THE progress made in medicine during the past half century has been due in a large part to the development of the science of chemistry. Much of the effective medical research that has been carried out has involved chemistry in a significant way.

The years have seen a steady change in the way in which medical discoveries are made. Chemotherapeutic agents were at first discovered by accident. Then there came a period during which a general investigation of the possible usefulness of chemical substances in the treatment of disease was carried out. In recent years great progress has been made by the synthesis and testing of very large numbers of new substances more or less closely related in structure to a substance known to have useful physiological activity; this method of attack has been very valuable.

For example, quinine, like many other useful drugs, was found to be useful in the treatment of disease by the people living in the region in which the plant containing this alkaloid grows. Salvarsan was found by Ehrlich to be valuable for the treatment of syphilis as a result of the planned investigation of the activity of a great many chemical substances in the treatment of this disease, in the simple hope that one of them would be found to have chemotherapeutic action. After the discovery of the bacteriostatic activity of sulfanilamide, a great many analogs of the substance were synthesized, and some of these were found to be still more valuable than sulfanilamide itself in the control of infectious diseases. The action of penicillin was discovered by accident; the knowledge that an extremely valuable antibiotic agent is produced by a mould then led at once to the vigorous investigation of the substances produced by other moulds, and to the discovery of many other effective antibiotics, including chloromycetin and aureomycin.

All of this work has been carried on in scientific darkness—or, at best, in a dim twilight. Except for the idea that sulfa drugs operate by inhibiting the capacity of the bacteria to utilize an essential substance, p-aminobenzoic acid, we do not understand the mechanism of action of any chemotherapeutic substance. In the absence of this understanding, research is necessarily in large part haphazard, and progress is slow. We can be sure that if a detailed understanding of the molecular basis of chemotherapeutic activity were to be obtained, the advance of medicine would be greatly accelerated.

It is my belief that we are just on the verge of taking this great step forward, that during the next ten or twenty years very significant progress will be made in the development of a real science of pharmacology, and that there will be great consequent progress in medical practice.

In order to achieve this end we must learn three things: the detailed molecular structure of the chemotherapeutic substances, the detailed molecular structure of at least some constituents of the organisms against which they are directed (the bacteria, rickettsial bodies, viruses) and of the human organism, with which the agents come in contact, and the nature of the forces involved in the intermolecular interactions between the substances and the organisms.

During the past 25 years very significant progress has been made in solving the first problem. The chemists of the last century had formulated the science of organic chemistry, and had succeeded in finding the structural formulas of many organic compounds. Since 1913 the X-ray diffraction method and other methods of investigation of the structure of
molecules have made it possible to find out exactly how atoms are attached to one another in molecules such as those of the sulfa drugs and penicillin. Chloromycetin, whose discovery was announced only last year, has gone through only the first stage of investigation — its structural formula is known, and it has been synthesized in the laboratory, but it has not so far been subjected to a detailed molecular structure examination, so that the exact shape and size of the molecule have not yet been determined. Aureomycin has not been put through even the first stage; the methods of organic chemistry seem not yet to have led to the determination of its structural formula. Nevertheless, it can be said that at the present time this problem has in principle been solved for the relatively simple chemotherapeutic agents, containing less than 40 or 50 atoms in the molecule.

The methods of molecular structure determination have sometimes shown the older structural formulas to be incorrect. An example is provided by the arsenobenzenes, such as salvarsan. The organic chemist has always written the formula for these substances with a double bond between two arsenic atoms, corresponding to the double bond between the two nitrogen atoms in azobenzene; recent X-ray investigation has shown, however, that the molecule contains a ring of six arsenic atoms, each bonded to two others by single bonds.

Progress in the solution of the problem of the molecular structure of living organisms has been slow, necessarily so because of the complexity of the substances involved. Probably the most important step that could be taken would be the determination in detail of the structure of some protein molecule. Professor Robert B. Corey and many other workers in our laboratories have been attacking this problem during the past fifteen years. This attack has included the investigation of the crystal structure of amino acids and simple peptides. The results that have been obtained are self-consistent, and make it possible to predict the interatomic distances in the polypeptide chains that are believed to be present in proteins with confidence that the values are correct to approximately 0.02 Å. In addition, the work on the amino acids and simple peptides shows clearly that the hydrogen bond is an extremely important structural feature, and that hydrogen bond forces must constitute an important part of the forces operating between segments of a polypeptide chain in one protein molecule and between adjacent molecules. It seems not unlikely that during the next few years the order of amino acid residues in the polypeptide chain of some simple protein will be determined, and that in addition the detailed configuration of the chain in the protein molecule will be discovered.

It is likely that some drugs operate by undergoing chemical reaction with a constituent of the living organism, and that others operate by the formation of complexes involving only forces that are usually called intermolecular forces. It is my opinion that, in general, the intermolecular forces that are involved are short-range forces, operating effectively through distances of only a few Angstroms, and that, in order to be effective, a chemotherapeutic agent must come into atomic contact with a molecule of the organism against which its activity is directed. The evidence about the nature of these forces that we have obtained in Pasadena has been provided by studies of the interaction of antibodies and simple chemical substances. I became interested in the general problem of the structure of antibodies and the nature of serological reactions through conversations with Dr. Karl Landsteiner, of the Rockefeller Institute for Medical Research, during the years 1936 to 1939. Experimental work in this field has been carried on in our laboratories by Professor Dan H. Campbell, Dr. David Pressman, and many other investigators. It was found that quantitative data about the inhibiting effect of simple haptens on the precipitation of precipitating antigens and antibodies with combining regions directed against simple chemical groups could be interpreted by the use of a theory of heterogeneous antibody, in such a way as to give values of the average equilibrium constant of combination of the hapten with the antibody, and hence of the standard free energy of combination of haptens and antibodies. It was then found that the values of the standard free energy of combination could be interpreted in a rough quantitative way in terms of the structure of the hapten. The first requirement for the formation of a good bond between the hapten and the antibody is that the hapten possess the proper size and shape. A deviation in size or shape corresponding to a change in dimension by as much as one Angstrom, a quarter of the diameter of a single atom, may lead to a great decrease in the power
of combination with the antibody. This effect is attributed to steric hindrance—it is believed that in the process of manufacture of the antibody a surface configuration of the antibody is produced that is complementary to that of the haptenic groups of the antigen, and that the degree of complementariness is such that a fit between hapten and antibody is not achieved unless the haptns correspond closely in size and shape to the original haptenic group. A second factor of importance is the presence in the hapten of a positive or negative charge corresponding to that in the original haptenic group. Presumably there is a complementary negative or positive charge built into the antibody. A determination of the magnitude of the interaction energy between the haptenic charge and the complementary charge of the antibody led to the conclusion that the complementary charge was within 2 Ångstroms of the minimum possible distance from the haptenic charge. A third structural feature operative in the system is the hydrogen bond. If the original haptenic group contains a hydrogen bond-forming group, haptns with a similar group are found to combine more strongly with the antibody, by about one or two kilocalories per mole in standard free energy, than closely similar haptns in which the hydrogen bond-forming group is not present. The fourth important type of intermolecular force is the electronic van der Waals attraction that operates between all molecules, corresponding to a potential energy inversely proportional to the sixth power of the distance between atomic centers. The magnitude of this interaction energy is proportional to the product of the polarizabilities of the interacting atoms, and it has been found that the change in standard free energy of combination with change in polarizability of the haptenes is in the predicted direction, and has the magnitude corresponding to contact between hapten and antibody, with the atomic surfaces in juxtaposition to within better than one Ångstrom.

It seems to me likely that the interaction between haptenes and antibodies can be taken as the model for the interaction between molecules of a chemotherapeutic agent and the protein molecules of the organism that is affected by the agent, at least in many cases. However, direct evidence for this hypothesis is lacking, except in the case of the sulfa drugs, where the competition with p-aminobenzoic acid, a molecule very closely similar in structure to those of the sulfa drugs, is indicated by the structural similarity of the molecules to operate through this mechanism.

An example of one way in which medical research may be carried out in the future is provided by some studies that have been carried out in our laboratories during the past four years on the disease sickle cell anemia. Drs. Harvey A. Itano, S. J. Singer, Ibert C. Wells, Walter A. Schroeder, and Robert B. Corey have collaborated in this work. This very serious disease, which afflicts about 1/400 of all American Negroes, is characterized by the presence in their venous blood of a large fraction of the red cells in abnormal shape. The change in shape occurs in response to change in the partial pressure of oxygen. When the oxygen pressure is lowered, the cells change from the normal biconcave disk to crescent, holly wreath, and other forms. This process is known as sickling. It is prevented not only by oxygenation of the hemoglobin, but also by combination with carbon monoxide, to form carbomonoxyhemoglobin.

We have discovered* that the hemoglobin present in the red cells of these individuals is different from normal adult human hemoglobin. This is the first time that any adult human beings have been found to possess hemoglobin differing from adult hemoglobin.

The difference between sickle cell anemia hemoglobin and normal hemoglobin is evident in a difference in the electrophoretic mobility of the two substances. This difference corresponds to a shift in isoelectric point by 0.23 pH units, with the isoelectric point of sickle cell anemia hemoglobin in the more basic region. The difference corresponds to a difference in electrical charge of about three electronic charges per molecule.

The characterization of dimethyl esters of porphyrins made from normal hemoglobin and sickle cell anemia hemoglobin by determination of melting points and by their X-ray diffraction patterns has given strong evidence that the heme of sickle cell anemia hemoglobin is identical with that of normal hemoglobin, and that the difference in structure of the two hemoglobin molecules is accordingly to be attributed to a difference in the globins. Amino acid analyses of hydrolysates of the two hemoglobins are now under way for the purpose of identifying the groups that are responsible for the difference of charge and other properties of the molecule.

We may picture the mechanism of the sickling process in the following way. Let us suppose that there is a surface region on the globin of the sickle cell anemia hemoglobin molecule that has a configuration complementary to that of a different region of the hemoglobin molecule, and that this structural feature is not possessed by normal hemoglobin. The situation would then be somewhat analogous to that which exists in antigen-antibody reactions. Under appropriate conditions these hemoglobin molecules might interact with one another at these sites in such a way as to cause at least a partial alignment of the molecules within the cell, resulting in the erythrocytes becoming birefringent, as is observed, and resulting also in a distortion of the cell membrane to accommodate the relatively rigid structure within its confines. The addition of oxygen or carbon monoxide to the cell might reverse the effect by disrupting the bonds, presumably through a mechanism of steric hindrance. The pathological effects of the disease are in general the results of the change in shape of the cells, which causes the flow of blood in the capillaries to be restricted, and leads to anoxia in the affected tissues.

We can accordingly describe sickle cell anemia as a molecular disease. Moreover, we may feel some confidence that we possess a detailed understanding of the nature of the disease—a more penetrating understanding than is possessed for any other disease. With this knowledge, the task of finding a chemotherapeutic agent no longer seems without hope; instead there appears the possibility of planning out, on the drawing board of the molecular architect, the specifications of a simple molecule that would have the power of combining with sickle cell anemia hemoglobin in such a way as to interfere with its pseudocrystallization, and thus to prevent the crisis of the disease. If such an agent were to be found, its discovery would represent the first time that a chemotherapeutic agent had been developed purely through the application of logical scientific argument, without the significant interposition of the element of chance.

Progress in a field of science is often significantly accelerated by the explicit prerecognition of its possibility, and the provision of suitable physical facilities for it. It seems to me that the time is now ripe for the foundation of a new institute of medical chemistry, in which basic medical research would be carried out by application of the most modern methods, and in which also young doctors and young chemists would receive training in the special fields necessary to give them well-rounded preparation for the job of attacking medical problems in this new way. I think that such an institute should be set up in a university, in close juxtaposition to strong departments of the basic sciences, rather than as part of a medical school, or as an independent institute. Progress in the field of structural medical chemistry, as described in the preceding paragraphs, is sure to be slow, because of the great difficulty of the problems; but the possible importance of the attack on this problem, with its promise for greatly increased health and happiness for humanity, is such as to justify our making a great effort to achieve it.