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SOME ASPECTS OF CHEMISTRY RELATED TO MEDICINE*

BY

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It is a great privilege to be the first to have the opportunity to congratulate the Board and all those who labour within these walls on the Bicentenary of the Middlesex Hospital. The Foundation took place shortly after the death of Boerhaave, of Leyden, the greatest of eighteenth-century teachers, and also near the date of the birth of Lavoisier. Thus the entire development of scientific medicine and modern chemistry occurred during the period now celebrated. I speak to you as a chemist, and my acquaintance with medicine is superficial—rather like a Nature-lover's knowledge of scientific botany and zoology. As a concession to my diffidence I trust I may be allowed to alter the title of my address from "Chemistry and Medicine" to "Some Aspects of Chemistry Related to Medicine."

There are few human activities that have no relation to medicine, and it is equally true that all branches of medicine are already connected, or are destined to be connected, with chemistry. It would be preaching to the converted to develop that theme as propaganda, because the clock will not be set back, and the fundamental nature, for medicine, of the science of the transformation of matter is already fully recognized. Chemistry is of service to medicine in very many directions, of which I will mention only the more important. There are the alloys, plastics, and other materials used to improve the technique of medical and surgical practice. Many of these are incidental to more general developments, but others have involved specific research. In the field of preventive medicine the purification of water, for example by chlorination, should not be overlooked as an application of chemistry, whilst the production of new insecticides and insect repellants is making an increasingly important contribution to hygiene. The huge subject of nutrition, involving vitamins, essential amino-acids, minor elements, and the balance of diet, is obviously a meeting-ground of chemists and physiologists.

Then, more directly, we have the general and local anaesthetics, the analgesics and hypnotics; also the substances which promote or inhibit various bodily functions—an omnibus definition which could embrace the natural and synthetic hormones, insulin and the liver factors, thiouracil, etc., and also groups such as the laxatives, diuretics, and so on. There is no danger of forgetting the chemotherapeutic agents, which we may class together irrespective of the mechanism of their action. Finally, we have the subject of toxicology, the use of chemical analysis and biochemical control in diagnosis, the blood groups, and immunology.

That list is by no means complete, and I shall make no attempt to cope with it.

As an organic chemist I propose to make some general remarks and to mention a few special themes, chosen because I happen to have been interested in them, and certainly not because of their intrinsic significance in the general picture. And first I want to emphasize that organic chemistry must still be developed for its own sake; it is very imperfect, and not yet a reliable handmaiden for other sciences. It is perfectly true that great success has attended the isolation of substances of physiological importance and that many of these have been ingeniously synthesized. As a result many medical scientists have come to the conclusion that our technique is adequate for almost any task. But the truth is that we can quickly cover only such ground as the advance of knowledge makes accessible.

Our position is similar to that of the metaphysicians, who always manage to catch up to the wave of scientific progress, but never take a step in front of it. Or, to take a closer analogy, chemistry is to medicine as mathematics is to physics. The physicist, however, has usually enough mathematical equipment to make it possible for him to appreciate the limitations of the power of mathematicians to solve his problems. He knows that an increase of these powers will inevitably raise his own potential, and he therefore encourages the pure mathematician even in work that seems devoid of any possible application.

In the case of organic chemistry applied to biological research it is easy to see the direct results of relatively recent improvements in laboratory methods such as micro-analysis, chromatography, molecular distillation, use of tracer elements, *x*-ray analysis of crystals, and ultra-violet and infra-red spectrography. It is well understood that this and that advance in physiology, or other medical science, would have been impossible without these facilities, or at least would have been greatly delayed. But what is perhaps not so widely appreciated is the debt owed to pioneers of structural and synthetic chemistry, to the discoverers of general reactions, and to those who have disclosed the mechanism of reactions and the relations between properties and molecular constitution.

The system of organic chemistry is a wonderful achievement, but the noble edifice that has been reared is still unfinished. The reason for stressing the point is that there may be some danger of too great a diversion of scientific man-power into *ad hoc* work, even if that consists of the wholly admirable studies of biological problems. It is perfectly true that some of these will be found beyond our present capacity to solve and that such research will disclose the existence of gaps in knowledge and may lead to the exploration of a rich territory.

In the past the study of natural products has indeed afforded that kind of stimulus. Outstanding examples are the carbohydrates, the terpenes, the alkaloids, the steroids, and the vegetable and animal colouring matters. These substances were easily accessible in quantity, and they were examined mainly for their purely chemical interest. If I may be pardoned a personal reference, I have been asked why I am still interested in the study of strychnine. Except as a tonic and vermin-killer it is of no particular use, and its biological significance as a waste product of the economy of the plant is not apparent. The answer is that we are interested in the behaviour of a unique molecule which contains no fewer than seven interlocked rings, and that we have faith that the investigation will add stones to that edifice I have already mentioned, on which others will later be placed. And whether that is so or not, the challenges of Nature have to be accepted. It is not for us to presume to assess the importance of new knowledge to future generations.

When Wieland and Windaus attacked the steroids it was from this point of view alone, though we must admit that the steroid hormones were a kind of bonus not likely to be often bestowed in such generous measure.

* Address at Bicentenary Celebrations of the Middlesex Hospital, May 20, 1946.

Penicillin Synthesis

The chemistry of penicillin gives a good example of quick success in one direction by the use of established methods and of failure in another, due to the fact that a certain field of synthesis has not yet been cultivated. After the preparation of penicillin concentrates, it was a matter of routine to find the conditions of stability of the antibiotic and, though it proved a difficult task, to obtain the pure crystalline sodium salt.

The determination of molecular structure was also far from easy, but it followed normal lines of procedure. A final doubtful point was cleared up by *x*-ray analysis of the crystals. The substance is relatively simple. Everything seemed plain sailing for the synthesis, and yet very strong American and British teams have been unable to achieve it in a practicable manner. It is very probable that penicillin has actually been synthesized, but the yield is only about 0.1% of the theoretical, and the method has therefore no practical importance as it stands. The explanation is that we are faced with a new kind of difficulty presented by the great instability of the molecule, combined with a lack of methods suited for the construction of the characteristic β-lactam unit, under the conditions imposed by the properties of the substance. All the known methods are too brutal for that delicate system. So we have to find some new method, and that sequence of operations is not what we had hoped for, and has indeed seldom been necessary for the synthesis of natural products of comparable complexity. Somewhat analogous were the syntheses of indigo by Baeyer, Heumann, and Sandmeyer, because there was no precedent for the reactions that were eventually discovered after many years of intensive work. Ziegler's device for overcoming the reluctance with which large rings are formed was entirely novel, and something similar to it may well apply to the case of penicillin.

Our medical friends, who have seen a whole series of vitamins and hormones synthesized very soon after their characterization and structural analysis, are keenly disappointed in us. Dr. Vannevar Bush remarked, "They tell me that it is only a question of removing a molecule of water." Alas, that is all it is!

While on this topic I will add that though total chemical synthesis, or rather synthetical manufacture, is not in sight, biosynthesis, by appropriate feeding of the mould, has given us new penicillins. Moreover, one of the penicillins has been chemically modified, with the production of substances of increased activity. Thus we already have a range of penicillins which, as in the case of the sulphonamides, will doubtless be differentiated in regard to their suitability for the treatment of infections. It follows that one of the advantages anticipated from chemical synthesis has been partly secured in a different way. I do not want you to conclude that the prognosis for synthesis is unfavourable. On the contrary, the problem is well defined, and will be solved—when we have had time to learn some more organic chemistry.

A Gap in our Knowledge: Proteins

The most obvious gap in our exact knowledge of substances of biological importance is in relation to the proteins. Their molecular complexity, and variety in complexity, continue to defeat us, but, nevertheless, great progress has been made and the outlook is promising. At Harvard University Medical School, Prof. Cohn and his colleagues have built up a most impressive laboratory, devoted to the application of physico-chemical principles and methods to the separation and study of proteins. There is room in this country for a similar "Institute of Protein Chemistry." There is no more important subject, and none that offers greater rewards to the investigator.

It is a matter for congratulation that Prof. A. C. Chibnall has brought his great experimental skill and critical faculty to bear on the analysis of proteins and the interpretation of the results; similarly, that Prof. A. R. Todd is so well on the way to the synthesis of sections of the nucleo-protein molecule and, incidentally, of the coenzymes. It is also good to know that the urgency of the work is recognized here and that Prof. E. C. Dodds has embarked on a study of physiologically active proteins. By contrast with these I am reminded of the useful "dead" proteins—wool, silk, leather, and even pea-nut protein. Much valuable work has already been carried out by the respective research associations—for example, Dr. Jordan Lloyd's leather team—and all that will come into the mill.

The indications are that the probing of the protein molecule will before long reveal the mode of organization of the units, but that is only the first step to a real understanding of their role in Nature. We are almost compelled to believe that the nucleo-proteins are keeping one of the secrets of life itself, and it is hard to resist speculations that connect the four great and peculiar branches of their molecules with a mechanism of biosynthesis of particular importance. To regard them as a kind of template, on which other molecules are moulded, is doubtless a crude conception, but the proliferation of viruses shows that in a suitable environment macro-proteins can reproduce themselves.

We know that the viruses and bacteriophages cannot be generalized and that they vary greatly in size, by a factor of at least 1,000, and in organization. It must also be admitted that the host may make an essential contribution to the reproductive process—for example, by the provision of raw material such as amino-acids. Nevertheless reproduction does occur, and some day we shall know how. That knowledge will be of the greatest consequence to the human race, and all the resources of physical and biological science should be brought to bear on the quest. The discovery of the intimate mechanisms of biosynthesis of proteins would clearly have repercussions in fields such as heredity and ageing, and it might show the way to the conquest of cancer and the viruses.

The study of living things necessarily starts with the family, then proceeds to the individual organism, then to its parts—morphology before physiology; it is a development from the outside inward. The physical sciences often adopt the same method; but the system of organic chemistry, like mathematics, proceeds from the simple to the more complex. It seems that the biologist and the chemist, using these different methods of approach, are nearing one another at the level of the proteins and viruses. Godspeed to their meeting.

I would now like to refer to a few matters of detail. As I have already said, the selection I have made is somewhat arbitrary and reflects my own recent interests.

Configuration of Antibiotics

The hydrolysis of penicillin—of all the penicillins so far as is known—affords a bis-homologue of cysteine called penicillamine. This is not the dimethyl derivative of natural *l*-cysteine, but of the optical antipode, *d*-cysteine. The configurations of the amino-acid units of proteins are related; they are all male screws or perhaps all female; we can't tell which. Thus penicillamine belongs to the "unnatural" family of amino-acids. Similarly gliotoxin is degraded to unnatural *d*-alanine, and the peptide group of antibiotics such as gramicidin seem also to be built up largely from unnatural amino-acids. It has just been reported that streptomycin can be degraded to *l*-glucosamine, whereas the natural glucosamine is the *d* form. These coincidences are significant.

Dr. J. W. Cornforth has suggested that the common factor may well be that the antibiotics are protected from destruction in the body by their antipodal configuration. This seems a reasonable view, and it leads to the conclusion that whereas optical activity is certainly not always an essential feature of a chemotherapeutic agent, yet, when the possibility exists, the *d* and *l* forms should always be tested separately.

Gause states that the *d*- and *l*-mepacrines are equally effective against malaria, but that the *d* variety is only half as toxic as the *l* variety. Hammick and Chambers, using the racemic compound, found that the *d* form is metabolized in the body and that the drug excreted in human urine consists entirely of the *l* isomer. The collation of these results does not spring to the eye, but, as in other matters, anything is more welcome than indifference.

Toxic Fatty Acids

Dr. N. Polgar has been studying the fatty acids of tubercle bacilli, first examined by Anderson. They are of interest because of their toxicity and power to produce lesions in experimental animals. The saturated phthioic acid, $C_{26}H_{52}O_2$, is typical of a whole range of these constituents that can be isolated from the bacillary bodies. The available evidence

indicates that it is 3:13:19-trimethyltricosanoic acid—that is, it is a straight-chain C_{23} acid with three methyl notches. A synthetical acid of this structure which has been obtained is probably a stereo-isomeride of phthioic acid. This, and a related unsaturated acid, are markedly toxic, and examination of near relatives shows that the property is highly constitutive. Polgar suggests that the methyl groups may facilitate dehydrogenation in their vicinity and that the products may antagonize some essential unsaturated fatty acid. It is too early to discuss this tentative hypothesis, but we no longer regard this investigation from the point of view of a direct attack on the bacilli. The objective is now to find a means of alleviating the symptoms of the disease and thus perhaps to give it a more favourable course.

Action of Carcinogenic Agents

The mechanism of the action of carcinogenic agents and the relation of carcinogenicity to constitution have been the subject of much research and discussion, but no generalization has emerged. This is certainly partly due to the fact that the biological experimentation has not been standardized and to the doubtful nature of many of the findings. Dr. I. Berenblum and I have surveyed the results and think that the weight of evidence indicates the possibility of reaction at an activated phenanthrene-type bridge in the great majority of cases; but there are apparent exceptions, and more than one mechanism may be involved. We do not intend to advance even a provisional hypothesis until more experimental evidence has been garnered.

One method of attack is to test substances derived from known carcinogens by replacement of a benzene ring by the isosteric thiophene nucleus. It has been found that such substances may be powerful carcinogens. In the case of 9:10-dimethyl-1:2-benzanthracene there are three benzene nuclei that might be so replaced. In two of the cases, that has been already carried out by Fieser, and the products are reported to be carcinogenic. B. Tilak has now made the third isomeride at Oxford. In this the phenanthrene bridge is replaced by sulphur, and the substance is not carcinogenic by subcutaneous injection. It is weakly carcinogenic in the painting technique, but the tumours show a tendency to regress. Many other examples must be studied, and the observations of Dodds, Lawson, and Williams that α-ethyl-β-sec-butylstilbene is carcinogenic can be brought into line with the phenanthrene-bridge idea only by assuming dehydrogenation of the agent *in vivo*.

There are many tantalizing indications of the possibility of a chemotherapy of cancer which is, however, never likely to prove so simple a process as the control of an infection by a sulphonamide or penicillin.

A considerable number of substances have been observed by Haddow and others to cause retrogression of tumours in experimental animals, but, so far as I am aware, none has found practical application. A different approach is mentioned by Prof. Gye in his recent report of the Imperial Cancer Research Fund. A delay in the appearance of mammary cancer in mice can be brought about by thiourea, which blocks thyroid activity and so lowers the basal metabolic rate.

That is, by way of digression, another fascinating story of the interaction of chemistry and medicine. It includes Harington's work on thyroxine, culminating in its synthesis, and the demonstration of its biosynthesis from the tyrosine bound in proteins; as well as the use of thiourea, then thiouracil or its alkyl derivatives, in cases of Graves's disease.

But the most dramatic indication that certain types of carcinoma may be amenable to chemical treatment arises directly from the work of Prof. E. C. Dodds, here at the Middlesex Hospital. It would certainly be carrying coals to Newcastle to describe the stages by which Dodds and his collaborators were led to the striking discovery of potent synthetic oestrogens, or to dilate on the proved value of these substances in medical and veterinary practice. I will only remark that as far back as 1933 Cook and Dodds noted that certain carcinogens exhibited oestrogenic properties, and the oestrogen–androgen relationships with various forms of cancer are now widely recognized and discussed. Arising from this, several American groups, and especially Huggins, were led to try stilboestrol, either as a substitute for or in conjunction with orchidectomy, in cases of cancer of the prostate. The early results were highly encouraging, but later experience suggests caution.

Inquiries which I made when in America in August of 1945 elicited that about 80% of the patients experienced marked improvement with retrogression of the tumours and repair in many cases. However, the tumours reappeared at various intervals in the majority of the cases, but some 20% remained cured after two years. If that is a fair statement and my arithmetic is correct, it means that at least two men in every hundred over 50 years of age will have reason to be grateful for the discovery of stilboestrol.

Modern Chemotherapy

At the present time the development of chemotherapy is no longer a question of the blind preparation of a series of related compounds to be tested and reported on as good, bad, or indifferent. That system went far to justify the remark of a physiologist at a committee of which I was chairman, that he "thought they had now devised an excellent system for turning down the substances produced by the chemists." Thanks to the discoveries of Woods and Fildes and others, we try to find some rational basis for chemotherapy and, be it right or wrong, a working hypothesis is invaluable. For example, the discovery of paludrine by Curd and Rose followed stages suggested by analogies in constitution to known active substances, as well as by a hypothesis of the mode of action of antimalarials. I commend their paper to your attention as an outstanding example of intelligently guided approach in this type of research. Incidentally, this is an opportunity to recognize with gratitude our debt to workers in the laboratories associated with chemical industry. Bayer 205, neosalvarsan, pamaquin, mepacrine, paludrine, prontosil, and sulphanyridine are a few examples of a long list of valuable agents which we owe to industry. Another modern development is the attention which is paid to the ease of absorption of the agents, their distribution in the body, the metabolic changes they undergo, and the side-effects they produce.

Hence successful medico-chemical research depends on effective co-operation, and this is most easily achieved when those trained in the different disciplines work under one roof.

For practical reasons, such as the dangers of amateur bacteriology and the upkeep of animal-houses, the chemist is normally the migratory component. But it is not enough to ensure that every medical research institute is equipped with a staff of chemists. The biologist is the first to encounter the problems, and even when they are clearly of a chemical nature there is often a serious lag before the appropriate chemist can make his contribution. In this respect we have compared rather unfavourably with some other countries.

Conclusion

Finally, I think that steps should be taken to improve the teaching of chemistry to medical students by drastic revision of the syllabus and by better laboratory facilities. In this way we may quicken the interest of medical men in general in developments which are sure to assume greater and greater importance. I venture to think, too, that a quicker route to medical scientific research should be open to a limited number of promising students, without the loss of the prestige of a medical qualification. That, I know, is a very thorny problem, and its solution would involve some break with tradition.

In some quarters faith in the eventual full success of the applications of chemistry to medicine is regarded as evidence of a materialistic outlook, and the defects of chemotherapy, as at present practised, are eagerly emphasized. Interference with physiological functions and the encouragement of resistant strains doubtless exist, but who can deny that mercury, salvarsan, sulphanilamide, sulphadiazine, and penicillin are milestones in a march of progress and that, without making extravagant claims to comprehend the whole field of medicine, the biologist and the chemist, hand in hand, can still do much more to alleviate the sufferings of humanity?

The Bureau of Current Affairs, 117, Piccadilly, London, W.1, has now produced the first numbers of its fortnightly publication, *Current Affairs*, which is available to civilian subscribers at 8s. 6d. per annum as well as to the Services; No. 3 comprises an article by Ritchie Calder entitled "Health of a Nation."