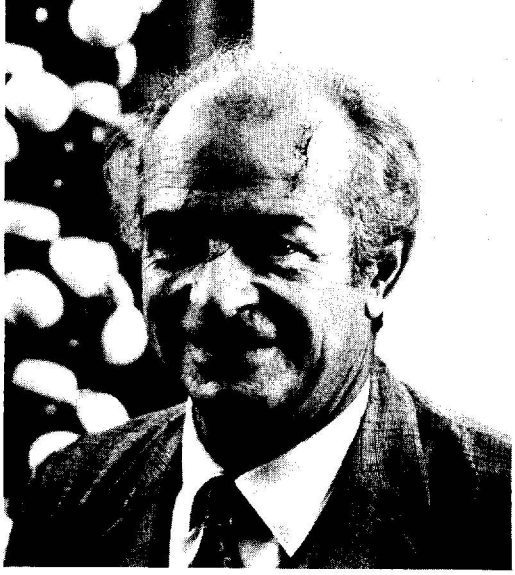

Molecular

An interview with

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AFTER WORKING on the molecular structure of simple substances, I had the idea back in 1934 of explaining the properties of hemoglobin in terms of its molecular structure—even though it is a very complicated molecule of some 10,000 atoms. I had published a few papers about it and expressed some ideas about proteins in general when the late Karl Landsteiner at the Rockefeller Institute for Medical Research invited me to talk with him. He asked me how I would explain the properties of antibodies in terms of their molecular structure.

My association with Landsteiner continued for two or three years, and finally he encouraged me to publish my ideas on the structure of antibodies and the nature of serologic reactions. During the time that Landsteiner gave me an education in the field of immunology, I discovered that he and I were thinking about the serologic problem in very different ways. He would ask, *What do these experiments force us to believe about the nature of the world?* I would ask, *What is the most simple and general picture of the world that we can formulate that is not ruled out by these experiments?* I realized that medical and biological investigators were not attacking their problems in the same way that theoretical physicists do, the way I had been in the habit of doing.

Hemoglobin and Sickle Cell Anemia

What attracted my interest to the red blood cell was an after-dinner conversation with William B. Castle of the Harvard Medical School, in which he talked about sickle cell anemia, the bizarre shapes of the red cells and other features of the disease. I merely listened with interest until he said that the red cells are deformed in the venous circulation and not in the arterial, where they resume a normal shape. I began to wonder: *What accounts for the difference?* The change in pH is small. The great difference is that on the arterial side the hemoglobin has been oxygenated. Could it be that these patients with sickle cell anemia form a different sort of hemoglobin molecule from that formed by other people, molecules that, when unoxygenated, behave like antibodies against themselves and have the power of clamping on one to another to form long, thin rods, which line up to form long crystals that finally exceed the diameter of the cell and deform it?

According to my own view of immune bodies, complementary structure is responsible for the specificity of combination between antibody and antigen. I now postulated that these hemoglobin molecules combine with one another because of complementariness of structure: The addition of oxygen to the molecule abolishes this, so that it does not occur with oxyhemoglobin. If this were so, we could explain what twisted the erythrocyte out of shape, led to its destruction in the spleen, produced stasis in the capillaries (because of the stickiness of the deformed cells) and gave rise to all the other features of sickle cell anemia—all in terms of the abnormal hemoglobin molecule. It would thus be a *molecular disease.*

Harvey A. Itano, a physician, came to work with me for a Ph.D. in chemistry, and I suggested that we study this problem of distinguishing the abnormal hemoglobin that I had postulated in sickle cell anemia. But every experiment that he carried out, for over two years—even using electrophoresis—gave the same results for normal and abnormal hemoglobin, for the techniques are difficult and the color of hemoglobin interfered. The idea, however, seemed to be so valid that we continued in spite of the negative results. Dr. Seymour J. Singer and Dr. Ibert C. Wells also joined in the work.

Finally, in the third year, we came to the crucial experiment. By electrophoresis at pH 6.9, we found that normal hemoglobin moved toward the anode, while that of sickle cell anemia moved toward the cathode.

Itano then examined the blood of parents—apparently normal persons clinically—and found the two kinds of hemoglobin to be present. This presented new facts in the field of genetics.

H. E. Garrod's concept of inborn errors of metabolism introduced the idea in 1923 that there are people with diseases caused by abnormalities in their genic constitution. As the geneticists viewed it, certain molecules were just not manufactured *at all* when an abnormal, recessive,

Disease

In 1949 molecular configuration was related to a disease—in particular, sickle-cell anemia. It thus became possible to speak of "molecular disease." Dr. Linus Pauling, who originated this concept, here explains what it implies for a wide range of the diseases of man.

allelic gene was homozygous. We showed that a defective gene may manufacture the molecule in much the same way as a normal gene does, except that the molecule it produces is abnormal.

Sickle cell anemia shows up only when the patient—the phenotype—has both genes for the disease. If he has only one gene for it, and the corresponding gene is normal, the anemia does not manifest itself clinically, but on the molecular level we find that he is producing both kinds of hemoglobin in a roughly 50:50 mixture. Each of the two genes sets up its own assembly line and begins manufacturing hemoglobin. It is only approximately 50:50, because the efficiency of the abnormal gene is low, and it produces only from 25 to 45 per cent of the hemoglobin. Whatever mutation is responsible for the abnormality of this gene has also interfered in some way with its efficiency.

The lesson for geneticists is that an abnormal gene may continue operating, giving rise to an abnormal product, rather than simply failing to produce anything. Presumably there is also a molecular abnormality in the gene, which is the cause of the molecular disease resident in the hemoglobin.

Other Abnormal Hemoglobins

These studies have gone further, and it has been shown that abnormal hemoglobins C, D, E and many others exist. That is, there are a dozen varieties of the molecular disease of hemoglobin. As to the degree of abnormality in sickle cell hemoglobin, it is astonishing how small it is: There is a discrepancy of only one-third of one per cent in the composition of the molecule, and it involves altogether only a dozen atoms. Of the 600 or so amino-acid residues present in hemoglobin, Dr. Vernon Ingram of the Cavendish Laboratories in England has shown that only two are abnormal. In both of these, one amino-acid residue of glutamic acid has been replaced by an amino-acid residue of valine. This is the chemical pathology of the molecular disease. Moreover, the presence of four oxygen molecules in the 10,000 atoms of hemoglobin is sufficient to overcome the sickling tendency of the abnormal hemoglobin.

As to other molecular diseases, we should probably have to include those hereditary disturbances in which a gene is so abnormal that its product is entirely absent. It is likely that in agammaglobulinemia there is a gene defect that leads to the production of either very little or no gamma globulin. Perhaps normal gamma globulin *is* produced, but there is too little to do any good. Perhaps, instead, an *abnormal* globulin is being manufactured and deposited somewhere in the body, although as yet such a thing has not been demonstrated. Similar diseases are acatalasia, phenylketonuria and galactosemia; probably in all these an enzyme is effectively missing, and a metabolic product accumulates to the point where it becomes toxic. In galactosemia, the enzyme galactose-1-phosphate-transferase is not present, so that galactose accumulates and produces mental deficiency and physical illness—unless it can be excluded from the infant's diet in the first place, by removing milk from the diet.

What must be learned is whether the defective gene produces a molecule that fails to work, or a molecule with undesirable properties (as in sickling), or no molecule at all. When, in the general sense, all these alternatives are considered, a disease such as atherosclerosis, with its prominent familial character, is probably also a molecular abnormality—one in which the subject is genetically left unable to withstand environmental stress due to the nature of his occupation or due to certain foods which he may take to excess. If his genes had been different, his molecules would have been different, and theoretically he could have withstood the adverse condition without developing disease.

Many of the possible etiologic mechanisms of cancer reduce to the problem of a molecular disease also. It is likely that this is true of all diseases having a clearly hereditary trend. Included among them is the very great problem of mental deficiency, for, as you may know, the curve for the distribution of the population by intelligence does not follow entirely the bell-shaped curve or Gaussian error function; rather, there is a rise at the low end which can be accounted for by mental deficiency due to such accidents as the inheritance of homozygous genes for galactosemia or phenylketonuria.

I have been hesitant—perhaps not hesitant enough—to say much about mental disease. I think that mental deficiency is often the result of a qualitative abnormality, and mental illness the result of a quantitative abnormality. That is, mental deficiency can result from complete absence of certain enzymes required for bodily function, while mental disease can be due to the presence of only half as much of certain enzymes as may be normally required, so that the person is less well able to withstand environmental difficulties. The vital chemical constitution of a person is, I believe, one factor; environmental burdens are another. END