CHEMISTRY IN THE SERVICE OF MEDICINE

Inaugural Lecture of the Professor of Chemistry delivered at the College on March 4, 1958

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I BELIEVE that when our successors come to look at this twentieth century from the perspective of history they will regard it as the period during which the real potential, for good or evil, of the scientific mode of thought was realized. There is no doubt that the influence of science on our lives may be traced to a much earlier stage of our civilization, but it is during the last few decades that we have witnessed a remarkable acceleration in the rate of discovery and application of new knowledge.

What has happened in chemistry is typical. It has been estimated that, during the first sixty-three years of the nineteenth century, the yearly average of research papers was considerably less than one thousand. In fact, the average for all branches of sciences during this period is said to be 3,100. In 1957 approximately 200,000 papers referring to various aspects of chemistry alone were published. It is just twice the number that appeared ten years ago. This reflects a process of expansion that is likely to continue. In order to give more point to the consideration of this process and the effect it may have on our lives I have chosen to examine at closer range that very limited aspect of chemistry which is concerned with the development of new medical remedies. This has been selected because it is related to research work which is in progress in Swansea. It is well, however, in considering this particular case, to bear in mind that it is only one illustration of what is taking place in a number of fields in which chemistry plays a part.

It has been estimated that 70 per cent. of all prescriptions today are for drugs discovered in the last ten years.

New compounds designed to conquer, relieve, or prevent almost every ailment continue to appear in rapid succession. In the case of the infectious diseases the position is made clear by the remarkable change in clinical practice during the last few decades. At the turn of this century the emphasis was on the alleviation of symptoms. Now antibiotics, sulpha drugs, and immunotherapy provide the means of controlling the majority of infectious diseases. Where a good remedy has not been found there is a reasonable expectation that one will become available if sufficient effort is applied to the task.

Diabetes, heart disease, rheumatism, cancer, nutritional deficiencies, and similar conditions may be grouped together as metabolic diseases. They can be attributed to a breakdown of normal chemical processes in living tissues. We are still far from the point where our knowledge permits us to remove the cause of all these syndromes. However, compounds are now available that go far towards correcting many. There are natural products like insulin, thyroxin, or the adrenocorticotrophic pituitary hormone to provide for hormonal deficiencies. There are products synthesized in the laboratory, like the various cortisone analogues. The vitamins are included in this group because they, too, are known to play a role in essential chemical reactions in the body. All these compounds have become readily available in the last thirty years to the clinician concerned with restoring normal metabolism.

The third group of drugs, that concerned with symptoms, has also been materially enlarged during this period. Antihistamines and tranquillizers are recent examples. Well-established remedies such as morphine have been modified and improved. We may well ask for an explanation for this rapid development of medical therapeutics. The answer is found in the consideration

of the joint efforts of biologists, chemists, and clinicians.

In the case of the infectious diseases, the genius of Pasteur and the careful work of Koch and others established the microbial etiology of infection. This made it possible to devise laboratory tests to determine the effectiveness of chemical compounds for the control of parasitic micro-organisms. These screening programmes permitted the examination of large numbers of compounds for toxicity against micro-organisms. The more effective substances were then submitted to animal tests, and, if these gave satisfactory results, to clinical examination.

The first outstanding success of such a programme was the discovery of salvarsan in 1909. This was followed by the development of new drugs for several tropical diseases—malaria, Leishmaniasis, helminthic infections, and others. For a time it appeared that there were no compounds which were effective against bacterial diseases but were not toxic to the host. However, in 1935 the sulphonamides were discovered—again as a result of a screening programme. The full potential of these compounds was barely realized when the concept of antibiosis received serious attention. With the realization that many fungi produce compounds, antibiotics, that protect them from attack by other micro-organisms, a new family of drugs of great potency became available. This was an old concept dating back to experiments by Pasteur but the possibility of using it as a means of obtaining new remedies was dependent on the vision of Fleming and Florey and the availability of new chemical techniques for isolating such compounds. Again, the screening programme was made the basis of the search for new antibiotics. For example, it has been estimated that the laboratory which discovered aureomycin examined

100,000 soil samples before it obtained a fungus which produced a novel antibiotic with useful characteristics. Once the fungus is selected, the chemist must develop methods for isolating the antibiotic from the culture fluid in which it is grown.

In 1891 it was shown that myxoedema could be treated successfully with thyroid gland. This raised hopes that other ductless glands or extracts from them might be used for the treatment of metabolic diseases. Efforts during the following thirty years were disappointing. It is true that Kendal, on Christmas Day 1914, isolated thyroxin from the thyroid glands, but this did not lead to a new treatment. The turning-point was the demonstration by Banting and Best in 1921, that insulin could be separated from the pancreas and used for the relief of diabetes. This seemed to put new heart into investigators in this field. There had been a growing suspicion that if the other endocrine glands did produce internal secretions the active compounds were so unstable or in such high dilution that it was not possible to isolate them. After the discovery of insulin, active preparations were obtained from the parathyroid, suprarenal cortex, pituitary, and the gonads, and put to clinical use. The search for these compounds was one of the most exacting ever attempted by chemists. Some of the hormones were unstable. They generally occurred in high dilution. To take one example, over half a ton of gonads from fifty thousand pigs were extracted in order to obtain twenty milligrams of the hormone progesterone. This work has led to a considerable array of steroid hormones and analogues prepared by synthesis. The biologically active polypeptide β-corticotropin was isolated four years ago by what must be regarded as one of the most involved procedures for isolating a pure compound. Five years ago, Du Vigneaud announced the first synthesis of a peptide hormone. This

synthetic compound, oxytocin, is now available commercially for clinical use. Work in this field still continues actively. It makes very special demands on the chemist both in the isolation studies and also in attempting to determine molecular structure on very small quantities of material.

The story of the discovery of the vitamins, the other class of compounds concerned with metabolic deficiencies is so well known that there is no reason to repeat it now. Apart from the recent studies on vitamin B_{12} the main work of isolation and characterization of the vitamins took place between the World Wars and at a time when chemists were using similar techniques in the study of hormones.

In the earlier stages of its history the concern of clinical medicine with the alleviation of symptoms of disease was based on the theory that the cause of a disease could only be removed by a natural process unassisted by drugs. The drugs used for the relief of symptoms were largely plant products. The continued use of these galenicals was commonly based on tradition rather than reliable testing. When the older drugs that crowded the pages of the herbals of the Middle Ages were subjected to biological testing during the latter part of the last and the earlier part of this century, the majority were found to have little value. This is not surprising, since the folk medicine from which they are derived had a mythical rather than a rational basis. Among primitive people illness was generally regarded as the result of supernatural forces. You will remember the commonly accepted Law of Signatures according to which a plant would be selected for treating a disease because some feature of it suggested the diseased tissue. Thus, the liver might be treated with a root because it had the shape or colour of that organ. The plant 'Eye-bright'

was used for centuries because a black speck in the flower suggested the pupil of the eye. Nevertheless, some of these old remedies have qualified and there is reason to believe that others may still be a source of useful compounds. The isolation of reserpine, the tranquillizer drug, from plant material used since antiquity in India and the discovery of ephedrine some thirty years ago as a result of chemical isolation studies on Ma Huang, a Chinese drug first described 5,000 years ago, are recent examples.

The processes which I have described indicate that a large proportion of modern drugs have found their way into medicine as a result of experimental work based on relatively simple concepts. The increase in biological knowledge, the availability of good laboratory testing techniques, the increased skill of the chemist in isolating natural products, when coupled with the widening scope of screening programmes has meant that there is greater expectation of discovering new remedies. However, one is bound to observe that these methods are still heavily weighted with empiricism. Is it not possible to use a more rational basis and reduce this degree of empiricism? There has been some development in this direction, but our understanding of the chemistry of life processes is so limited that this is still in its earliest stages. Nevertheless, the implications of this work are so important that I shall attempt to outline some of the considerations here.

The first essential for an understanding of these ideas is the recognition that life processes depend on the interaction of different molecules. For example, molecules of oxygen in the air react with molecules of haemoglobin in the blood; other molecules in the blood react with those in liver tissue and so on. All the functions of living tissue depend on molecular interactions. The interactions

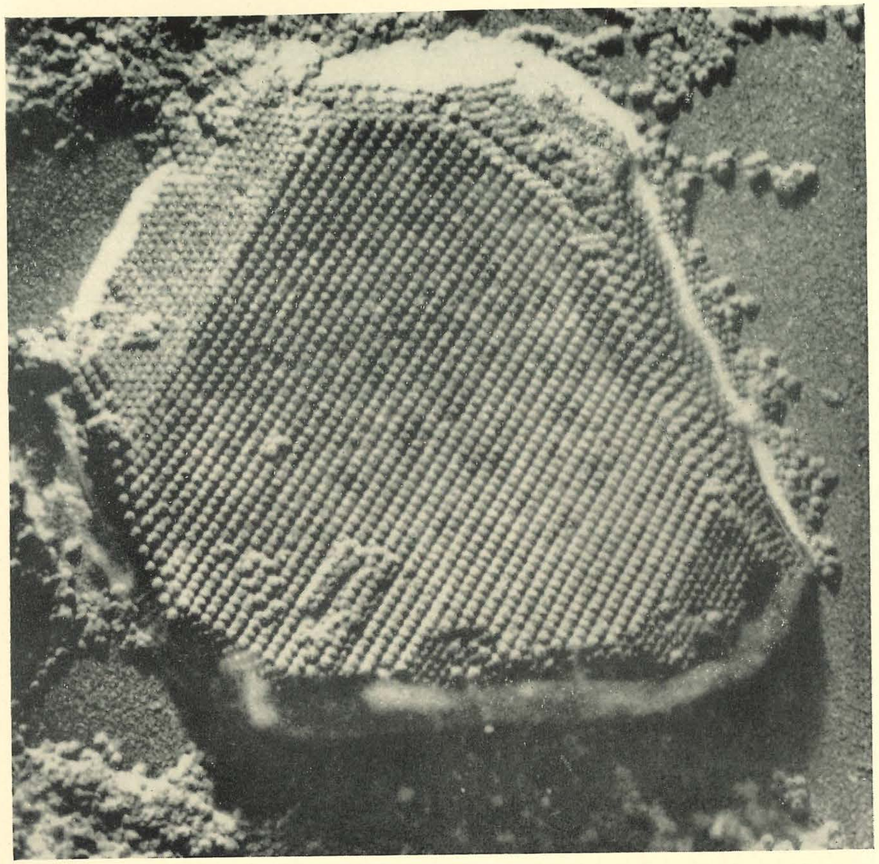

FIG. 1. Photograph (magnification 48,750 ×) of crystal of southern bean mosaic virus protein showing individual molecules. [After W. G. Wyckoff.]

between molecules are interpreted in terms of molecular structure—the arrangement of the different atoms of the molecule in three dimensions. If we know the structure

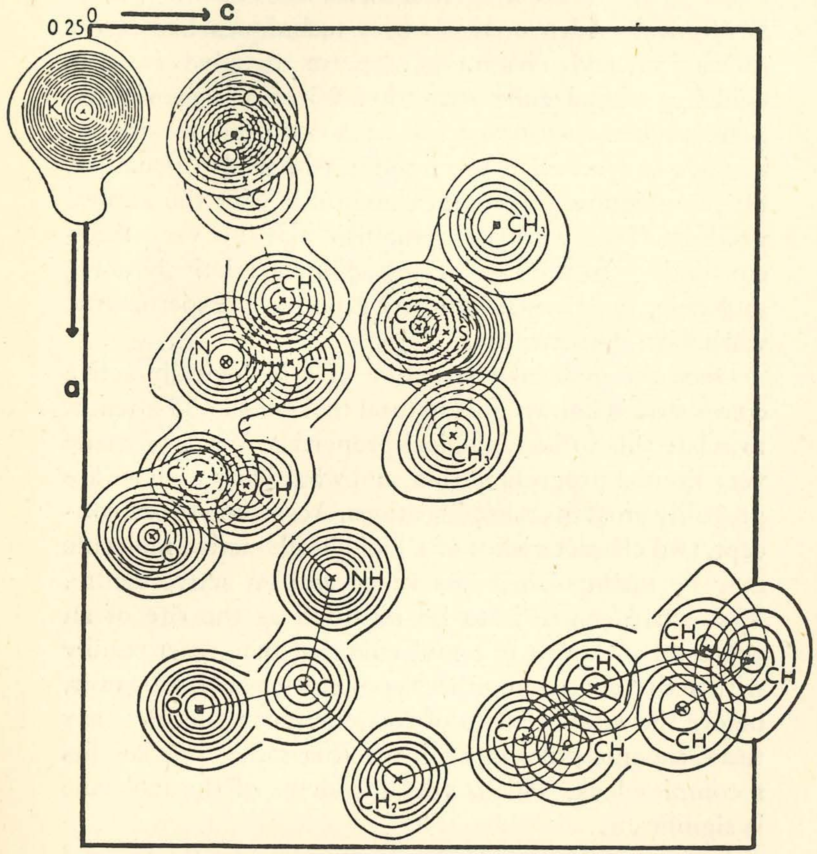

FIG. 2. Electron density distribution diagram of potassium benzylpenicillin. [After G. L. Pitt.]

of a molecule we can anticipate much of its behaviour. Unfortunately, molecules are so small that we cannot observe structure directly. We must deduce it from indirect evidence. This falls into two categories. When a

molecule is broken into small pieces which are so simple that their structure is known, the structure of the whole may be deduced by putting the pieces together—rather like a jigsaw puzzle in three dimensions. Secondly, there is physical evidence which uses techniques like X-ray diffraction and absorption spectra to give indirect evidence of molecular structure. When it is considered that the correct structure has been deduced, an attempt is made to synthesize a compound with such a structure, by unambiguous steps, and compare it with the natural product. This work on structure may be very time-consuming. In the case of penicillin, a relatively small molecule, over seven-hundred reports of experimental work have been written.

Once the molecular structure of a biologically-active compound is known, it is natural that we should attempt to relate this to its biological properties. We have made very limited progress in this, and what ideas we have are probably gross oversimplifications. According to one concept, two characteristics of a biologically-active molecule may be distinguished—its shape and an active centre. The active centre is to be regarded as the site of an aggregate of atoms in a molecule that may react readily with active centres in other types of molecule. However, before the active centres of two different molecules may react, the molecules must fit together rather as a key fits a complex lock. This is why the shape of the molecule is significant.

Let us consider some simple illustrations. Barron and colleagues took a compound from living tissue, an enzyme, which is known to facilitate the breakdown of acetic acid by oxidation, a process involved in the metabolism of fats. They studied the effect of adding two compounds, separately, to the acetic acid–enzyme mixture. When one of these compounds, fluoroacetic acid,

was added, the breakdown of the acetic acid was completely inhibited. In the case of the second compound, chloroacetic acid, there was no inhibition. This result may be attributed to the fact that the small fluorine atom, but not the larger chlorine atom, permitted the derivative of acetic acid to fit the specific shape in the enzyme molecule intended for the acetic acid molecule.

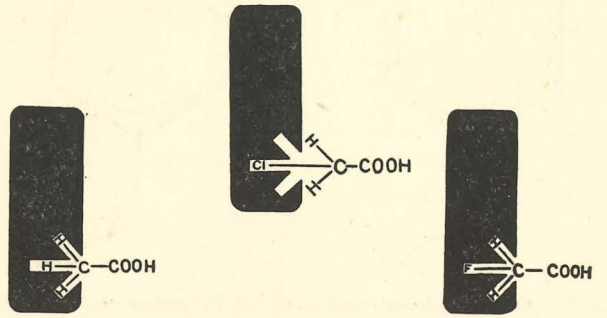

FIG. 3. Diagrammatic representation of interaction of enzyme molecule with molecules of acetic acid, chloroacetic acid, and fluoroacetic acid.

The sulpha drugs provide another illustration. The shape of the sulpha drug molecules is so closely similar to that of P.A.B. (*para*-aminobenzoic acid), an essential for the life of many bacteria, that it can occupy a site in an enzyme in the bacteria intended for the P.A.B. This prevents the P.A.B. from participating in the normal life processes of the bacteria. The organism dies but the host is not affected because the process involving P.A.B. does not play the same vital role. This is the Woods-Fildes theory of competitive inhibition. There is a rapidly growing list of examples. Other compounds have been designed with a molecular architecture which enables them to prevent the growth of bacteria. There has been some limited success in controlling a form of cancer in this way.

There are cases where it has been possible to produce

compounds with the same active centre and essential feature of shape as a compound occurring in nature, but,

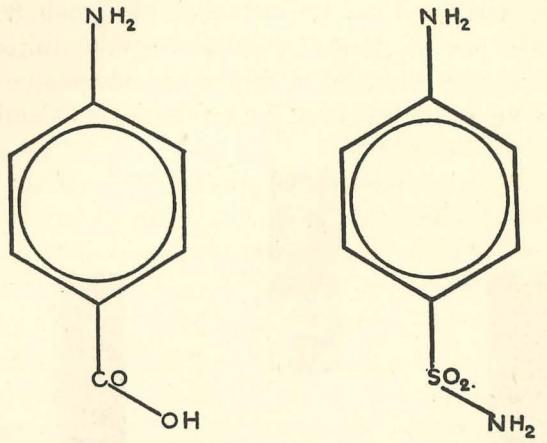

FIG. 4. Diagrammatic representation of P.A.B. (*para*-aminobenzoic acid), on left, and sulphanilamide.

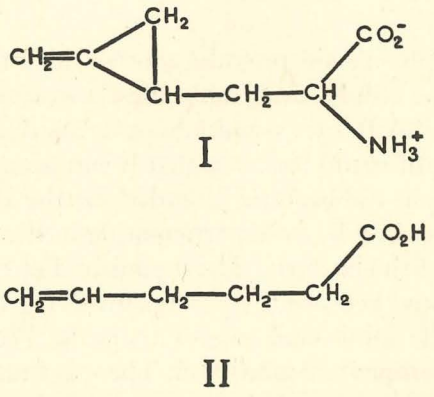

FIG. 5. Hypoglycin A (I) and a smaller molecule (II) with hypoglycemic activity.

overall, without the same degree of complexity as the natural compound. I shall illustrate this with a recent

example from our own experience of the last few months. We isolated from natural sources a new amino acid, hypoglycin A, which has the very unusual property of lowering the sugar content of the blood (compare the action of insulin). After the molecular structure of this compound was defined, it was found to be possible to design smaller and simpler synthetic compounds with the same biological property.

Simplified versions of morphine, steroid hormones, and others have been prepared. Quite evidently this indicates a means whereby the chemist may tailor new biologically-active molecules.

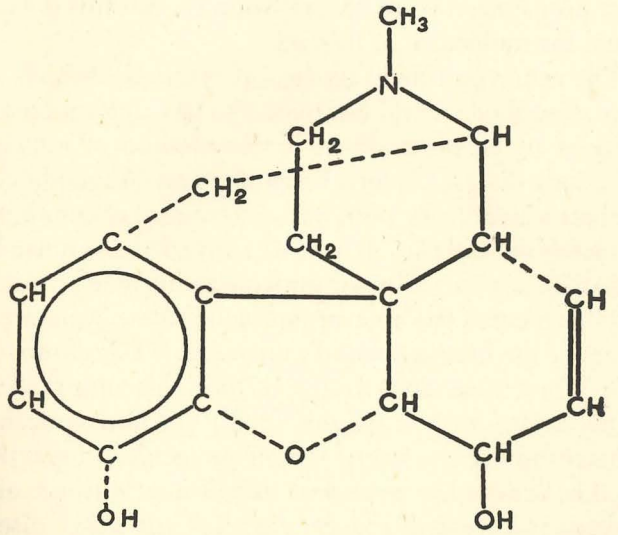

FIG. 6. Representation of morphine molecule showing (dotted lines) sections which are not essential for analgesic activity.

Today, once the shape of a molecule the size of morphine has been defined, it is generally possible to achieve a synthesis in the laboratory. It deserves mention that

the improvement in the technique of synthesizing molecules of a moderate size has another significance in this field. It has made it possible to prepare in the laboratory large quantities of biologically-active compounds of which, if we depended on natural sources, we could not obtain sufficient quantities. The vitamins are outstanding examples of this. The case of progesterone is another. It is now prepared by partial synthesis in batches weighing hundreds of pounds, whereas, as was mentioned earlier, it is not readily accessible from natural sources. There are cases such as penicillin, streptomycin, and aureomycin where the particular subtlety of the molecular constitution makes laboratory synthesis less practicable than preparation from natural sources, but this is exceptional for molecules of this size.

The achievements in medical therapeutics which have been described should not mask the fact that much more remains to be done. Even if the method of attack on infectious diseases is now becoming encouragingly clear, the battle is far from won. Before a rational chemotherapy of metabolic diseases can be developed there must be a remarkable increase in our understanding of life processes —in particular the interpretation of these processes in terms of the interactions of molecules. This requires not only a precise understanding of the molecular structure of molecules both large and small, but also a means of accounting for the energetics of molecular interactions. As this knowledge increases, so will our prospect of removing the cause of cancer, diabetes, and other diseases of metabolism. These are evidently not the only fruits of such advances. Already, there are indications that such knowledge may be applied to the control of some of the processes associated with old age and mental diseases. It is not difficult to visualize the effect that greater understanding of the chemistry of life could have on other

applied aspects of life sciences such as agriculture, nutrition, microbiology.

A precise description of life processes in terms of chemistry and physics—i.e. in terms of transformations of matter and energy at the molecular level—must be regarded as one of the great challenges of modern science. It is probably as intricate a problem as can now be stated. However, recent progress encourages us to believe that the goal may be realized.

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