BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 2 1947

THE PART OF CHEMISTRY IN THE NEW THERAPEUTICS*

BY

Sir HENRY DALE, O.M., G.B.E., F.R.C.P., F.R.S.

The relations between Chemistry and Medicine have varied very widely over the centuries. In origin they were more closely related than some others of the major departments into which science has become differentiated, but I shall not discuss the more precise nature of their original connexion—whether chemistry arose from attempts to explore the therapeutic aspect of medicine, or whether chemistry and medicine began together to grow out of the teaching and experiments of the alchemists. It is of interest, I think, to note that chemistry and the physiological basis of medical knowledge seem to have acquired a common interest at some of the great formative periods in the history of experimental science—with the advances made by Boyle, Hooke, Mayow, and their group towards the end of the seventeenth century, and again with those due to Priestley and Lavoisier a century later, from which we are accustomed to date the rise of modern chemistry.

Organic Chemistry in Medicine

In the earlier part of the nineteenth century organic chemistry became differentiated as the chemistry of the products characteristic of the tissues and the activities of living organisms. Then the success of chemists in reproducing some of these, and imitating others, by artificial synthesis attracted organic chemistry for a period into exploring a vast new range of artificial compounds of carbon, to meet demands of industry and the arts as well as to extend knowledge and theory of the reactions and properties of such organic compounds and the scope and methods of practicable synthesis. A case could be made, I think, for suggesting that in the latter third of the nineteenth century medical science may have been retarded on that side of its development by default of the earlier linkage with chemistry. So far as the experimental disciplines of medicine were using chemical methods at that period, they were using them, in the main, at a relatively superficial level, so that men spoke in those days of "chemical physiology" and "chemical pathology." It might be suggested, on the other hand, that such delay represented a phase of preparation for later advance; that medical science was indeed engaged in necessary levelling, clearing, and tilling of the land, and that in the new century organic chemistry, with an immensely strengthened equipment, would the more rapidly make fresh and fertilizing contact with physiology and pathology, and that seed and soil would then alike be ready to produce the harvest of biochemistry and chemotherapy which we are even now reaping.

You will have in mind the recent loss from our British circle of scientific men and from that of the world's leaders in biochemistry of Frederick Gowland Hopkins, whose active years bridged the turn of the century. His earliest attempts and achievements show Hopkins to have possessed a natural genius for the methods and ideas of organic chemistry and a special interest for applying these to problems of biology and medicine. But Hopkins, I know, had in those earlier years the feeling that, whatever the precision and the significance of his results, since his work was done with a biological or medical approach and in a medical centre it would arouse no interest and obtain no recognition in the circles of official chemistry. One who preceded Hopkins as a pioneer of such true biochemistry in this country and in the world—J. W. Thudichum—had received little recognition as a chemist and even opposition and discredit from others using chemical methods in medical science, though many of his remarkable discoveries, made much in advance of their time, have in later years been rediscovered, confirmed, and reinstated. Hopkins was, happily, to live long into the era of recognition and honour for biochemistry and for himself as one of its pioneers and leaders, and to remain its active devotee till his recent death in the fullness of years.

Whatever the factors which may have contributed to the change, as we now approach this century's middle years and look back to its beginning we become aware of the astonishing range and rapidity with which a new community of interest and action has developed between chemistry on the one side and experimental medicine and biology on the other. First on its organic side, and then at the numerous growing-points on its margin with physics, we see chemistry acquiring relations of growing intimacy and deeper penetration with almost every active phase of advance in the physiology and pathology of animals and plants, and the accent becomes ever stronger on the chemistry in biochemistry. A speaker with suitable equipment could easily use the whole of the time at my disposal in expounding the transforming effects of this more intimate association with chemistry on any one of a large number of special aspects of biological or medical investigation—advances in structural knowledge of the different types of the organic components of the living substance, of the proteins, the carbohydrates, the fats, the lipins, the nucleotides and nucleic acids, of their metabolism, and of the specific differences and immunological reactions, of some of them; of the range of characteristic end-products—alkaloids, purine derivatives, and the rest—of the metabolism of animals and plants; of systems of enzymes and

*A lecture delivered at the XIth International Chemical Congress, London, 1947

coenzymes and their specific substrates; of vitamins and hormones. An attempt merely to complete such a catalogue would make too heavy a demand on my time and your endurance. I must choose one limited field of such co-operative action of chemistry with experimental medicine for more detailed discussion; and I propose to invite your special attention to some of the recent contributions which synthetic chemistry has made to the specific medicinal treatment of diseases, and in particular of diseases due to infections.

Search for Specific Remedies

It is of interest to recognize in retrospect that the very conception of a specific therapy of diseases, in the sense of a systematic search for remedies dealing with their causes, is of remarkably recent origin. Till the end of the nineteenth century was becoming near it was almost a matter of assumption that the function of medicinal treatment was to relieve symptoms, and that the removal of the cause of a disease must be left to nature. Then began the recognition that certain diseases were due to defects of natural hormones, and, later, that others were due to the lack of vitamins in the food. Such are not here my special subject, and in passing we can only note the revolutionary contribution which, by the identification and synthesis of these substances largely in the short interval between the two world wars, chemistry, in alliance with experimental medicine, has made to the specific prevention and treatment of such diseases of deficiency. The first world war was nearing its end before the hormone of the first deficiency disease to be treated by replacement—thyroxine—was isolated by Kendall, and that war was well behind us before to-day's chairman, Dr. Harington, made a new landmark in this application of chemistry to biological problems by determining the structure of thyroxine and making it by synthesis. Many, of course, of these chemical achievements have helped to turn the page to further fascinating chapters of research in experimental physiology and biochemistry—as by providing clues, for example, to a new understanding of enzyme-coenzyme systems, on which depend essential component reactions of the life-process. Chemistry has also made a beginning in the production of artificial substances of relatively simple structure but with activity so nearly identical with those of complex hormones as to enable them to replace the latter effectively in therapeutics (cf. stilboestrol, hexoestrol, etc.). Perhaps we get the most impressive idea of the completeness and the rapidity of the change which has occurred in the therapeutic outlook in this direction by recalling that, when the first world war began, the nature of diseases such as rickets and pellagra, widely prevalent in large communities, was still completely mysterious—we did not even know that they were diseases of dietary, or indeed of any kind of deficiency—and that before the second world war broke out chemistry had achieved the artificial production of the missing dietary factors, or vitamins, needed for their complete prevention or treatment.

I must make only passing mention of another kind of specific treatment in which natural immunological methods were employed against diseases due to infections by bacteria. This also had its beginning before the nineteenth century ended. Though it has undergone extensive and practically important developments, which have in recent years tended more and more to the side of preventive treatment, I think it can be said that chemistry, whether physical or organic, has only begun as yet to unravel the fascinating tangle of its complexities. Researches such as those of Oswald Avery and his colleagues, of the late Karl Landsteiner, and of Linus Pauling give abundant assur-

ance, however, of a rich harvest for chemistry from further cultivation of this field.

A New Quest

I am going to ask your attention in rather greater detail to the remarkable and even exciting developments during recent years in the specific treatment of the causes of infection, the direct suppression of the infective agents, by administration of remedies which are artificial products of chemistry or in any case unnatural to the infected human or animal body—the method of which the pioneer, the first and most determined advocate, and the inspiring genius was Paul Ehrlich. Pharmacology at the beginning of the century dealt almost entirely with the effects of drugs on the symptoms. There were a few exceptions—mercury, used since the fifteenth century for a specific treatment of syphilis; cinchona (quinine) and ipecacuanha (emetine), used since the seventeenth century for the specific treatment of malaria and amoebic dysentery respectively. Ehrlich determined to lead a new quest for remedies, and particularly artificial ones, which dealt with the causes of infections, and he called it “chemotherapy.” His conception of the process, as Ehrlich's ideas were apt to be, was picturesque and diagrammatic: he was going to find substances with a maximal affinity for what he pictured as “chemoreceptors” of the infecting parasite and a minimal one for those of the tissue cells of the patient.

It was natural to direct the search first to the discovery of remedies for protozoal infections, since the evidence appeared to show that the body did not protect itself against these by an effective reaction of immunity. There seemed, for example, to be no adequate production of antibodies against the protozoal parasites responsible for malaria. Ehrlich, who with his cousin Carl Weigert had been a chief agent in the introduction of the use of the synthetic dyestuffs into medical histology, had actually tried an experimental therapy of malaria with methylene blue as early as 1891, basing the attempt on its specific affinity for the malarial parasites as visible in a stained film of blood, and on his knowledge, from other researches, of its relatively low toxicity. This attempt, not wholly successful, led no further, probably because of the limitation then of experiments on malaria to the naturally infected human subject. Only later, after Ehrlich's death, with the use by others of the malaria-like organisms which infect birds, did progress ultimately begin in the chemotherapy of the malarial fevers of man.

The effective beginning of modern chemotherapy was made with diseases due to trypanosomes, infection with which Mesnil and Nicolle had shown to be transmissible in endless series in rats or mice. Ehrlich seized the opportunity offered, and, following with Shiga the line of his established interest in the dyestuffs, found the benzidine dyestuff trypan-red as the first effective cure for such an infection in mice. Trypan-red is now only of historical interest, but it provided the starting-point, not only for all modern chemotherapy, but for the particular line of advance that led to “germanin” (“suramin”), the most effective, on the whole, of remedies for trypanosomiasis yet discovered.

Since this new and effective beginning nearly forty-five years ago chemotherapy has of course extended widely and occupies a position of outstanding and still rapidly increasing importance in the treatment of infections. We have not time for more than a glance at a few of the other lines of research in this field which have led to important practical success. The discovery by Thomas and Breinl, in Liverpool, of the activity of the organic derivative of arsenic, atoxyl, on experimental trypanosomiasis in small

animals, gave Ehrlich and his co-workers a new starting-point for researches on the chemotherapy not only of diseases due to trypanosomes but of others, and even more generally important ones, due to spirochaetes. The culmination of this line of advance was in "salvarsan" (arsphenamine) as a remedy for syphilis, relapsing fever, and other spirochaetal infections, with, more recently, the use of the arsenoxide from which Ehrlich and Bertheim had actually made salvarsan by reduction, but which Ehrlich had put aside as too toxic, apparently from lack of a sufficiently systematic trial of suitable methods for its administration.

We have seen that Ehrlich's first abortive attempt at a better chemotherapy for malaria was made with methylene blue, which proved to be no satisfactory competitor with quinine, which, since the introduction of cinchona from South America to Europe in the seventeenth century, had been used empirically for the specific treatment of malarial fevers long before their nature was known. Apart from this very important application, quinine had of course been used in relatively trivial dosage for the routine and domestic treatment of a large range of febrile conditions on which it had no specific action. It was very fortunate that some years before the recent war, clues furnished originally by consideration of the structures of quinine and methylene blue had led research workers for German industry to the discovery, by experiments on malaria-like infections of birds, of one substance, "atebrin" (mepacrine), which was at least as effective against malaria as quinine, and that an intelligent anticipation of what might be coming had led to the manufacture in England and in the U.S.A. of sufficient quantities of mepacrine to meet the need before Japan had seized the cinchona plantations on which the world depended for quinine. Then followed a vigorous and organized campaign of co-operative research in Britain and the U.S.A. Chemists in a large number of academic, official, and industrial laboratories produced substances for trial on different types of malaria-like infections in birds, and eventually, in a few favourable cases, on malaria in man. The evidence yet available seems to give the first claim to a relatively simple substance named "paludrine" (Curd, Davey, and Rose), with a chlorophenyl group attached to a diguanidine nucleus, for superior activity in both prophylaxis and treatment of malaria over any remedy hitherto available, together with a remarkable freedom, in dosage effective for such purposes, from any toxic effects. And if such a result could be achieved in a few years under pressure of wartime necessity there seems no reason to assume that something even better may not be within reach of further effort. The chemical research leading to paludrine has given what may be a very important clue in the strong suggestion it affords of an association of anti-malarial activity with groupings susceptible of tautomeric changes.

The Sulphonamides

Those must suffice as examples of the success of chemistry in producing such specific remedies for infections with protozoa and spirochaetes, though there are several others which could be cited if time allowed. For many years, by contrast, synthetic chemistry had a conspicuous lack of success in discovering analogous artificial remedies for the bacterial infections more familiar to ordinary experience in temperate climates—pneumonia, septicaemias, and the rest. There appeared, indeed, to be plenty of excuse for the long-prevalent outlook which had almost accepted the view that the methods of chemotherapy were inapplicable to bacterial infections and that the specific treatment of these must be left to immunological agents. Then in 1935 there was a sudden and dramatic change in the situation. Domagk's "prontosil," and the sulphanilamide found

by Trefouel, Bovet, and Nitti to be its effective moiety, were soon established by clinical trials in this country, in the U.S.A., and then in all the world to be highly effective against streptococcal infections in particular, and for the first time conditions like streptococcal septicaemia following childbirth came under effective treatment. Then came the first preparation by Ewins and Phillips of the first derivative of sulphanilamide—sulphapyridine—with a sufficient enhancement of activity to make it effective against pneumonia (pneumococcus) and cerebrospinal fever (meningococcus), as discovered by Whitby. A series of others followed in rapid succession: some, such as sulphathiazole and sulphadiazine, with a generally higher effectiveness and lower toxicity; others, like sulphaguanidine and sulphasuxidine, owing their special use to the restriction of their actions largely to the bowel and its lining membrane, having particular effectiveness in the treatment of bacillary dysentery; yet others suitable only for local application to infected wounds. In their different ways and various applications it is not too much to say that, with the production of this series of sulphanilamide and its derivatives coming just when it did, chemistry, working in alliance with experimental medicine, had changed the whole aspect of the treatment of wounds and diseases of campaign, in the war which was to follow within a few years of the primary discovery. And we have only to look back to the available methods of dealing with the serious bacterial infections before 1935 to recognize the revolutionary change which chemistry, in its applications to chemotherapy, has also produced in the prospect of sufferers from these bacterial infections under the normal conditions of peace.

The discovery of substances with such a potent remedial action against infections by bacteria, which can so readily be maintained in culture on artificial media, provided new possibilities also for investigating the fundamental nature of the chemotherapeutic process. It soon became clear that the action of sulphanilamide and its derivatives, even in concentrations much greater than could ever be produced in the body fluids of the patient, was not to kill the bacteria but simply to suspend their multiplication, the curative effect in the living body being therefore not due to a direct killing of the infecting organisms but to a restrictive action on their power of growth and invasion, sufficient to tilt the balance in favour of the natural defences of the body. Chemistry has further provided at least a first hint of the nature of this bacteriostatic action. From bacteria susceptible to the action of sulphanilamide a substance could be extracted which, if present in sufficient concentration in the culture medium, neutralized the bacteriostatic action; and this was identified by Woods as *p*-aminobenzoic acid.

It seems likely, then, that sulphanilamide and its derivatives can somehow preoccupy the position, in relation to some enzyme system concerned with growth and multiplication of the organisms, that *p*-aminobenzoic acid would normally fill, and can thereby suspend the growth process. This can be only a part of the story, since other quite effective bacteriostatic agents, not distantly related in general molecular configuration to sulphanilamide, are unaffected in activity by the presence of *p*-aminobenzoic acid. Nevertheless, I think we can conclude that observations like those of Woods are opening the way to an interpretation of the action of the substances, and eventually of a much wider range of chemotherapeutic actions, in terms of chemically rational conceptions instead of in those hitherto current, which, in some cases at least, have been little more than impressive or picturesque labels for the unknown. There is a fascinating field here still inviting patient exploration,

and I venture to hope that we—medical biologists and chemists alike—shall be able to resist the temptation to simplify the problem unduly and to accept too easily as a solution a correspondence which may be no more than an indication; though a most valuable one, of the nature of one of the factors involved in a much more complex mode of action. Meanwhile any hint is of value which will give chemistry a rational clue to follow in this quest.

Penicillin

Hard on the heels of the revolution in the chemotherapy of the bacterial infections came that due to the renewed investigation by Florey, Chain, and their co-workers on penicillin, the existence of which had been made clear by Fleming's observations ten years earlier, and which had then dropped almost out of memory after a tentative chemical investigation by Raistrick had revealed its acidic nature and solubilities, but had suggested a baffling instability under conventional procedures for its separation. The story of how such difficulties were overcome, of the extraordinary potency and harmlessness of penicillin revealed by freeing it from undesirable concomitants, of large-scale manufacture rushed ahead to meet war's needs, the constitution of the now several penicillins determined by a great co-operative effort of British and American chemists and even confirmed in one case by an artificial synthesis (De Vigneaud)—all this is one of the almost romantic scientific achievements of chemistry, working in close alliance with medical biology, attained under the stimulus of the needs of armies in the recent war. And the magnitude of the opportunity now open to chemistry in this new field of antibiotics can as yet be no more than a matter of hopeful speculation.

Symptomatic Treatment

In the time at my disposal, even one aspect of the rapidly expanding service of chemistry to scientific therapeutics which I have chosen for special mention can only be presented thus in selective sketches with but little detail and with no attempt to make the presentation inclusive. There is only time left to me, before I conclude my lecture, to make it clear that, while I have specially dealt with the elimination of the causes of disease as a relatively novel aim and achievement of therapeutics, made brilliantly selective by an alliance of growing intimacy with chemistry, I am by no means depreciating the importance of the alleviation of symptoms. In this direction, also, chemistry has been furnishing a wealth, even in some directions an embarrassing excess, of alternatives—competitive ranges of hypnotics, analgesics, local anaesthetics, diuretics, laxatives, and so forth. And if anybody should doubt the real value, on balance, of the service which chemistry, with intelligent medical use of its gifts, has thus rendered to the ease and the safety of afflicted humanity let him go, for an impression of contrast, to any friend who has had the experience of anaesthesia for operation two or three decades ago and again in recent years. Nor, I think, can it be doubted that in this field of symptomatic treatment again a strengthening collaboration is enabling both chemistry and pharmacology to replace a shallow empiricism by an ever stronger foundation of scientific understanding. If I may be allowed to mention two examples, which have caught my special interest as having some relation to physiological studies of my own, we have recently seen the emergence of a series of synthetic pharmacological antagonists to histamine for the treatment of asthma and other allergic manifestations, and, even more recently, the use of D.F.P. (di-isopropyl-fluorophosphonate), a potent and permanent antagonist of cholinesterase, to relieve the dangerous post-operative paresis of the intestines.

ANOMALOUS MANIFESTATIONS OF MALNUTRITION IN JAPANESE PRISON CAMPS

BY

R. G. S. WHITFIELD, M.R.C.S., L.R.C.P.

Late Surgeon Lieutenant-Commander, R.N.V.R.

In a leading article in the *British Medical Journal* of June 22, 1946 (p. 958), the following passage appeared: "But in the Tropics and in war-stricken European countries field workers have demonstrated repeatedly that the clinical picture shown by malnourished or starved populations may often differ widely from textbook descriptions. As Stannus has pointed out, unknown or ill-defined deficiency diseases probably far outnumber those whose characteristics are already plainly established." Nearly four years in eight Japanese prison camps convinced me of the truth of these remarks, and three clinical conditions are described as illustrations.

Diet

Dietetically the period falls into two divisions:

1. *White Rice Period (January to October, 1942).*—Rice (polished), about 10 oz. (280 g.) daily; wheat flour (white), about 8 oz. (230 g.) daily; sugar, about 1 oz. (28 g.) daily; taro root and sweet potatoes, 4 oz. (115 g.) sometimes; vegetable soups of spinach, turnip tops, chrysanthemum leaves, onions, cabbage, about 8 oz. (uncooked); vegetable oil, about 1 oz. daily for frying; meat, fish, whale, approximately 3 oz. (85 g.) three times weekly until June, then diminishing. The daily diet is summarized approximately in Table I. There were almost certainly deficiencies

TABLE I

	Calories	Protein (g.)	Fat (g.)	Vit. A (I.U.)	Vit. C (mg.)	Thiamine (I.U.)	Nicotinic Acid (I.U.)	Riboflavin (I.U.)
Normal requirements	3,000–4,000	100	100	5,000	75	2,000	23,000	1,600
Probable minimum requirements	2,000	30–40	20–30	2,000	15	900	10,000	1,000
1942 diet	1,800	40–45	30	3,400	35	500	250	700

in pantothenic acid and pyridoxine (vitamin B₆), and possibly in biotin, vitamin E, and folic acid.

2. *Barley and Bean Period (November, 1942, to August, 1945).*—Whole-grain barley and millet were substituted in the rough proportion of three parts barley, one part millet, and one part polished rice. Meat—usually rancid pork—2 oz. (57 g.) monthly; fish, 4 oz. (115 g.) monthly; seaweed, 40 g. daily. Other foods according to season were the usual Western vegetables, plus daikon (a sort of giant radish-turnip), daikon tops, soya-bean paste and curd, sweet potatoes and tops, taro roots, egg-plant, pea-pods, bracken stalks in brine, dried octopus, snakes, wasp grubs, and the pupae of silkworms ("1 pupa = 2 hen's eggs"—any Japanese). Soya beans were issued fairly regularly and were our most valuable food. Deprivation always produced an increase of sickness. The calorie value varied from about 3,000 (1943) to 1,500 (1944). Thefts of food by the Japanese and the prisoners, and the unbelievable trading in food that went on, made it impossible to know how much was being eaten; and because of the intermittent and, in many cases, constant diarrhoea, together with the unexplained nocturnal diuresis, we could not estimate what was being absorbed. The unreliability of Japanese vitamin B injections (prepared from yeast or rice