacture both normal adult human hemoglobin and sickle-cell-anemia hemoglobin;

molecules of the two kinds of hemoglobin are present in each red cell of these parents, in about equal amounts. The genetics of sickle-cell anemia is accordingly clear: there are two genes involved in the manufacture of hemoglobin; in normal human beings each of the genes is a gene for normal adult human hemoglobin, and manufactures this hemoglobin, whereas in the sickle-cell-anemia patient both genes are sickle-cell genes, which manufacture sickle-cell-anemia hemoglobin, and in the heterozygotes there is a gene of each kind, and both kinds of hemoglobin are manufactured.

Since the discovery of sickle-cell-anemia hemoglobin ten years ago about 20 different abnormal human hemoglobins have been discovered, associated with many different diseases, previously unrecognized as distinct clinical entities.

The gene abnormality responsible for the disease is evidently a minute one. The hemoglobin molecule consists of two identical parts, each containing about 300 amino-acid residues. It has been shown that all but one of the amino acids are the same in normal adult human hemoglobin and sickle-cell-anemia hemoglobin, and that the 300th, located somewhere in one of the polypeptide chains, is different: it is a residue of valine in sickle-cell-anemia hemoglobin, and of glutamic acid in normal adult human hemoglobin. It is likely that the gene that is involved in the manufacture of the hemoglobins is similarly altered by a small amount, one part in 300, in its mutation from the normal adult human hemoglobin gene to the sickle-cell-anemia hemoglobin gene.

It is only ten years since the molecular basis of sickle-cell anemia and of the other hemoglobinemias was discovered, and the details of the difference in molecular structure of the hemoglobins responsible for the diseases have not yet been worked out. We may hope that as more and more information is gathered about the molecular nature of these diseases it will, in the course of time, be possible to develop on the basis of this information an effective therapy for them, and thus to decrease the amount of human suffering that these mutant genes cause.

It is likely that all of the diseases that result from inborn errors of metabolism can similarly be described as molecular diseases. For example, phenylketonuria results from the failure of the patient to manufacture an effective enzyme, in the liver, that catalyses the oxidation of phenylalanine to tyrosine.

About two percent of viable children born have gross physical or mental defect because of their inheritance of defective genes. Many more suffer from minor hereditary defects, which in the long run may cause more human suffering than the major defects, because they are not removed so effectively from the pool of human germ plasm by the infertility of their hosts. The rate of manufacture of defective genes by mutation is increasing, as a result of the existence in the modern world of mutagenic agents, such as x-rays used in medicine for diagnostic and therapeutic purposes and of the radioactivity of fallout from the testing of nuclear weapons. The geneticists of the National Academy of Sciences-National Research Council Committee that submitted its report in 1957 estimated that high-energy radiation causes about ten percent of all mutations. The exposure of the gonads of Americans to background radiation, from cosmic rays and natural radioactivity, amounts to about three roentgens during the first thirty years of life. Medical x-rays provide approximately the same exposure. The estimate that I have made of the exposure due to radioactive fallout, for nuclear explosions carried out at the average rate of the past few years, is about 0.3 roentgens in thirty years.

There is nothing that we can do about the damaging of the pool of human germ plasm by cosmic rays and natural radioactivity. It is, of course, possible by good medical practice to decrease somewhat the exposure of the gonads to medical x-rays, as by shielding the gonads whenever an exposure of some other part of the body is being made. Another effective way is through the use of x-ray films of increased sensitivity, and through the limitation of roentgenographic examination to cases when there is significant medical justification.

The damage done by radioactive fallout can be limited through the cessation of the tests of nuclear weapons. It is worth while to attempt to make an estimate of the number of human beings who might be kept sane by the act of stopping the testing of nuclear weapons.

The effects that we shall discuss are genetic effects that would appear in the population in the United States during the next few generations. I shall assume that the average population of the United States during the next few generations will be 200,000,000. Of this total, ten percent, 20,000,000, may be expected to spend some time during their lives in a mental hospital. I assume that there is a strong hereditary factor involved for eighty percent of them; that is, for 16,000,000. If the testing of nuclear weapons were to be continued at the recent annual rate for a period long enough to expose the germ plasm of the entire population to the fallout dose, an estimated number of mutations corresponding to an additional 160,000 cases of mental illness would be produced in the population of 200,000,000. The tests that have already been carried out can be similarly estimated to cause mutations that will result in serious mental disease in 23,000 people in the United States. I think that it can be a source of satisfaction to us that at the present time no nation is continuing its tests of nuclear weapons, and that the Geneva Conference on an International Agreement for the Cessation of Nuclear Explosions is continuing, and may soon lead to the formulation of an effective agreement.

I am astounded by the rapid progress that has been made during recent years in the understanding of the molecular structure of human beings. Ten years ago I would have said that the discovery of the structure of deoxyribosenucleic acid and the formulation of a reasonable molecular mechanism for its self-duplication would be something that our children or granchildren might achieve, but not we ourselves; yet the Watson-Crick proposal seems to be satisfactory. The exploits of the nuclear physicists during the last few decades show how fast progress can occur, when the time is ripe. I believe that the next fifty years are going to be the golden years for biology and medicine. I believe that it will be possible to make great progress, during the next few decades, in the control of mental disease.