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CHAIRMAN'S ADDRESS

Fifty Years of Pharmaceutical Progress

In choosing the subject of my address at this eight-seventh Conference I have been influenced by several considerations, not the least of which is that eighty-six addresses have been given previously, covering almost every aspect of pharmacy and its allied subjects, and that therefore my choice must to some extent impinge upon ground already covered by my predecessors in this chair. I was influenced also by the thought that this year of 1950 marks the completion of a half-century of progress in the sciences of chemistry, physics and medicine, and also in the fields of social welfare and legislation, which has without doubt affected pharmacy in its various branches to an extent greater than had been experienced in any like period in the history of our profession. My other reason was a personal one. Although I cannot claim a full fifty years of active association with pharmacy, the period I have chosen for review, which from a pharmaceutical standpoint may be dated by the British Pharmacopœias of 1898 and 1948, was in its earliest years when I first took up a test-tube in the pursuit of chemistry in its application to pharmaceutical analysis. For these reasons I have taken as the title of my address to you to-day "Fifty Years of Pharmaceutical Progress."

I shall of necessity include under this title developments in fields other than pharmacy. A new concept in the world of pure science, or a new line of approach in medical research, or a new application of scientific principles to engineering, may at the time of their birth seem far removed from the realm of pharmacy. They may, nevertheless, either singly or in combination, prove to have a considerable influence on the production or the very nature of the drugs which the pharmacist may in course of time be called upon to know about and handle in the exercise of his vocation.

I will illustrate this relationship with one example; there are numerous others which could provide a fruitful source of interest and instruction to anyone who takes the time and trouble to delve into their history. In the last pharmacopœia one of the new preparations is injection of aneurine

hydrochloride. The busy pharmacist who supplies an ampoule of this preparation and the equally busy doctor who administers the drug to his patient have little time to consider the processes which resulted in its existence. Yet this small ampoule embodies in miniature a characteristic story of the combination of creative ideas, patient research, scientific knowledge and technical skill resulting in a valuable addition to the list of medicaments.

In my example, the history begins with Sir Gowland Hopkins's inspired forecast of the existence of accessory food factors. Research in the field of human deficiency diseases confirmed the idea by the discovery of the presence of a curative substance in rice polishings and later by the isolation from this source of an impure active substance which in minute doses was effective against beri-beri. Organic chemical science solved the constitution of the vitamin and then elaborated its synthesis and the technical chemist was then able to produce the drug we now know as aneurine hydrochloride. The story does not however end here. The drug was now available to the medical profession, but its solutions were found to be unstable unless sufficiently acid. Acidity in excess being undesirable in a solution given by injection, it became necessary to control the acidity between limits ensuring stability on the one hand and tolerance by the patient on the other. It was equally necessary to control the dosage of drug in the ampoule. Progress in physical chemistry supplied the necessary knowledge for these controls. The modern conception of acidity in relation to hydrogen ion activity had resulted in the evolution of electrometric instruments which could measure the hydrogen ion potential with great accuracy and the now familiar method of *p*H adjustment supplied the answer to control of acidity. For dosage control, physical methods were also available, in this case by the newly developed methods of fluorimetry. Finally, the skill of the glass technologist was called into play in the provision of the container, the glass of which had to withstand long contact with the solution of the drug without yielding alkali which would upset its stability.

This interplay of new conceptions and discoveries in the various sciences, of which the above instance is an example, has been responsible for the evolution of classes of compounds of entirely different character from the older drugs, remarkable in general for specific action and very great potency. The vitamins and hormones are examples. In addition, developments in organic chemistry have resulted in an enormous output of synthetic compounds, many of which have been shown by pharmacological testing to be capable of use as curative agents in place of naturally occurring drugs.

The medical scientist has consequently had placed at his disposal new therapeutic agents of proved activity with which to conduct his own researches into the causes and treatment of human disease. The branch of medicine known as chemotherapy, to which I shall refer again later, and which has marked a significant change in medical practice, has

developed largely as a result of the availability of these new compounds. The extent of the changes resulting from this progress in chemical and medical science and from the newer aspects of medical treatment may be illustrated by some comparison of medicine and pharmacy as practised to-day with the conditions which applied at the beginning of the century.

The drugs and galenical preparations used by the pharmacist, in particular those included in the pharmacopœia, are an indication of current medical practice in the treatment of human ailments, and consequently of medical thought and outlook. A comparison of the official drugs and preparations of the pharmacopœias of 1898 and 1948 enables one to appreciate how far methods of treatment have changed from the alleviative and palliative treatment of symptoms to the direct attack on the causal agent responsible for the condition. In the earlier pharmacopœia drugs were mainly natural products of vegetable or mineral origin and there were only a dozen or so of organic compounds prepared by synthetic means. Substances of animal origin, with the exception of those included only for their physical virtues in the compounding of preparations, as for example fats, waxes, colouring and sweetening agents, accounted for still less a number. Cantharides, ox bile, cod liver oil (its vitamin content unknown), two enzymes, pepsin and pancreatin, and one hormone, thyroid, constituted the total in this class. Relics of former medical methods of treatment persisted in the presence of musk and leeches.

Galenical preparations were, on the whole, similar to those which are in common use to-day, although, with the exception of a small group which contained the more potent alkaloids and a few solutions of easily assayed inorganic drugs, they were not required to comply with any standard. Notable differences in the character of preparations were the large number of plaster masses, now entirely eliminated from the pharmacopœia, and an extensive list of pill masses which, with a few exceptions, have also lost their official status. Other changes in methods of administration of drugs are shown by the complete absence of compressed tablets—the only official tablet being the trinitrin tablet in the familiar chocolate base—and by the paucity of preparations intended for use by injection, of which four only were included under the title of hypodermic injections.

By way of contrast, the present pharmacopœia contains a host of drugs and preparations indicative of the new methods of treatment, including the acridine and other medicinal dyes, anti-malarial drugs such as mepacrine and pamaquin, a group of drugs derived from barbituric acid, numerous of the "sulpha" drugs derived from sulphanilamide, as well as biological preparations such as insulin, liver extracts, preparations of the pituitary gland, heparin, sera and vaccines, and the œstrogenic hormones. Most of these were quite unknown at the beginning of the century. The presence of seventy-five injections of these and other drugs is significant evidence of the changed trends in methods of administration.

I will now turn from this general aspect to a consideration of some

of the developments in different fields affecting pharmacy which have played their part in bringing about the changes I have indicated.

Developments in Chemistry

In considering this aspect of my subject, I will first deal with the growth of synthetic organic chemistry in its relation to the elaboration of large numbers of substances of therapeutic value, and continue with an account of the more recent development of the chemotherapeutic agents.

During the first twenty or thirty years of the century the principles of medical treatment maintained their traditional character. Drugs were usually administered for the purpose of alleviating the patient's condition. The prevailing attitude was summed up by Sir Henry Dale in a recent reminiscence. He said " One of the clear impressions left by my student days in hospital, at the beginning of the present century, is that of surprise and disappointment at the lack of conviction, and even of interest, which our teachers showed in medical treatment, in contrast to the care and enthusiasm which they devoted to diagnosis.... Treatment would so often be prescribed with no better hope than to make the patient easier by alleviation of his symptoms, leaving Nature to deal, if possible, with the cause of the trouble." He went on to say, in relation to the paucity of specific therapeutic agents then prevailing, " It is clearer to me in retrospect that it was at the time that there were very few remedies then which were even expected to deal with the cause of disease."

This being the general outlook of the times, it is not surprising that the ideas and energies of organic chemists were directed principally towards the evolution of new compounds which, by reason of their molecular structure in relation to the known constitution of naturally occurring active principles of vegetable drugs, might be expected to exert similar activity. A new branch of science, that of practical pharmacology, was called into service as a necessary complement to chemistry in order that the trial of the thousands of derivatives so prepared might reveal which had the desired action to the best degree, and whether such action was accompanied or not by toxic or other undesirable activity.

Although the main goal of this research was the discovery of new drugs exhibiting similar action to naturally occurring compounds of proved activity, and generally to improve upon Nature, the knowledge which accumulated of the effect of certain groupings in the molecular structure was of a great value when, at a later date, chemists turned their attention to the synthesis of drugs of specific activity against particular classes of organisms; and thus assisted in the advance of chemotherapy. This period in the evolution of pharmaceutical chemistry has been productive of many notable achievements, some arising from the elucidation of the constitution of complex natural substances, others from the successful building up by synthesis of the counterpart of the natural drug or of a new series of derivatives which have proved to have inherent medicinal virtues. Aspirin, one of our commonest and most widely used organic drugs, represents an outstanding example of a purely synthetic substance which

by reason of its effectiveness has become almost a household word. It may surprise some of you to hear that it was only introduced to medicine at the beginning of the century and did not become an official drug until 1914. Other achievements of this period were the synthesis of local anæsthetics such as orthocaine and procaine, the introduction of the barbiturate group of hypnotics, and the development of the acridine dyestuffs.

Effects of the First Great War

Synthetic chemistry continued to occupy the centre of the picture until well after the first Great War of 1914-1918. The war had profound influences in accelerating progress in all branches of chemical and medical science. One of its permanent effects was the establishment on a firm basis of the fine chemical industry in this country and in the United States of America, resulting in a great impetus to research and requiring the education of a large body of trained chemists for all its branches. Another was the extraordinary growth of the application of preventive treatment in medicine arising from the necessity of maintaining millions of armed men in a state of fighting fitness in spite of wounds and of living under conditions conducive to the rapid spread of disease. The end of the war also left millions of human beings in the blockaded countries in a state of serious ill-health as a result of continued malnutrition, and the study of their condition pointed the way to a fuller understanding of nutritional needs and to the essential importance of the vitamins in the treatment of deficiency diseases. The stage was now set for the great advance in chemotherapy which was to follow and which has run parallel with progress in synthetic organic chemistry from that time onwards.

Chemotherapy

I must now retrace my steps in order to give a brief review of this important aspect of the perpetual struggle between mankind and the diseases which afflict him.

The German chemist, Ehrlich, following on the discovery that malaria, sleeping sickness and certain other tropical diseases were due to parasites capable of transmission from one host to another by such agencies as the bite of an insect, began a search for chemical agents which would have a toxic action against these parasites without unduly affecting their host; he thus introduced a new conception into the treatment of disease to which he gave the title of chemotherapy and his ideal chemotherapeutic agent was defined as a substance which would possess a maximum affinity for the parasite and a minimal affinity for the organs of the affected subject.

His first attempts had been in the direction of finding an alternative to quinine as an anti-malarial agent. Methylene blue and various other dyestuffs were tried, but with no real success until much later, when others who followed Ehrlich produced the active drug suramin, which although

colourless, had been derived from a study of the dyes trypan red and afridol violet. Suramin found its main use as a trypanocide, and Ehrlich's successors continued the search for anti-malarial drugs to a successful conclusion when they produced plasmoquine (pamaquin) and atebrin (mepracrine). The later discovery of paludrine (proguanil) is a purely British contribution in this field of research.

Ehrlich, subsequently to his earlier investigations, turned his attention to the organic arsenicals as agents against spirochætal infections, and his discovery of salvarsan not only revolutionised the treatment of syphilis, but established chemotherapy as a new factor in medical treatment. Until 1935 its applications were confined to the treatment of diseases of protozoal origin. In that year Domagk announced the anti-bacterial properties of prontosil, a new drug obtained by the condensation of *m*-phenylenediamine with sulphanilamide. This discovery opened the field of chemotherapy to include the more familiar diseases of Western civilisation, many of which are due to bacterial infection. When it became recognised that the activity of prontosil was due to the sulphonamido- group in its molecule and that sulphanilamide was in itself an active antibacterial, development in this field was rapid. It has resulted in the synthesis and trial of many hundreds of derivatives of sulphanilamide, of which a few have proved to possess outstanding activity. Most of these compounds exert a preferential activity against particular organisms; some are more liable to produce toxic effects, or may have undesirable side-reactions; consequently these factors have to be taken into account when deciding on the drug of choice for the treatment of different conditions

Another group of anti-parasitic agents, the amidines, has been the object of much research during the last fifteen years. In one respect they have an interesting history. The first compound of this class, synthalin, was introduced into medicine for the oral treatment of diabetes, following on observations that a simpler substance, guanidine, caused a fall in the blood sugar content when administered to healthy animals. This led to an investigation of its possible value against the parasitic trypanosomes by interference with their metabolism. Although the effectiveness of the amidines as anti-parasitics was proved by these researches, it was not for the expected reason but rather because they were found to exert direct trypanocidal activity. Further developments in this field are still to be expected and as chemotherapeutic agents the amidines may become of great importance in the treatment of many tropical diseases, notably sleeping sickness.

The final chapter in the review of chemotherapeutic development is still in process of being written and I can only refer briefly to the discovery of the antibiotics. Once again the urgent necessities of a great war gave an impetus to scientific advancement, on this occasion culminating in the isolation of penicillin and its commercial manufacture in huge quantities within a remarkably short time. This is a recent story and has been told elsewhere. Discoveries of other antibiotic drugs have followed, and will

probably continue as a result of the intensive research which the opening of this new field has engendered, with incalculable possibilities in the progress of medical treatment.

Quality Control and Standardisation

The changes which have occurred in the variety and nature of drugs, arising from the advances in other fields which I have just summarised, have been accompanied by a great expansion in the control of their purity and strength which has extended to the whole of the substances and preparations used in pharmacy. As some classes of the newer preparations are not amenable to assay by chemical methods, this expansion has not been confined to pharmaceutical chemical analysis, but has embraced new methods of testing based on the sciences of bacteriology and pharmacology.

As I have said earlier, the requirements of the older pharmacopœias demanded little in the way of standardisation. The three revisions which have appeared during the last fifty years have each marked stages in the progressive control of quality of official drugs and preparations. Progress along similar lines has brought the non-official medicaments into a like position. The British Pharmaceutical Codex, having first come into being as a book of reference and information, published by direction of the Pharmaceutical Society for the benefit of prescribers and dispensers, has, in the course of successive revisions, extended its scope and has become a book of standards covering most non-pharmacopœial drugs and galenicals which are in common use. Its requirements have the effect of law in many parts of the British Commonwealth and, although not having expressed legal status in this country, its standards are generally given considerable weight in the pharmaceutical industry. The book has therefore become complementary to the pharmacopœia in the control of quality of the materia medica of to-day.

Its production represents a piece of pharmaceutical progress which our profession may regard with pride as one of their contributions to the general advance in pharmaceutical knowledge, as it has been fostered by our own Society and brought to its present state of importance as a result of the collaborative work of successive men and women, most of whom have had a pharmaceutical training

In addition to the main body of standards the Therapeutic Substances Act, by its regulations, imposes stringent standards for all preparations to which the Act applies.

The maintenance of the present-day standards has imposed a considerable responsibility on the pharmaceutical manufacturing industry. Whereas at the beginning of the century a small analytical laboratory with one or two chemists sufficed for the testing of the products of a wholesale drug house, routine quality control now requires the provision of extensive laboratories and skilled staffs whose function is to assay the products of the manufacturing departments, to prove the absence of undesirable impurities which might have a toxic or deleterious action, and

to ensure that all injectable preparations are sterile. To fulfil this function, workers trained in analytical and physical chemistry, practical pharmacology and bacteriology are needed in considerable numbers. New methods and techniques have become necessary and the analyst relies not only on chemical reactions but on spectrophotometry, fluorimetry, polarography and other electrometric techniques in order to deal with the problems of his profession.

I have so far drawn your attention mainly to the effects of scientific progress in various fields indirectly affecting pharmacy, and it is perhaps desirable, lest undue emphasis may have given a distorted picture, to attempt to put them in their proper perspective as seen against the practice of medicine and pharmacy as a whole. They constitute additions to, and not replacements, of older practices. The mass of knowledge which has accumulated gradually and progressively since the study of drugs and their action began to be recorded many centuries ago is still in process of accretion, and for most complaints of non-specific origin treatment of symptoms remains the common practice and will probably continue to be for some time to come. Old beliefs in the value of individual drugs may die for lack of supporting evidence. Drugs may disappear from the pharmacopœias as they become outmoded and their places are taken by others of more certain action, but the well-established and proved remedies remain as the principal media of medical treatment. A famous physician—I believe it was Lord Horder—put the matter in the right light in a pithily worded warning that one should not dismiss the accumulated experience of three thousand years on the evidence of the latest galvanometer reading.

There is therefore no likelihood that the practice of pharmacy will undergo any revolutionary change in character as a result of the changes I have mentioned; on the contrary, they may in some degree allow him to exercise his skill and training in new directions.

Legislation and Pharmacy

The factors which have most directly affected pharmacy and the pharmacist during the last fifty years have resulted from the mass of new legislation, concerned either with social welfare or with the direct control of pharmacy and the sale of medicines.

At the beginning of the century the practice of pharmacy was governed by the Pharmacy Act of 1868, with certain amendments, although some of the provisions of the original Act of 1852 were still in force.

The chemist and druggist of those days—the title "pharmacist" at that time was reserved to those possessing the Society's higher qualification—was at liberty, if he so wished, to keep his premises open until late hours and expected equally long hours of service from his assistants. He was not required to keep a special guard on those habit-forming compounds which have since been classified as Dangerous Drugs, although he had to be careful to whom he sold arsenic and a few other poisons. Neither was he forbidden to recommend and sell remedies purporting to

cure venereal diseases or certain other complaints which have since been the subject of restrictive enactments.

In order to qualify for his title, he had to undergo an apprenticeship which gave him a good grounding in the practice and art of dispensing and also to fit himself by study of the sciences related to pharmacy. The examination he had to pass at the end of this training was a severe test of his practical skill and care in the exercise of his vocation, but did not demand anything like the theoretical knowledge of the sciences of chemistry, physics, botany, and physiology—either pure or applied—which is required nowadays.

The relationship between the individual qualified chemist and druggist and his chartered body was a loose one. If he had the wider interests of his profession at heart he would apply for membership of the Pharmaceutical Society and might continue his studies and sit for the "Major" diploma. On the other hand, once qualified and registered as a chemist and druggist, the individual owed nothing but a moral loyalty to the Society and was not required to become a member of it. Subject to his duties as an ordinary citizen, he was free to carry on his business much as he pleased. If, as is possible in all professions, he turned out to be a "black sheep" there was no professional statutory body empowered to investigate his conduct and either call him to order or expel him from the profession.

It is a tribute to pharmacists as a class and to the traditions and training of pharmacy at that time, that, in spite of this lack of professional control, pharmacy maintained a general standard deserving of the high respect which it received from the public which it served.

Beginning with the Poisons and Pharmacy Act of 1908, which incidentally gave the right to the chemist and druggist to use the title of pharmacist, new legislation affecting all branches of pharmacy was to come with great regularity. An outstanding landmark was the passing of the first National Health Insurance Act of 1911, which, with its successor of 1936 and the recent National Health Service Act, has considerably altered the relationship between the pharmacist and the community. The Shops Act of 1912, although not solely concerned with pharmacy, regulated the hours of work in the retail pharmacy and the duties of the pharmacist to his employees in this respect.

The Venereal Diseases Act of 1917 prevented the recommendation and sale to the public of remedies for these diseases; later legislation extended the prohibition to other conditions for which unqualified treatment is undesirable. The vice of drug addiction which began to assume serious proportions after the 1914-1918 war was responsible for the control of a class of habit-forming drugs which came to be known as Dangerous Drugs after the passing of the first Dangerous Drugs Act of 1920. The growth of chemotherapy introduced into pharmacy the class of potent drugs which came under stringent control under the provisions of the Therapeutic Substances Act of 1925. The Pharmacy and Poisons Act

of 1933 directly affected the pharmacist and the practice of pharmacy. This Act has made every pharmacist a member of his professional Society, liable to the payment of an annual retention fee, and answerable to the Statutory Committee of the Society with respect to his professional conduct. Briefly, this Act has replaced the loose relationship which obtained between the individual and the chartered body at the beginning of the century by a constitution of pharmacy on the lines of the other closed professions.

Pharmacy in the Future

The question remains: Where does pharmacy now stand in relation to this changed state in the surrounding fields of science? In the eyes of the community the conception of the pharmacist as a trained exponent of the science and art of the compounding of medicines, and as a confidential guide, still remains. The esteem in which he is held will, in the future, depend in a large degree on the maintenance of this reputation. There is no finality in the advance of scientific knowledge. Research will continue to produce results—new drugs, improved preparation of galenicals, new methods of treatment, and new methods of analysis and control. Pharmacy cannot stand still in a world of change. The chief danger which confronts it is that of failure to make progress on parallel lines to advancements in these other branches.

Pharmaceutical education and training, while giving due emphasis to the importance of the main function of pharmacy, and providing some knowledge of those parts of chemistry and other sciences which lie on its borderland, should also be directed towards a widening of general knowledge and culture. This cannot be gained from a mere storage of facts, but only by study of the history, development, and principles of these sciences. The pharmacist of the future will need this wider outlook if pharmacy is to hold its own. Though some forms of research are the province of the chemist, physicist, or biologist, there remain other fields in which chemists trained in the pharmaceutical applications of these sciences can find ample scope for utilising their particular skill and knowledge. This Conference has, from its inception, provided the arena in which such matters may be ventilated and discussed. Its continued value to the community will depend upon the willingness and zeal of the present and future generations of pharmacists and others engaged in pharmaceutical pursuits, to devote themselves to this branch of investigation and research. The proceedings of the science sessions of previous Conferences provide a long record of the endeavours of such men in the past and represent a tradition which should be prized by their successors in the future. It is a tradition worthy of upholding and deserving of the best efforts our profession can make to maintain and strengthen.