BRITISH PHARMACEUTICAL CONFERENCE LONDON, 1953

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CHAIRMAN'S ADDRESS

THE PHARMACIST AND THERAPEUTICS

IN this the Coronation year of Her Majesty Queen Elizabeth II, we are assembled for the 90th meeting of the British Pharmaceutical Conference. This Conference was founded in 1863 through the foresight of men who had the scientific development of pharmacy at heart, and who doubtless realised the contributions which improvements in the practice of pharmacy could make to medicine. Three years previously Oliver Wendell Holmes, who was described by Sir William Osler as the most successful combination of physician and man of letters the world had ever seen, stated in an address to the Massachusetts Medical Society, "I firmly believe that if the whole materia medica as now used could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes." Although these words were spoken in America, it is obvious from the records of contemporary British practice that they could have been applied to the materia medica of this country, and that on both sides of the Atlantic Ocean, pharmacy and medicine still retained much mediæval empiricism. A major step towards the advancement of pharmacy was taken shortly before the first full meeting of this Conference, with the publication of the first British Pharmacopœia. This volume replaced the pharmacopœias previously issued separately by the Royal College of Physicians of London, Edinburgh, and Dublin. It was the first attempt to secure, within the British Isles, uniformity of formulæ and methods of preparation for commonly used drugs and galenicals, but its reception by pharmacists was not unattended with criticism. The hope expressed by Henry Deane, President of the Conference for that year, that members of Conference would do all they could to promote and ensure an improvement in every future edition has been abundantly realised. During the whole of its history this Conference has consistently provided opportunities for the exposition and discussion of advances in pharmaceutical practice. The proceedings of the Science Sessions record many original investigations which have led to improvement in methods of preparation, formulation and analytical control of substances used in therapeutics including those that are official in the British Pharmacopœia and the British Pharmaceutical Codex. The eighth British Pharmacopœia (1953) becomes official to-morrow (September 1st) and a new edition of the Codex is expected to be published next year. It is appropriate at this stage in our history that we should review some of the contributions which have been made by pharmacy to the materia medica of to-day.

A memorandum issued in 1952 by the Pharmaceutical Society to the

Minister of Health included the following among the services that should be rendered by the pharmaceutical department of a hospital:—

To obtain and be responsible for the nature and quality of drugs, medicinal preparations, dressings and chemicals such as antiseptics and reagents.

To make preparations to be used in dispensing prescriptions; to prepare other products for medical or surgical use, and to formulate preparations to meet special needs.

To dispense prescriptions. To assist in the development of new methods of treatment.

To assist in efficient prescribing by advising upon the nature and properties of substances used in medicines, and upon the selection of the most suitable substances and forms in which they should be prescribed.

This comprehensive definition of the functions of a pharmacist is applicable in whatever branch of the profession he is engaged. In general terms then, it can be said that the primary function of the pharmacist is to provide the drugs, and preparations of drugs, needed by doctors for the treatment of their patients. These drugs must be in a state of purity and of assured activity, and they must be in a form suitable for the appropriate method of administration, be it by mouth, by parenteral injection, by application to the skin or mucous membrane, or by insertion into one of the body cavities. To the pharmacist, therefore, belongs responsibility for the preparation and quality of drugs, and their formulation into preparations acceptable to both doctor and patient. In order to carry out these functions the pharmacist must obviously have a thorough knowledge of the chemical and physical properties of the substances comprised by the materia medica of to-day, he must be familiar with the analytical methods used in their assay and be able to apply the principles involved in their formulation. To this must be added a basic knowledge of physiology and pharmacology to provide the background for advice upon prescribing.

The Materia Medica

One of the outstanding features of pharmacy and medicine to-day is the wide use that is made of synthetic substances, and of isolated active principles, and the decline in the use of crude extracts, decoctions, infusions and tinctures made from drugs of the plant kingdom.

Although the use of synthetic compounds has increased greatly during the last 10 or 20 years, it had its origin before the beginning of the present century. At the meeting of this Conference held in Liverpool in 1896, the President, William Martindale, described the introduction of synthetic compounds into medicine as a novelty. 20 years later, C. A. Hill in his address as President stated, "Notwithstanding the phenomenal 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, 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."

Since these words were spoken, there has been a definite change from nature to the laboratory as the principal source of medicinal substances. This has effected changes in the practice of both therapeutics and pharmacy. The production and supply of simple vegetable drugs and their galenical preparations is a diminishing, though still important, part of pharmaceutical work. The pharmacist in retail practice has less opportunity than had his predecessors of a generation ago to exercise his skill in compounding. He is called upon to an ever increasing extent to supply drugs which, by the very nature of the processes involved in their production, must reach him in a state ready to be administered. The production of insulin, the manufacture of the antibiotics, the sulphonamides, the derivatives of barbituric acid, the sex hormones and the antihistamine drugs, to quote but a few examples, are essentially large scale operations suitable only for specially constructed plant. Compressed tablets, capsules and sterile solutions for injection, which together constitute a large part of dispensed medicines, are prepared more economically on the large manufacturing scale than at the dispensing counter.

Some idea of the growth and magnitude of the industry engaged in the production of synthetic chemicals and isolated principles and of its importance to the life and health of the nation, can be gained from figures published in the *Final Report of the Census of Production for Drugs and Pharmaceutical Preparations for the year* 1948. During the 10 years preceding the year of the Census the number of persons employed in Britain in the industry almost doubled, and its gross output expressed in terms of value, more than trebled. The output of aspirin in all forms rose from about 2 million lb. to 5½ million lb. The production of insulin increased to 6 times the pre-war amount to a total of 4500 million units per annum. In 1948 the production of barbituric acid and its derivatives amounted to 90,000 lb.; the annual production of sulphonamides was approximately 890,000 lb. The production of chloral hydrate was nearly 250,000 lb., and of sex hormones 25,000 oz. Since 1948 there has been a continuous increase of production in volume as well as in value. The production of penicillin, which was only at the rate of 190,000 mega units per week in 1948, had risen to almost 1,300,000 mega units per week by 1952. If we consider that 300,000 units is an average single daily dose, then these figures mean that approximately 625,000 doses were produced each week in 1948, and in 1952 the figure had reached over 4 and a quarter million. In that period too, new drugs such as streptomycin, *p*-amino-salicylic acid and the histamine antagonists have all added to the total production which is now valued at approximately £90 million per annum. Of this amount approximately one-third is exported overseas.

Informative though these figures are, cold statistics can convey but little impression of the contribution made by pharmacy—using the term

in its widest sense—to the national welfare, the advancement of medical science and the saving of human life. That this contribution has been considerable will not be disputed, but it is revealed in its true perspective only when it is examined in the light of those other factors which have influenced medical progress during recent years, and the advances in other branches of scientific endeavour which have been adapted to the requirements of the pharmaceutical laboratory.

On the one hand there has been the awakening of the national conscience to the need for the prevention of disease, and the care of the sick, reflected in the gradual evolution of the Public Health Service, and in particular in the National Health Insurance Act of 1911, and the National Health Service Act of 1946. On the other hand there has been the increasing attention given to research, in clinical medicine and pharmacology, and within the pharmaceutical industry itself. Planned and organised research for the development of new products and the improvement of old ones is now accepted as essential to the progress of pharmacy. Not only do manufacturers examine and attempt to develop discoveries made in their own laboratories, but they must follow very closely the discoveries made by workers in academic centres and always be ready to adapt their methods and their products to the ever advancing flow of knowledge. The result is that the pharmaceutical industry to-day, occupies an unique and essential position in regard to the development of new remedies and the discovery of new therapeutic uses for previously known compounds. As a result many of the substances now official in the British Pharmacopœia, and many more included in the British Pharmaceutical Codex, had their origin in the research laboratories of manufacturing pharmaceutical houses.

This position has been achieved by the application of knowledge gained in the sciences of chemistry, physics, pharmacology and biology to the design of new drugs and the manufacture of pharmaceutical preparations. 40 or 50 years ago almost the only methods employed by pharmacists for making the products needed for dispensing prescriptions were those of maceration or percolation with alcohol and water, decoction, concentration by evaporation and crystallisation. For the most part, reliance was placed on simple methods of volumetric and gravimetric analysis, the determination of melting point, or boiling point, refractive index and specific gravity as guides to purity and activity. Many galenicals were evaluated on their content of total extractive. The adaptation of scientific methods, including fractional precipitation, chromatographic separation, molecular distillation, potentiometry, polarography, spectrophotometry, biological assay and microbiological assay, has provided the tools with which the weapons of modern therapeutics have been fashioned.

Organic Syntheses

The discovery of a new drug with specific therapeutic properties is seldom due to mere chance circumstances, but is often the result of carefully planned and co-ordinated research to which organic chemists, biochemists, pharmacologists, physicians and pharmacists have all

contributed. This research may consist of the routine "screening" of the biological properties of a series of known compounds, or it may be a deliberate attempt to build molecules of predictable pharmacological action. In order to achieve the desired end it is often necessary to examine scores, or probably hundreds, of compounds in order to determine whether the required pharmacological properties are present. Some guidance in the search for new compounds can be obtained from the systematic examination of naturally occurring substances and synthetic compounds of known pharmacological properties and known chemical structure. This will yield information regarding the relationship of chemical structure to pharmacological action. A specific type of biological action is usually associated with a particular basic molecular structure. This activity can be quantitatively modified by alterations of chemical structure which do not involve alterations to the basic configuration. The preparation of a series of homologous compounds or derivatives based on the original primary structure, and a quantitative study of their biological properties must be undertaken in order to find one which possesses a high degree of specific biological activity with only a minimum of unwanted or toxic side effects.

Studies of this type have been used in the development of derivatives of barbituric acid, synthetic œstrogens and other sex hormones, histamine antagonists, sulphonamides, sulphones, antimalarial drugs, neuromuscular blocking agents, ganglionic blocking agents, analgesics and local anæsthetics. It is inevitable that the synthetic pathway to the development of new drugs leads to the production of many compounds which have qualitatively similar pharmacological properties and are used for the same purpose. The doctor is thus able to choose from among a wide range of compounds.

Vegetable Materia Medica

It must not be inferred that vegetable materia medica have been entirely supplanted by the synthetic products of the chemical laboratory. Some examples can be quoted to show that this is far from being the case. There has recently been a revival of interest in the peripheral vasodilator action of preparations of *Veratrum viride* as a means of treating hypertension, and in the dilator effect on the coronary vessels of preparations of *Ammi visnaga* for the relief of angina of effort. These possible clinical applications have led to systematic chemical and pharmacological examination of the constituents of these two drugs, resulting in the case of *Veratrum viride* in the preparation of a stable extract, and, in the case of *Ammi visnaga*, in the isolation of khellin. Liquorice has assumed an importance above that of a demulcent and sweeting agent by the discovery that glycyrrhizinic acid has a pharmacological action on salt and water metabolism closely simulating that of deoxycortone. Many crude vegetable drugs find their way into commerce in large quantities. Senna, aloe, podophyllum, cascara and rhubarb are still extensively prescribed as purgatives. Volatile oils and fixed oils from plant sources are used in many pharmaceutical preparations. We are still dependent upon opium for

supplies of morphine and related alkaloids, on cinchona for supplies of quinine, on ipecacuanha for emetine, on digitalis for cardiac glycosides, on nux vomica for strychnine, on belladonna for atropine and on ergot for ergometrine. Some of these strongholds are already being assailed by the synthetic organic chemist. The synthesis of morphine on a laboratory bench scale has recently been accomplished, and in the case of quinine, atropine and morphine, synthetic alternatives possessing some of the pharmacological properties of the natural alkaloids are available. Studies now in progress on the biogenesis of alkaloids and other plant constituents may be expected to point the way to increasing the yield of these naturally occurring medicinal agents.

The industrial adaptation of the metabolic activities of some micro-organisms has made these members of the plant kingdom important contributors to the materia medica. Moulds and fungi grown under controlled conditions in suitable culture media produce the antibiotics penicillin, streptomycin, aureomycin, terramycin and some others; *Aspergillus niger* grown in a medium containing molasses produces citric acid; cyanocobalamin is produced together with streptomycin as a metabolic product of *Streptomyces griseus*; a microbiological transformation of steroids using *Rhizopus nigricans* has greatly simplified the synthesis of cortisone, and an exo-cellular enzyme produced by the coccus *Leuconostoc mesenteroides* during its growth on a medium containing sucrose is used for the production of the polysaccharide dextran.

Animal Materia Medica

Substances developed in the animal body—hormones, antitoxins, human blood and plasma—are important items of materia medica. The British Pharmacopœia describes methods for the preparation of several derivatives of human blood, and defines tests for their identification and assay. The production of antitoxins contained in the serum of animals, has long been a specialised part of pharmaceutical enterprise. Interest in some of the antitoxins may be renewed, in view of the prevalence of strains of bacteria resistant to the commonly used antibiotics and chemotherapeutic compounds.

Of the hormones produced by endocrine glands, cortisone, and corticotrophin have assumed great importance in therapeutics, although their production in this country is not yet large enough to satisfy all requirements. Cortisone is one of many steroids secreted by the cortex of the adrenal gland. The story of its isolation, chemical characterisation and synthesis, is one of the most fascinating themes of modern organic chemistry. The first synthesis from deoxycholic acid was a long and complicated process involving 32 stages. The total synthesis from *o*-toluidine involved 48 stages. Sterols obtained from vegetable sources—stigmasterol, diosgenin, sarmentogenin and hecogenin—have been investigated as alternative starting materials with a view to shortening the synthesis and increasing the yield of cortisone. Progress along the pathway towards increased production on a commercial scale has been considerably eased by two important recent developments. The first is a method of

biosynthesis in which minced adrenal glands are incubated under ærobic conditions with synthetic deoxycortone, and the second is the microbiological transformation of steroids using *Rhizopus nigricans* to which reference has already been made.

Corticotrophin (adrenocorticotrophic hormone or A.C.T.H.) is obtained from the anterior lobe of the pituitary gland of pigs, cattle and sheep. Despite the inherent difficulties of the process of extracting the active principle from the glands, considerable progress has been made towards its isolation in pure condition. From pig pituitary glands, a highly active fraction has been obtained by extraction with glacial acetic acid, followed by fractionation with ether and acetone, adsorption on oxycellulose, digestion with pepsin and lyophilisation. This fraction has been termed corticotrophin B. Another product, also of high potency, has been produced from sheep pituitary glands by fractionation of an acid-acetone extract. This fraction has been termed Preparation E. These two preparations differ from one another, and from concentrates of corticotrophin previously described, in their chemical and physical properties. If, as indeed may be the case, either of these substances proves to be a single chemical entity, greater exactitude will be given to the pharmacological and clinical evaluation of the adrenocorticotrophic hormone.

It is just 30 years since the first commercially produced injections of insulin were made available to diabetic patients in Great Britain. In the intervening years much research has been directed to so modify the original soluble insulin as to prolong its action in the body after injection, with the object of controlling the level of blood sugar in patients with diabetes mellitus by a single daily injection. Successive steps towards the achievement of this objective, have been protamine insulin, protamine zinc insulin and globin insulin. During the last few years, workers in several laboratories have re-investigated the effect of zinc ions on the crystallisation of insulin at different *p*H ranges and in the presence of different buffer salts. One outcome of these studies was the crystalline protamine zinc insulin compound at first called N.P.H., to which the approved name isophane insulin has been given. This preparation is used in neutral suspension containing sodium phosphate as the buffering agent.

The most recent development has resulted from the discovery that if an acetate buffer is substituted for the phosphate or citrate buffer previously used for making insulin suspensions, it is possible to precipitate the insulin over a range of *p*H approximating to that of body fluids by the addition of an amount of zinc equivalent to that present in protamine zinc insulin (0·02 mg./10 units). In the absence of citrate or phosphate ions the physical character and the solubility of the zinc insulin compounds depends upon the *p*H of the solution from which it is precipitated. By appropriate modification of the conditions it is possible to precipitate zinc insulin compounds in either amorphous or crystalline forms, containing more zinc in chemical union than is present in soluble crystalline insulin. The two physical forms of this insulin zinc compound differ somewhat in their hypoglycæmic action; that of the crystalline form is much more prolonged

than that of soluble (unmodified) insulin, whereas the amorphous form has a relatively rapid action not unlike that of soluble insulin.

The ideal preparation of insulin for the treatment of diabetes mellitus would be one that is relatively rapid in its effect on absorbed glucose, constant in its action and of sufficiently long duration to enable the blood sugar to be maintained within normal limits by one single daily injection; it should not produce any form of local reaction. The mixture of the amorphous and crystalline zinc compounds suspended in acetate buffer, to which the approved name insulin zinc suspension has been given, may come very close to this conception of the ideal, because it combines rapidity of action with prolongation of effect, and is free from foreign protein. This preparation, which will become available this autumn, will avoid mixing two preparations, one short-acting and the other long-acting.

3 years after the introduction of insulin, therapeutics registered another significant and life-saving advance in the discovery of the effectiveness of raw liver in the treatment of pernicious anæmia. It was not long before extracts containing the active substance or substances were produced, but progress in this field was hampered by lack of knowledge concerning the identity and nature of these active substances and by the fact that there was no laboratory method by which the activity of liver extracts could be assessed—the sole criterion was the clinical response of patients suffering from pernicious anæmia. Attempts to separate clinically active material from inert matter were numerous; for the most part they followed traditional lines of extraction with solvents, enzymatic digestion, precipitation of inert matter with heavy metals or by selective solvents, and charcoal adsorption followed by elution. Gradually it became possible to prepare solutions for injection in which the active material was presented in relatively high concentration, although these still contained considerable proportions of inert matter. The isolation of folic acid from liver and other sources led to the conclusion that this substance was the anti-pernicious anæmia factor, a conclusion subsequently shown on clinical evidence to be erroneous.

It was the application of chromatographic methods of separation and the development of a microbiological method of assay that provided the means for the isolation of the substance now called cyanocobalamin, in a yield of less than 1 g. from 4 tons of liver. The discovery that cyanocobalamin is produced by *Streptomyces griseus* as a metabolite together with streptomycin opened up a new source for commercial production in greater quantity and at less cost.

Analytical Control

Chemical Investigation

For a substance to be suitable for use in therapeutics it is essential that its pharmacological and therapeutic activity must not vary from batch to batch. During the development of a synthetic compound, or the purification of an active principle extracted from its natural source, much information is gained about its physical and chemical characters—solubility, melting point or boiling point, specific rotation, refractive index—and

from data of this type it is possible to draw up specifications of characters and tests by which the substance can be identified, and quantitatively analysed.

The separation of active constituents from their natural sources, and the purification and characterisation of synthetic organic chemicals have been greatly assisted by refinements in methods of chemical and physical analysis. Many of the newer techniques involve the use of costly physical instruments, with the result that the analytical control of the purity of medicinal substances is rapidly becoming the work of the specialist and the capital expenditure needed to instal this modern equipment in a laboratory reaches astronomical amounts. Among the newer techniques which have been employed in the development of new preparations and in the assay of old ones are spectrophotometry, chromatography and polarography.

Absorption spectrophotometry finds wide application for the characterisation of pharmaceutical substances, and for determining their purity and concentration in solution. It is used for the determination of vitamin A, cyanocobalamin, calciferol, some sex hormones, chloramphenicol, many alkaloids and antihistamine drugs.

Absorption in the infra-red region is now assuming importance both for qualitative and quantitative analyses and for providing information about chemical constitution. It was used, for example, in elucidating the chemical structure of cyanocobalamin and of the penicillins.

Two modifications of spectrophotographic methods, namely flame photometry and the "porous-cup" technique, have been applied to the determination of lithium, potassium, iron, silicon, magnesium and other metallic ions in pharmaceutical preparations, and appear to give results of sufficient accuracy to justify their further use.

Chromatography has greatly assisted the isolation and purification of many of the antibiotics. It has provided methods for the separation of noradrenaline from adrenaline; for the fractionation of digitoxin from admixture with other digitalis glycosides and aglycones. Application of this method to the separation of ergot alkaloids, and to the assay of ergometrine and ergometrinine in mixtures, has supplied information about the changes which take place in injection of ergometrine maleate on storage. It has also provided satisfactory methods for the determination of the hyoscine in solanaceous drugs and of strychnine in nux vomica.

The use of a suitable ion exchange resin as the adsorbing column makes it possible to separate the salts of weak organic bases into their component ions. This method has been used for the determination of some alkaloids and local anæsthetics.

Polarography gives satisfactory results in the routine assay of morphine, diamorphine, strychnine and riboflavine contained in injection solutions, tablets, and some galenical preparations. It may also be used for the assay of trace metals in pharmaceutical preparations, and for the determination of iron, arsenic and antimony in their compounds. A polarographic method for the determination of the purity of insulin has been described, and polarographic determination of chloramphenicol in solution buffered at *p*H 4 is said to give results which agree with those obtained by biological assay.

Biological Tests

It is possible to guarantee a constant degree of pharmacological activity from a given weight of most drugs, by rigid control of chemical composition and physical characteristics. There are, however, some drugs, mostly of biological origin, which cannot be reduced to a state of uniform chemical purity, and in which the proportion of active substance to inert matter is liable to vary in different preparations. The biological activity of these substances cannot be precisely predicted from chemical and physical properties and must be controlled by biological assay, in which the response of animals to doses of the substance is compared with the response of a similar group of animals to doses of a standard preparation of the same substance. It is an essential condition of such assays that tests with the sample under examination and with the standard preparation should be carried out at the same time and under identically comparable conditions. Biological assay is required for about 30 substances of the British Pharmacopœia. A laboratory, properly staffed and equipped, where biological assays can be carried out, is therefore an essential auxiliary to manufacturing pharmaceutical plants.

When a new substance is being developed and examined in order to assess its possible use as a therapeutic agent, biological tests are of value, in conjunction with chemical and physical methods as an indication of progressive stages in the isolation and purification of the new substance. Methods of biological assay used in conjunction with chromatography have facilitated the purification of the adrenocotricotrophic hormone, and the isolation and characterisation of the hormones present in adrenal cortex extract. In the case of the former, the method is based on the depletion of ascorbic acid from the adrenal glands of rats after removal of the anterior pituitary gland. A microbioassay, using radioactive isotopes, which measured the ratio of sodium and potassium excreted in the urine of adrenalectomised rats following injection of adrenal cortex extract, combined with paper chromatography, has led to the separation of a new crystalline steroid possessing a high degree of activity on electrolyte metabolism.

Before any new substance can be released for clinical use the pharmacological examination must extend beyond the demonstration of its specific biological activity *in vitro* and *in vivo*. Its rate of absorption, distribution through the body tissues and excretion must be investigated. Information must be obtained concerning its therapeutic index (that is to say the ratio of effective dose to toxic dose), its chronic and acute toxicities, its action on blood pressure, respiration, the central nervous system, the heart, blood, kidney and liver. If the drug is one that is intended to be used for external application its local effects on the skin and mucous membranes. must be studied to ascertain whether it causes irritation and sensitisation. If the substance is shown to have a desirable therapeutic property it must be free from serious side effects before it can be considered acceptable for therapeutic use.

Whether use is made of the whole intact animal, pieces of animal tissue or bacterial cultures as the test object, all methods of biological assay

have one feature in common—that of individual variability. It is therefore necessary to invoke the assistance of statisticians in order to assess the accuracy of the results, and, indeed, to plan the experiments so that reliable information may be obtained with a minimum expenditure of labour and materials. With proper planning of the experiment and appropriate mathematical treatment of the results, biological assay is capable of ensuring uniformity of action between different preparations of the same substance within comparatively small limits of error.

The Formula

A most important part of the pharmacist's work is the formulation of medicinal substances into preparations suitable for administration. It is here that pharmacy is seen both as a science and an art. A science because proper formulation must be based on a knowledge of the physical, chemical and pharmacological properties of the substances to be compounded, and an art because it requires the exercise of skill based on experience. Often this part of the pharmacist's work is taken for granted and it is too little realised that the preparation of a compressed tablet, solution or suspension for injection, an ointment, emulsion or suppository, for example, is possible only after considerable laboratory research. The discussions on the subject of pharmaceutical formulation at recent meetings of the Conference will be still fresh in your memories but it may be appropriate to recapitulate some of the fundamental principles.

The aim of formulation must be to present a drug in a form in which it exhibits its characteristic properties, is safe and convenient to use, and stable for a reasonable period of time under the prevailing climatic conditions.

During the last decade, the practice of pharmacy has been dominated by the need for supplying active preparations of the antibiotics, penicillin, streptomycin, chloramphenicol, and, more recently, aureomycin and terramycin. The dispensing of penicillin solutions and suspensions for parenteral use, and the formulation of creams and ointments for external application, brought into prominence the necessity for observing strict asepsis in manipulation, and revealed numerous incompatibilities which had to be overcome before satisfactory formulation was accomplished. The study and solution of these problems has formed the basis of a number of papers contributed to the Science Sessions of this Conference. The survey of the pharmacy of antibiotics presented at our Symposium Session last year gave an indication of the complexity of these problems, and the manner of their solution.

The problems presented by the formulation of the antibiotics are special examples of problems incidental to the formulation of preparations of any drug for therapeutic use, and their satisfactory solution is reached by the application of the same general principles. In the design of preparations intended for administration by mouth the effect of saliva, the gastric juice and the pancreatic secretion must be taken into consideration, so also must the extent and manner of absorption and excretion of the drug. Palatability and æsthetic appearance are necessary, but are secondary in importance to the stability of the drug in solution or suspension.

The formulation of preparations for parenteral injection presupposes a knowledge of the solubility of the drug in water for injection or other solvent, the *p*H of the solution, the stability of the drug on storage, and on sterilisation, its compatibility with bactericidal compounds which may be used as preservatives, and with sodium chloride or other electrolyte which may be used to render the solution isotonic. Pain on injection, must be avoided, and solutions intended for intravenous injection must not contain pyrogens.

In the preparation of suspensions for intramuscular injection, consideration must be given to those factors which influence the rate of absorption of the drug from the site of injection—particle size, viscosity of the medium, or the presence of an anion radical which will delay the absorption or excretion of the drug.

In the formulation of ointments and creams for external application it is necessary to know whether the drug is intended to pass through the layers of skin, or to remain unabsorbed on the surface.

The formulation of tablets is intimately linked with the rate of disintegration of tablets in the alimentary tract—a matter of great importance if the *pilula perpetua* of Pereira is not to find its counterpart in modern medication.

The Clinical Trial

When a drug has emerged from the scrutiny of pharmacological examination with an indication that it possesses some property that may have practical application in the treatment of disease, and has been formulated into a form suitable for administration, there arises the necessity for testing it on human patients. Ideally every new drug should be submitted to controlled and impartial trial in which its effects on a disease process are carefully observed and the results compared with those of other forms of treatment previously in use for that disease. This method has not always been followed in the past, indeed, it has often not been possible to adopt it. Had it been employed many of the alleged remedies of bygone years would never have seen the light of day. As it is, too many of them have persisted to the present time because of the absence of incontrovertible evidence of their worthlessness. To draw conclusions from insufficient data will lead to erroneous deductions. This error does not belong entirely to a past era. Even to-day claims for therapeutic activity are sometimes based on clinical impressions derived from the observation of one or two patients only!

Ideally the clinical trial should follow the general principle of all biological assays in that it must be carried out on a sufficiently large number of patients and must provide for an adequate series of controls, whenever this can be done without endangering the lives or well-being of patients. If withholding treatment from a patient would mean the difference between survival and death, then clearly no control is possible, other than that supplied by the doctors' clinical impressions, or by the case records of a similar group of patients treated by other methods.

Controlled clinical trials have their greatest usefulness when it is

possible to measure some biochemical or pathological change brought about in response to the administration of the drug, e.g., the blood sugar response to the injection of insulin, the rise in the number of red blood-cells in response to the injection of liver extract or of vitamin B_{12}, the healing of the lesions of pulmonary tuberculosis shown in X-ray photographs during treatment with streptomycin, and the disappearance of parasites from the blood of malaria-infected patients.

By whatever method the clinical evaluation of a drug is attempted, the process requires careful planning, critical examination of the progress of the patients, and systematic recording of the results. It should be conducted by a team of investigators which should include a physician, a biochemist, a pharmacist, and preferably also a statistician. This is essentially the province of the physician, but it is one in which the pharmacist, particularly the hospital pharmacist, can and should collaborate. From it will come the final proof of the successful outcome of the chemical, biological and pharmaceutical research that has preceded it.

Not only do trials on human subjects make it possible to assess the value of a drug in the prevention or treatment of disease, and also to determine the effective dose range, but they reveal side-effects such as nausea, vomiting, headache, giddiness, skin rashes, tinnitus and other symptoms which cannot be detected from animal experiments.

The quantitative evaluation of drugs in man is usually difficult because it is not often possible to obtain continuous and objective records of the drug effect. Furthermore, the number of subjects, the number of observations and the range of doses that can be used are all necessarily limited. Where quantitative methods have been devised they have sometimes revealed that the relative potencies of the members of a group of compounds having qualitatively similar pharmacological actions do not correspond to the deductions made from the results of tests on animals. This is true, for example, of the synthetic œstrogens and of the synthetic muscle relaxants, the relative potencies of which in man differ from their relative potencies in rats. Quantitative methods have been adapted successfully to the study of the antihistamine drugs and the synthetic analgesics of the methadone type.

International Aspects

Many of the substances and methods mentioned in the foregoing brief survey had their origin in countries outside Great Britain. Similarly, many of the discoveries made in our islands have proved of benefit in the relief of human suffering in all parts of the world. Pharmacy like other sciences knows no national boundaries. Its discoveries and methods are applicable the world over. Its difficulties are common to all those who practise it wherever they may be. There is obvious need for the closest collaboration and exchange of information by pharmacists of all nations. Already there is much evidence of the growing recognition of this need. In a world which is rapidly shrinking with the speed of modern travel, we cannot afford to ignore it. The presence in this country during the past summer, and at this Conference, of pharmacists from the

Commonwealth and the Dominions as well as from a number of other countries, will do much to foster this collaboration. The International Pharmaceutical Federation, the Franco-British Pharmaceutical Commission, the International Conference on Military Medicine and Pharmacy and the International Pharmacy Students Federation all provide opportunities for the exchange of views between pharmacists of different nationalities. The invitation given to the International Pharmaceutical Federation to meet in Great Britain during 1955 is a welcome step towards the greater participation of British pharmacists in pharmaceutical affairs beyond the shores of our own islands.

The World Health Organisation is to-day taking a greater interest in matters of purely pharmaceutical importance. The necessity for international agreement on standard preparations for use in biological assay has been recognised for many years and has been met by the work of the Permanent Commission on Biological Standardisation set up under the Health Organisation of the League of Nations, and now the World Health Organisation. It is over 50 years since the advantages of using the same name for the same preparation throughout the world were first enunciated at an international conference, but only within the past two or three years has a serious effort to secure such uniformity been made by the establishment of a list of international non-proprietary names for several hundred substances. It is to be hoped that the opposition which has recently arisen in America will not be allowed to vitiate the success of this important contribution to saner pharmacy. In an attempt to extend international agreement on standards for drugs and pharmaceutical preparations, the International Pharmacopœia has been produced by the World Health Organisation Expert Committee on the Unification of Pharmacopœias. The British Pharmaceutical Conference has reason to be proud of the fact that one of its Vice-Chairmen, Dr. C. H. Hampshire, C.M.G., who was Chairman of our meeting in London in 1933, was Chairman of this Expert Committee and directed the labours of those who produced this very material evidence of international pharmaceutical collaboration.

The Pharmacist's Responsibility

In whatever capacity the pharmacist is engaged, be it in the manufacturing laboratory, in the pharmaceutical department of a hospital or in retail business, he or she has a position of great responsibility in regard to the life and health of the community. Under the National Health Service, the pharmacist-contractors of Great Britain dispense more than 200 million prescriptions each year. To this must be added the not inconsiderable number of prescriptions dispensed by hospital pharmacists for both in-patients and out-patients. Medicines are made for the sick, and the pharmacist's ultimate responsibility is to the patient. Every stage in the preparation of a medicine, from the manufacturing laboratory to the dispensing counter, is subject to rigid control—and by control in this context is meant something much more than the analytical control referred to earlier in this Address. It means constant vigilance, checking and cross

checking to avoid errors in manufacturing, compounding and dispensing; errors that might endanger the lives of countless numbers of people if they were perpetrated. To-day, although the emphasis is passing from the bottle of medicine to the compressed tablet, capsule and injection solution, and individual prescriptions have been largely replaced by the standard preparations of the British Pharmaceutical Codex and the National Formulary, or by the finished products of manufacturers, the knowledge of the chemistry and pharmacology of drugs required by the pharmacist, is greater than ever it was at any previous time in our history. As the number of highly potent drugs increases, the pharmacist must be ever more vigilant and his knowledge must keep pace with modern developments.

To equip him to discharge these responsibilities the pharmacist in embryo must undergo a course of training in a recognised teaching institution embracing the basic natural sciences and the specialised subjects of pharmaceutics, pharmaceutical chemistry, pharmacognosy, physiology and pharmacology, and forensic pharmacy. In addition, he must serve a period of articled pupilage to gain an insight into the practice of pharmacy before he is admitted to the register. Thus, the pharmacist acquires a store of knowledge, both academic and practical, which is of the greatest value when it is allied to the knowledge of the physician. Too often in the past has pharmacy been regarded (even by pharmacists themselves) as the mere handmaid of medicine. Rather should it be said that pharmacy is co-partner with medicine, with equal responsibilities, and with equal opportunities to serve the public. Pharmacy and medicine are, in fact, inter-dependent, and together fulfil vitally important functions in the health services of the country.

During the lifetime of this Conference therapeutics has emerged from the darkness of empiricism into the dawning light of an exact science. Pharmacists can be proud of the part which they have played in bringing about that advance, and they can be prouder still of their responsibilities to further it in the future.