Progress in Science and Pharmacy.[1]

By CHARLES ALEXANDER HILL.

TWENTY-FOUR years have passed since the British Pharmaceutical Conference met in this great city of Liverpool. On that occasion the late William Martindale in his presidential address dealt with the use in medicine of "active principles" in substitution of the natural, *i.e.* naturally occurring, drugs. At the same time he described the introduction of synthetic substances into medicine as a novelty.

To-day it is fitting to reflect upon the changes in pharmacy wrought by progress in science—progress in chemistry and biochemistry, in physics, in physiology, and in the science and practice of medicine; next, to examine the extent to which active principles and synthetics have replaced natural drugs; then tentatively to survey the lines upon which future development may be expected.

Of the changes that have occurred the increased use of synthetic drugs is the outstanding, though by no means the only, feature. It is noteworthy that important discoveries of new vegetable drugs are practically unknown. The animal kingdom, on the other hand, has furnished us with drugs of the first importance; of these the products of the pituitary body, the thyroid gland, and the suprarenal gland afford notable examples. The importance of these discoveries is in nowise diminished if the active principles have been synthesised and can be produced artificially.

The use of synthetic remedies in medicine is sometimes said to date from the introduction of antipyrin in 1884, but chloroform and chloral hydrate had long been known and used, and synthetic salicylic acid was freely used in 1877. Hypnone (acetophenone) followed in 1885 and antifebrin (acetanilide) in 1886. These were succeeded by phenacetin, sulphonal, and trional, and since then there has been a steady flow of new synthetic drugs.

To-day the world's annual consumption of phenazone or antipyrin may be roughly estimated at 100 tons, of phenacetin at 250 tons, and of medicinal salicylates (sodium salicylate, methyl salicylate, aspirin, and salol) at no less than 2500 tons, and these are a few only out of the multitude of pure chemical substances used in medicine.

Notwithstanding the remarkable extent to which synthetic drugs have come into use, and despite the increased employment of active principles according as our knowledge of these progresses, the use of the drugs themselves in the form of galenical preparations, whether "standardised" or not, continues to a remarkable, and perhaps significant, extent. Furthermore, as we shall see, signs are not wanting of a growing recognition of the truth that many a drug and many a food may contain valuable properties not readily determined by chemical methods. It may be only slowly that the full value of a drug discovered empirically can be stated in scientific terms. Paradoxical as it may seem, the tendency to-day, with advancing scientific knowledge, is to recognise the failure of the active principle to replace the parent drug.

When it happens, the replacement of a natural drug by a synthetic substance may be conceived as proceeding ideally in four stages. First, the drug is examined chemically, and from it is isolated a pure substance, frequently an alkaloid or a glucoside, which upon being subjected to physiological tests is found to have an effect similar to that of the parent drug; such a substance is termed the "active principle" of the drug. The second stage is to determine the chemical constitution of the isolated active principle; this, in general, is a matter of extreme difficulty, taxing the resources of our most brilliant organic chemists, which, indeed, is equally true of the third stage, which consists in effecting the synthesis of the substance. Once the synthesis has been successfully accomplished we arrive at the fourth and last stage, which is the manufacture of the substance upon a commercial scale. The case of suprarenal gland and adrenalin affords an illustration.

It does not follow as a matter of course that if the synthesis of a substance be accomplished the artificial or synthetic article will replace the naturally occurring one. Supposing quinine were to be synthesised, it is by no means to be assumed that it would be cheaper to produce it on a large scale in the laboratory than to get Nature to conduct the synthesis, and then to extract the alkaloid from cinchona bark and afterwards purify it. It has been amply illustrated in the case of cinchona bark that it pays to subsidise Nature and to encourage her to increase her yield. Intensive culture may be a better business proposition than laboratory manufacture.

Synthetic Drugs.

By far the larger number of chemical substances used in medicine are not the active principles of natural drugs. It would lead me beyond the confines of my address to attempt even a cursory survey of what has been accomplished in the limitless field of synthetic drugs, to the enormous consumption of which I have already made reference, or to make more than the barest mention of the fact that synthetic organic substances are employed as antiseptics, anæsthetics, narcotics, hypnotics, and antipyretics, and in the treatment of diseases, notably those of parasitic origin.

Nor need I remind you of the many attempts made by chemico-physiologists to correlate chemical constitution and physiological action. Much chemical and physiological work has been done in this fascinating field of research, and certain generalisations have resulted by deductive reasoning from very numerous data, yet it has to be admitted that really very little is known of this borderland subject. The physical condition of the substance, its solubility, especially its relative solubilities in different solvents ("partition coefficient"), its adsorptive power, osmotic properties, and other physical properties, have as much to do with its physiological action as has its constitutional formula.

It may indeed be that the purely chemical action of a drug is destined to play a subordinate *rôle* in therapy, and that, in the past, the physical action has not been sufficiently considered.

Chemotherapy shows us clearly that the physiological action of a substance is not due to one constituent only of that compound, but that it also depends largely upon the molecular orientation of the compound and the ratio of adsorption which exists between it and the protein colloidal particles through which this or that constituent is going to act. Consider arsenic, for example. In the treatment of disease plain liquor arsenicalis is not so effective as colloidal arsenic sulphide, nor is the latter so effective as arsenophenylglycine, nor the last so effective as diaminoarsenobenzene. They all contain arsenic, but the last, in virtue of its amino-groups, is able to be adsorbed in very large quantities by the protein colloidal particles; consequently, the greatest amount possible of the element gets taken up. So far as can be seen at present, the amino-groups are of great

[1] From the presidential address delivered at the Royal Institution, Liverpool, on July 20, at the fifty-seventh annual meeting of the British Pharmaceutical Conference.

importance in a chemotherapeutic compound, especially if they can be placed in the ortho-position to the element one wishes to incorporate.

Of greater importance than the group is the molecular orientation; one needs only to mention the effect of introducing an acetyl group to illustrate this point. Compare diorthoaminothiobenzene with its acetyl derivative; the former is practically a specific for metallic poisoning, while the latter is as inert as plain colloidal or sublimed sulphur. Even diparaaminothiobenzene cannot compare with the ortho-body. The addition of an acetyl group to salicylic acid results in a new analgesic property, while at the same time the undesirable after-effects of salicylates are in some measure eliminated. A similar addition to phenetidin gives us phenacetin with its valuable antipyretic properties. On the other hand, the addition of an acetyl group to parahydroxyphenylethylamine (an active principle of ergot) results in a loss of activity. The introduction of an acetyl group into the choline molecule converts this comparatively inert substance into a powerful heart poison. Highly interesting is the case of aconitine. This intensely poisonous alkaloid is the acetyl derivative of benzaconine, the latter substance being relatively non-toxic. Yet the introduction of further acetyl groups into the aconitine molecule does not increase, but diminishes, its toxicity.

Recent Advances in Biochemistry.

Theoretically, every ingredient of a drug or preparation must have some effect, though it may be so small as to be inappreciable by any known means; and some drugs and foods have constituents minute in quantity, and therefore long unknown, of the very highest degree of importance. Indeed, recent advances in biochemistry have proved the existence in drugs and foods of physiologically active substances which give a rational explanation of facts based upon experience and established empirically.

Fresh in the memories of all of us is the discovery of the cause and cure of beri-beri, constituting one of the romances of medical science. Beri-beri is a disease of a high mortality which ravaged tropical countries and caused much misery. It had long been connected in the minds of the investigators with the rice which formed the staple food of the populations affected by it, but it has only recently been discovered that the disease is caused by the refinements of rice-milling, brought about by the introduction of machinery. It was observed by Eijkmann, the medical officer to a prison in Java, that the poultry of their establishment suffered from symptoms remarkably like those of beri-beri, which was common in his gaol, where the inmates were fed on a rice diet. Investigations showed this observer that the fowls could be quickly cured by adding to their diet the pericarp and embryo of rice removed during the process of milling.

From this starting point there was established by research a complete correlation between the occurrence of beri-beri and the consumption of steam-milled rice. In districts where rice is polished by hand the disease does not frequently occur, because it rarely happens that the whole of the pericarp and embryo are removed by hand. Fowls fed on polished rice quickly suffered from polyneuritis, and birds almost at the point of death were quickly rescued, it was found, by the administration of a watery extract of rice polishings. Thus was beri-beri found to be caused by the absence from the diet of a substance soluble in water and present in rice polishings.

This water-soluble constituent belongs to a class of accessory food substances which have been somewhat unfortunately named "vitamines." Work on these vitamines can scarcely be said to have a chemical basis, since all attempts to isolate them have failed. At least three have been recognised: (1) water-soluble B factor, which prevents beri-beri, occurs in the seeds of plants and the eggs of animals, in yeast and liver and grain cereals.

Scorbutus or scurvy is a disease which in former times caused high mortality. Sailors particularly were subject to attack, this being due to the fact that they were not obtaining another water-soluble vitamine, (2) the anti-scorbutic factor. The disease yields readily to a diet of potatoes, cabbages, and most fresh fruits.

Thirdly, there is a fat-soluble vitamine; this is present in cream and butter and beef-fat, and affords us a rational explanation of our natural preference for real butter over vegetable margarine. Cod-liver oil, which may be regarded as intermediate between foods and drugs, has long enjoyed a deservedly great reputation as possessing qualities superior to those of other oils. These qualities are due to the fact that good cod-liver oil has a high vitamine content, and is therefore important in the prevention and cure of rickets. On the other hand, vegetable oils, such as linseed, olive, cottonseed, coconut, and palm, contain only negligible amounts of this vitamine.

Biochemistry shows us the importance of other accessory substances besides vitamines. Enzyme action has been shown to be modified or stimulated by the presence of other substances termed co-enzymes. Parallel phenomena have been observed in the digestive processes of mammals in the remarkable activating nature of bodies termed hormones.

It would be beyond the limits of my address to go further than these somewhat brief indications that naturally occurring drugs and foods contain substances that long remained unsuspected and still longer unrevealed, but quite enough will have been said to show how unsafe it is to substitute one thing for another.

Research.

It is not easy to state concisely what is to be distinguished as pharmaceutical research. All will agree that it means something more than an improvement in processes for the exhibition of drugs in pharmaceutical preparations. Does it mean problems arising out of the cultivation of drugs not hitherto grown within the Empire, or the intensive cultivation of indigenous drugs with a view to increased activity, or the chemical investigation of drugs for their active constituents; or, again, does it mean research in organic chemistry for the production of new synthetic remedies, or does it mean pharmacological experiments, or all of these things? I would submit to you the following consideration: We have seen that pharmaceutical preparations of drugs continue to find employment even after the active principles of those drugs have been isolated, and are readily available in a pure state. We have seen that drugs and food-drugs are found to have valuable properties which cannot be stated in definite terms in the present state of our knowledge. Further than this, as our knowledge of such bodies as vitamines, enzymes, and hormones advances, so increases our respect for the natural source of such bodies—they may be glands or they may be seeds—whether as a food or as a remedial agent. Such may be the fate of many an "old-fashioned" remedy about which hard words have been used merely because it was not fully understood. Here then, it seems to me, is presented a most fitting subject for pharmaceutical research: to determine and control the conditions of collection and preparation of the parent drug, the process of treatment and manufacture and the conditions of storage, to discover characters and devise tests within the scope of the skilled, trained pharmaceutical chemist without involving experiments upon living animals, so that the pharmaceutical preparation exhibiting the drug shall be both active and uniform.

The Future.

The annual meeting of the British Pharmaceutical Conference affords a great opportunity for all pharmacists to meet each other on common ground and consider their common interests. Is not the present a period in pharmaceutical history at which it is fitting that all of us whose lot is cast in pharmacy should band together for our common welfare? The demands of the business side of pharmacy are to-day so imperious and so obvious that there is a danger of neglecting what, to my mind, is of primary importance if we are to persist. If I am asked what path should be pointed out for pharmacists to pursue in order that the present condition of affairs may be improved and the outlook for the future made more bright, then I say without doubt that the answer lies in cultivating assiduously the scientific side of pharmacy; in the promotion, encouragement, and assistance of pharmaceutical research; in the improvement of pharmaceutical products; and in keeping pharmacy abreast of advances in chemistry, physiology, bacteriology, vaccine-therapy, and other kindred subjects.

Only by giving first place to the professional side of pharmacy, keeping as distinct as possible the purely business side and declining to mix with pharmacy proper business in things so far removed from drugs as to be derogatory to the calling of pharmacy—only thus will it be possible to maintain and enhance the esteem in which pharmacists are held by their fellow-men, both medical men and laymen, as well as public bodies and Government Departments.

The British Pharmaceutical Conference exists for "the cultivation of pharmaceutical science" and "to maintain uncompromisingly the principle of purity in medicine." Let pharmacists see to it that the conference receive full and generous support, and that no effort be, spared to enable it to carry out these worthy objects. Thus shall pharmacists prosper and pharmacy flourish.

Medical Science and Education.

IN his wisely eloquent presidential address to the British Medical Association meeting at Cambridge Sir T. Clifford Allbutt struck many a nail on the head. He began with the claim that the universities, ancient and modern, from Alexandria to Edinburgh, have made the professions, and stated the university ambitions to be building up character, training in clear thinking, and imparting particular knowledge and experience. He confessed, however, that the new universities compare ill with the old in nourishing the imagination. There is need to learn how to teach; there is need for simplification by more blending of details into larger principles; and there is need to beware of letting our teaching stiffen into formulas. Another point, refreshingly illustrated, was the debt of other sciences to medicine, for what impulses have come from medical studies to cytology, to organic chemistry, to bacteriology, and so on, up to philosophy, as the address itself shows. In medical research, as elsewhere, natural observation is yielding more and more to artificial experiment as investigation penetrates from the more superficial to the deeper processes. "The progress of medicine must in large part be endogenous." "Mere observation—Nature's march past—will not count for much now; and as to family histories—well, they vary with each historian." Once more Sir Clifford Allbutt made a plea for the study of the elements and phases of disease in animals and plants—a comparative pathology that would stir the imagination of young workers and save the world from a wastage as unnecessary as it is incalculable. "Yet no one stirs, save to gyrate each in his own little circle. There is no imagination, no organisation of research, no cross-light from school to school, no mutual enlightenment among investigators, no big outlook. . . . How blind we are!" After a very severe but timely criticism of psychotherapy—a criticism which is not marked, however, by any lack of appreciation of the fruitfulness of experimental psychology—Sir Clifford Allbutt closed with some discussion of the immediate problems of general practice and preventive medicine. There is inspiration in the whole address (see *British Medical Journal*, No. 3105, pp. 1–8), not least in its final glimpse of the possibilities before medicine as a social service and international bond.

At the same meeting of the British Medical Association there was an exceedingly important discussion on the place of "preliminary science" in the medical curriculum—a discussion which will lead, we hope, to some highly desirable changes. In his introductory address Sir George Newman indicated several reforms—a quantitative lightening of the curriculum at both ends, a fresh orientation of the preliminary sciences in relation to the training of medical students, but, above all, more biology and more real biology. "It is the biological outlook and spirit that is required, the capacity 'to see great truths that touch and handle little ones'; for biology, pure and applied, is the most educative, germinative, and dynamic subject in the whole curriculum." Prof. S. J. Hickson emphasised the value of biological studies in cultivating habits of verification and precision, in preparing the ground for subsequent anatomical and physiological studies, and in introducing the student to practically important sets of facts, either very concrete as in the case of parasites and their carriers, or more theoretical as in the case of heredity. He recommended a reduction in the number of "types" so as to make room for more important studies, better orientation of what is taught, and more emphasis on fundamental questions—admittedly difficult as it is to handle them well in teaching beginners. Prof. A. Keith urged that "anatomy could be made a living, practical part of medicine if only the teacher would ask himself: Could this fact help me in diagnosis and treatment?" Sir Ernest Rutherford, speaking of physics, insisted on the necessity for a sound training in the fundamental methods and principles of the science before the medical curriculum is begun, and for a subsequent professional course oriented in a judicious way to future studies in physiology and the like. Prof. Lorrain Smith laid emphasis on the fundamental value of the preliminary sciences as a training in method and criticism, but maintained that the general introduction at present supplied is wasteful in its discontinuity with what follows later. It misses part of its aim because its bearings on more professional studies are not made clear. Prof. A. Smithells, speaking of chemistry, indicated some ways in which more value could be got out of the present opportunities if there were more adjustment to the particular ends in view. In general, there seemed to be agreement (see *British Medical Journal*, No. 3105, pp. 8–21) on two points: (1) The need for making sure of a firmer grasp of principles, and (2) the need for a re-orientation of the class-teaching in relation to the particular needs of the medical student.