REPORT OF A SYMPOSIUM ON FORMULARIES AND FORMULATION

A SYMPOSIUM SESSION was held on Friday, September 8, at 9.0 a.m., Mr. A. D. Powell, Chairman of the Conference, presided and the opening speakers were Professor J. P. Todd, Mr. H. S. Grainger, Miss M. A. Burr and Dr. A. Wilson.

THE THEORETICAL ASPECTS

Professor J. P. Todd said that his brief was the theoretical aspects of formulæ, formulation and formularies. He had no great practical acquaintance with formularies, unless one included in this category the British Pharmacopœia and the British Pharmaceutical Codex. In Scotland, they had little use for formularies and they foresaw possible danger in their development. It was possible that formularies might become so nationalised, and even internationalised, that there would be one book for all the formulæ in common use. This, of course, would not commit the prescriber to work exclusively on this national or international formulary, but it might produce a state of affairs where medicines were produced in some central institution, in London or even in Amsterdam, packed in cellophane containers and despatched all over Europe. He imagined that the effect of such a development on the future of pharmacy would be somewhat catastrophic.

It would be interesting to speculate on the growth and development of formulæ over the years, as possibly the devising of a formula is bound up with the development of civilisation itself. Formulæ—not necessarily pharmaceutical formulæ—must have occurred early in man's history. Formulæ made with the various drugs would develop in the course of time, so that we had at an early stage in our history collections of these formulæ, and notably the Pharmacopœias of London, Edinburgh, Dublin and, not least, Glasgow. The early pharmacopœias, however, were not formularies in the sense in which we use the term to-day, when the National Formulary tends to be the focus of attention and of great importance to every one of us. The early pharmacopœias were descriptions of preparations of the drugs then in use with standards and directions for making them. Pharmacopœias being, even from the earliest days, conservative in their views, there arose other works which tended to be more advanced and which could take greater liberties, due to the fact that they could, without running the risk of being taken seriously to task, introduce substances which might not prove themselves later on. Works of this kind tended also to become repositories for drugs which had been cast out of the pharmacopœia. In this way there was produced the second type of formulary, which has proved of great value over the years. The modern formulary tends to be more of a guide to the medical man; it suggests suitable compounds and admixtures of substances for the treatment of various ailments, and is less a book of directions to the dispenser. Some of the old books of many hundreds of years ago have survived the passing

of time and some of these and their formulæ are the old masterpieces of pharmacy. We should treat these old formulæ with the respect which is due to an old masterpiece; we should carefully preserve their history and hand it down to succeeding generations.

Professor Todd defined "formulation" as the art of presenting a substance in a form in which it best exhibits its characteristic properties. While every formula should have this as its primary object, other requirements were usually called for, such as safety in use, stability, convenience, elegance, or possibly the satisfying of some special demands due to special circumstances. It was to meet the demand for the secondary properties that the greatest ingenuity and skill were necessary. As a rule the primary objective was presented by the pharmacologist, whose work had followed the preparation by the chemist or other workers of the substance itself; it remained for the formulator to make the most of the primary objectives and enhance these if possible by meeting the secondary properties required. For example, the sulphonamides were first used orally, but they were quickly applied to the treatment of open wounds. The day of greasy bases for application to open wounds having passed, it was left to the formulators to incorporate these substances in oil-in-water creams which had the great advantage that they could be readily and painlessly removed in order to dress the wound; water was miscible with these creams and could remove them easily. The formulator, however, could rarely rest on his laurels, and it was found, when these creams were used on wounds, that a new bacterial flora developed in them which were resistant to sulphonamides, so that the preparations became of much less use. At that time, penicillin became available, and the formulator then had to devise ways and means of presenting penicillin in such preparations in such a way that it would exhibit its characteristic properties and not be destroyed in the process. The problem was thus temporarily solved, but in due course a bacterial flora developed which resisted penicillin.

Work of this kind implied co-operation between a number of specialists, one of whom was, of course, the formulator. In this connection, the skill and knowledge of the retail pharmacist were not used as they ought to be. There were rare exceptions to this, but the medical man and the local pharmacist rarely discussed a problem and attempted to solve it. The hospital pharmacist did this work regularly, and it could be one of the most important aspects of pharmacy in the future if it were developed.

The art of formulation has changed in character in the last few years. There is no doubt that there was plenty of art in old-time pharmacy, if there were but little science. Drugs were chiefly vegetable or inorganic in character, and many of them possessed romantic properties which inspired faith, but according to current medical opinion they had very little real action. The old formularies—purely local formularies, in the sense that they were old books of recipes treasured almost by every pharmacist—contained lists of drugs which read like a quotation from Keats: Irish Moss, Quince Seeds, Dragon's Blood, Almond Oil, Otto of Roses, and so on. The new remedies, the properties of which could be measured and the results submitted to statistical analysis, had altered

all this in the course of a lifetime, but there was still a great need for craftsmanship, which unfortunately was tending to die out.

There was a gap existing between the old-type formulation and that of the new remedies, and this gap required filling in. He could not believe that the pharmacy of the future, the new drugs which were coming on the market in such profusion, offered so little to the skilled pharmaceutical formulator as simply to be dissolved in sterile water and injected. There was ample evidence of the need for the skill of the pharmacologist and the bacteriologist, but there seemed very little left for the pharmacist. In the New Remedies Index issued by the Pharmaceutical Journal, 90 per cent. of the substances were complex organic chemicals but the pharmaceutical directions consisted of the words "Dissolve in sterile water." The remainder was made up of so much of a gram of the substance in the form of a tablet.

Now, what sort of pharmaceutical future does that offer? If the stark simplicity of the many preparations listed together with the compilation of international formularies and the making up of drugs at some central point were taken to represent the future of pharmacy, the outlook was not very bright. It was up to the pharmacist to develop a better future and no one was going to look after his interests—and incidentally those of the public—except the pharmacist himself.

One of the fields, however, which still offered great scope for ingenuity, and possible alternatives to parenteral administration, was the formulation of preparations, such as ointments and creams, balanced to allow of controlled absorption of the active principles. The sulphated fatty alcohols and substances like the wool alcohols, by careful blending with the older types of base, offered great scope for medication through the skin. The preparations in which water constituted the continuous phase have profoundly modified the properties of skin applications, and ointments and creams now offered possibilities for medication in this way which were not available with the older paraffinoid and lard types of base.

Far from being an impermeable barrier, the unbroken human skin afforded a ready means for the introduction of certain types of medicaments to the blood stream. If a solution of a water-soluble drug such as a sulphonamide were applied to the shaved skin of the rabbit, the sulphonamide could be detected and measured in the blood drawn from an ear vein inside 5 minutes. It might, in fact, be a dangerous procedure to apply preparations of this type over large areas. The application of a 10 per cent. sulphonamide cream to a large open wound had on one occasion proved fatal, although a 3 per cent. cream had occasioned no trouble. There were great opportunities and fields for research in discovering the possibilities of applying some of these drugs in this way. The sex hormones were already being prepared in this way, and there were commercial preparations on the market.

The introduction of tablets represented one of the advances made in the method of presenting substances for internal use. There was now the strict requirement that tablets should disintegrate in the human

stomach, and great credit should be given to those who had emphasised this point so thoroughly. Professor Todd said that many years ago he had been called in to a post-mortem examination where the colon of a patient was filled with tablets of quinine sulphate. These tablets dissolved in dilute sulphuric acid only with great difficulty.

The formulation of coatings which would prevent the disintegration of pills and tablets during the early stages of digestion was an interesting problem. When emetine bismuth iodide was first introduced for the oral treatment of amœbic dysentery there was a difficulty in that no matter how the emetine bismuth iodide was administered it was promptly returned. The properties of emetine were not sufficiently disguised by the insoluble compound which was used, and so various methods of coating the pills were attempted. Pills were used, as tablets were as yet unavailable. They were even coated, unsuccessfully, with wax. In this question of coating pills there were now definite signs of advance. When a property became measurable, it was then possible to make comparisons and to decide where progress had been made. Modern X-ray serial photography had solved some of the problems by enabling the formulator to follow the course of the pills through the alimentary system, thus enabling him to pick just that combination of solubles and insolubles which would allow the tablet or pills to dissolve at the right point.

Having found a suitable formula which possessed the necessary characters and had proved chemically suitable, the formulator was sometimes confronted with difficulties when he transferred the small to the large scale. Substances which remained in impalpable powders in pilot trials had the unhappy knack of crystallising out from large volumes during slow cooling, or preparations to whose success water was fatal were milled in wet mills. These call for readjustment and care but are seldom insuperable. There was still scope for research and ingenuity in the devising of better methods of presentation, and if the trials and troubles were great, satisfaction was equally great when success was achieved. There was no royal road to formulation; having defined the task the formulator must try over and over again until he reached his goal. This may mean fifty, sixty or a hundred attempts, but it was only by such painstaking effort that a good formula could be produced.

The Hospital Formulary

Mr. H. S. Grainger said that this was probably as appropriate a time as could be found for discussing the hospital formulary, especially with regard to its general use and status in the hospital, for two main reasons. The first was the appearance of the National Formulary, which was now familiar to every practising pharmacist, and which was intended to cover the needs both of general practitioners and of hospitals so far as the commoner medicaments were concerned. Its compilers had obviously envisaged the disappearance of the individual hospital pharmacopœias, because the preface states: "It is not suggested that hospitals should restrict the range of preparations in use, although it is hoped that duplication of formulæ of substantially the same composition will be

avoided, and that the scope of the formulary will obviate the need for individual hospital formularies for general medicine." The second reason was that changes in materia medica have considerably altered the status of the formulary within the hospital itself.

It might be useful to review the *raison d'être* of the hospital pharmacopœia or formulary, and it was convenient to refer to the formulary of Westminster Hospital. This publication originated in 1828, although there was in existence an earlier document, going back to 1721, which is referred to in the Minutes as a "pharmacopœia." This early document was just a list of the main drugs used in the hospital, which was compiled "to lessen the cost of medicines and (assist) the procuring them at best hand." It was used as a sort of tender form for the apothecaries of London in purchasing drugs for the hospital. From this list there gradually arose a compilation of formulæ which was eventually made into the hospital pharmacopœia of 1828. The primary purpose of the hospital pharmacopœia, therefore, was economy, and the pharmacopœia was an effective instrument to that end.

Until about the last two decades, almost the whole of the materia medica in use could be and were extemporaneously dispensed and were presented in the time-honoured form of draughts, mixtures, pills, ointments, lotions, plasters and so on. It was only recently that the great advances in microbiology, pharmacology and organic chemistry had produced the highly specific and complex substances the names of which, though perhaps less euphonious, were becoming more familiar than the old botanical names.

The hospital formulary contained all the remedies at that time deemed necessary and which were available in the hospital. Until very recent times, it was a rule at Westminster Hospital that no house officer was allowed to prescribe any drug which was not in the pharmacopœia, so that it was a comparatively simple matter to keep a firm grip on the drug bill. That is not possible now that most of the medicines used are chemical substances which come from the manufacturers' laboratories already formulated and ready for use.

One field, however, in which the hospital pharmacopœia could assist in the economical use of drugs was in presenting suitable alternative formulæ for compounded proprietary preparations. In many cases the hospital formula for such preparations was frank plagiarism, and no apology was made. The hospital pharmacist's criteria were clear. The first was that the product made in the hospital should be at least as efficacious; secondly, it must be as elegant as he could make it, though he did not claim in hospital practice and under hospital conditions to attain the degree of elegance which some proprietary manufacturers achieved; thirdly, it must be cheaper to the hospital than the proprietary preparation. This last point, of course, needed very careful consideration. One had to allow for the time and personnel available, and for other considerations such as the value of the overheads of one's department, and so on.

It was not always easy to produce an elegant preparation, and considerable effort was required in order to find suitable methods for hospital production. For example, the proprietary preparations of aluminium oxide gel were usually rather costly. The British Pharmaceutical Codex instructions did not produce an aluminium hydroxide gel which would necessarily be uniform from batch to batch, which had the correct thixotropic properties and was elegant and effective in use. When a suitable product had been devised, it was necessary to include it, for obvious reasons, in the hospital formulary. It was preferable not to use the proprietary name, or the words " substitute for " preceding the proprietary name.

The second function of the hospital pharmacopœia was that of a record of the preparations in use in the hospital and designed to meet the needs and predilections of the medical staff of that particular hospital. This is the chief reason why the National Formulary will never adequately supplant the hospital pharmacopœia.

On one occasion it had been necessary to devise an easily assimilated fluid preparation containing complete vitamin B requirements. This preparation was effective and subsequently it became the routine treatment for patients undergoing a certain treatment. It found its place in the formulary as Elixir Vitaminorum B (Westminster Hospital formula).

Wherever possible the National Formulary preparation was used, but there were some occasions when the hospital preparation was more acceptable and for this reason the hospital pharmacopœia was retained. It would, however, be republished under the title " Westminster Hospital Supplement to the National Formulary."

The third function of the hospital pharmacopœia was the part which it played in the training of medical students. The student's chief tool which enabled him to apply his theoretical knowledge in the ward was the hospital pharmacopœia, which contained those preparations which had the approval of his teachers and which by long practice had been accepted. The hospital pharmacopœia should be under constant revision by the medical staff and the pharmacist to see whether obsolescent preparations should be removed, or whether new preparations which had come into use should be included. In order to include these, the new formulary of the Westminster Hospital would be printed on pages which fit into a loose-leaf binder, for more ready revision. Most hospital formularies in the past have not been revised frequently enough.

As to nomenclature, indication of formula rather than function was to be preferred; but the medical student and the busy practitioner did not think primarily in terms of drugs but in terms of diagnosis, and he looked for a remedy the composition of which was secondary in his thoughts.

There was, however, a danger in that tendency being carried too far. Indeed, one senior physician went so far as to suggest that medical students should not be worried with quantitative memorisation of the doses, but that the latter should all be expressed in units—1 for a normal dose, 2 for a strong and 3 for an extra strong dose—and that the pharma-

cist should be saddled with the recollection of what that particular amount should be. For these reasons, we must stick to the nomenclature which is indicative of composition as an *aide memoire* to the student.

So far as hospital formularies were concerned, however, a place must be conceded to tradition. The traditional names should be added in parenthesis, in order to encourage and maintain interest in formulation among the medical staff. Where new preparations associated with the name of a particular medical man are introduced, tradition requires that within the bounds of the hospital that name should be given a place in the hospital pharmacopœia. As an example, there was a recently introduced preparation with the formula: glucose, 400 g.; arachis oil, 100 g.; powdered acacia, *q.s.;* water to 1000 ml. People do not remember the formula, but they have asked, "Do you remember that stuff that Dr. Bull uses?" and it has become known as "Bull's Mixture," so it is called "Emulsio Glucosi (Bull's Mixture)."

This sort of thing, however, can get out of hand, as in the case of a preparation which became known as "Mist. Euthanasia." This preparation contained morphine, hydrochloride, cocaine hydrochloride, alcohol and honey. It was intended for the alleviation of pain *in extremis*, and it should therefore be as pleasant as possible. This had been renamed "Haustus E."

In spite of the common point of view that medicines should be nasty, improvement could be made in some preparations at present in use. Certain brands of aspirin have been criticised for being prepared as confectionery instead of as a medicament, but the National Formulary or most hospital formularies cannot be accused of erring on this side. The formularies in use in Westminster Hospital for the last 80 years had undergone little change in the flavourings used—chloroform, peppermint, liquorice and occasionally tincture of orange. Considerable improvement could be made by experimenting with the new synthetic flavourings, and with new blends of some of the old preparations such as nutmeg, cloves, and oil of lime. Formulations of the kind discussed were still worthy of imaginative cosideration.

The Point of View of the Retailer

Miss M. A. Burr said that a retailer viewed formularies and formulation from many angles in a practical manner with a direct bearing on his own profession, business and training; his relationship with the prescriber and the patient; and, to-day, his dealings with the Ministry of Health. To-day the retailer was bound to regard the Ministry as his chief customer. The retailer bore in mind also the very important fact that formularies, past and present, were issued for the guidance of the practitioner.

The close relationship which exists between the retail pharmacist, the prescriber and the patient was very important and had provided the retail pharmacist with valuable practical knowledge. Much greater use could have been made of this knowledge in the revision of formularies.

Doctors were in the majority on the Committee which compiled

the 1929 Formulary and the present compiling Committee had a majority of pharmacists, but it was to be hoped that in the preparation of future Formularies there would be an increased number of retail pharmacists on the Committee.

When the formularies were considered which were in use prior to 1929 and even as far back as 1911, it was seen that that was a period of many formularies, formularies which caused a great deal of extra work and confusion in retail practice. There were similar titles used for different prescriptions. The National Formulary was the result of the progress which had been made, and it presented a uniform collection of prescriptions available in any part of the country.

Many retail pharmacists would like to see this uniformity carried a step further by the merger of the National Formulary with the British Pharmaceutical Codex. It could be seen, from the recent amendments to the National Formulary, that it was the desire of the compiling Committee to bring the National Formulary into line with the B.P.C. The formulary section of the B.P.C., for example, could be presented in a separate concise volume. The Danish Pharmacopœia, 1949, was published in three volumes, the third volume being devoted to formulæ.

In spite of the notice from the Ministry of Health, some doctors continued to use titles from the National War Formulary, and even from earlier formularies. They knew that on such occasions chemists might refer a prescription back to the doctor to be written in full, but retail pharmacists present would agree that this was no easy task. To encourage medical practitioners to use the National Formulary, and to stimulate a greater interest in and promote a better understanding of the preparations of both the National Formulary and the B.P.C., perhaps more publicity could be given to these preparations, for example at medical exhibitions.

Retail pharmacists would acknowledge the advantages gained by the use of these formularies in the State dispensing service. The National Formulary has a place in the National Health Service, but not an exclusive one. Freedom in prescribing should be encouraged and maintained. Some members had viewed some of the findings of the recent Cohen Report with concern. There may be a danger in over-emphasising the use of formularies.

In retail practice it was realised that one of the chief uses of formularies was economy. There were many aspects here that retail pharmacists had observed, the chief being the apparent lack of knowledge on the part of many practitioners of the National Formulary, particularly from the quantity point of view. The Committee compiling the Formulary had given much thought to this point and had stated the amounts to be dispensed, if not otherwise stated by the practitioner. To-day the wastage of both formulary and proprietary medicine must be enormous. The frequent dispensing of a pint of medicine to be taken in teaspoonful doses made one wonder what value the last ounce or so had. The same remarks apply to dressings. In regard to dosage, some consideration was long overdue. The pharmacist took the greatest care in preparing

the prescription, which was then administered in many cases in the most inaccurate manner. She was not referring to the patient who dispensed with any type of measure and drank straight from the bottle, or who doubled the dose and decreased the space of time between administrations, but to the domestic teaspoon. This could prove a most serious menace in the administration of children's medicines, and especially those containing certain potent drugs.

In the children's section of the Formulary there was great need for revision. The argument that medicine should not be too palatable might be a good one, but mothers would soon convince the Formulary Committee on this point. More use could be made of the vitamin syrups, blackcurrant and rose hip, where the ingredients would not destroy the vitamin C content. Colour was another point that needed consideration.

It would be advantageous if we had a uniform size and colour of tablets, and particularly, if coated, a standard colour for the coating. The proprietary list of the Formulary required amending at more frequent intervals and to be presented in a more useful way to the practitioner. With regard to the symbols for grains and grammes, a more explicit notice was needed than the general notice in the National Formulary. Preferably practitioners should use either grains or grammes and not both in writing a prescription.

To future revision Committees considering the presentation of the National Formulary the use of larger and clearer type in printing was recommended. It would also be helpful to have a thumb index, and paper of a different colour for the infants' section would be appreciated.

The Point of View of the Medical Practitioner

Dr. A. Wilson said that the year 1950 was one which seemed to encourage everyone to reflect on the changes which have taken place since the beginning of the present century. It was appropriate, therefore, that formularies and formulations should be discussed at the Conference, for this subject was intimately concerned with the practice of medicine and, in particular, might have a profound influence on the prescribing habits of the medical practitioner.

All would agree that remarkable advances had been made in the basic medical sciences and that these were reflected in the practice of medicine. There was ample evidence that custom and tradition had given place to a more certain and scientific approach to the diagnosis and prevention of disease. It would be reasonable, therefore, to expect comparable changes in the therapeutic methods which were employed to-day. It could not be denied that considerable advances had been made in therapy, but these were often overshadowed by inconsistencies and redundancies, many of which were evident in the drugs and preparations that were still used.

Much confusion arose from a failure to distinguish those drugs or preparations that had definite therapeutic and pharmacological activity from those relatively inert mixtures which, as Professor A. J. Clark has said, were administered from force of habit to gratify in an innocuous

manner the popular desire for a bottle of medicine. There was no doubt that the placebo had a very important part to play in therapeutic practice, but such preparations should be clearly recognised for what they were by all who prescribed them, and should not be confused with those which were designed to produce a specific therapeutic action.

In this connection, from the point of view of the medical practitioner, it was relevant to consider where he got his information about the nature and action of drugs. Apart from text-books and journals, the chief source was in pharmacopœias and similar publications. Professor Gunn, a man of considerable experience in these matters, said " Pharmacopœias can be taken to reflect, *conservatively,* the tendencies of pharmacological and therapeutic progress." This opinion might be modified with respect to modern pharmacopœias, but it was obvious to anyone who studied the history and development of these publications that they had never given full satisfaction to the therapeutic excursions of doctors and pharmacists. This was evident by the appearance at an early date of national formularies, codices and even extra pharmacopœias.

All these books were originally designed as books of reference for those engaged in prescribing or dispensing medicines, but most of them had been extended to meet the needs of analysts and others. They had thus become the medium for laying down standards not only for drugs which were active therapeutic agents but also for substances which were used in commerce and by the laity. This was as it should be, for society must be protected against the fraudulent seller of drugs, however potent or inert these drugs might be. It seemed strange, however, that, although such publications were undoubtedly the guardians of purity and constancy for drugs in common use, those in Britain did not appear to be upheld by any legal enactment.

Matters concerning the source, purity and methods of preparing drugs had become the domain of experts in these subjects, and the interest of the medical practitioner in pharmacopœias and allied publications was therefore mainly centred in those parts which dealt with preparations suitable for administration to his patients. This information, however, was not readily available. In our own British Pharmaceutical Codex, although it was contained in Part VI, there was to the medical practitioner who consults it a real risk of being submerged in a sea of infusions, decoctions and fluid extracts.

In this connection it was appropriate to comment on the question of fresh infusions. There were strict injunctions for the pharmacist to get these off his premises before they were more than 12 hours old. What use were they to a patient after that? The history of cinchona bark also made very fascinating reading, but was it necessary to keep this history alive by describing preparations of it in the B.P.C. which apparently were not incorporated in any of its formulæ?

Much the same criticisms applied to the U.S. National Formulary. The problem of selecting drugs and preparations was undoubtedly bound up with the major one of deciding the nature and scope of these publica-

tions. Too often it was apparent that in this matter decisions were based not so much on the effectiveness of the preparation as on the extent to which it was used.

There was an interesting account in the U.S. National Formulary of how this might be settled. An attempt was made to co-operate with the American Medical Association in preparing a National Formulary, but the American Pharmaceutical Association could reach no agreement with them. The medical men favoured a selection based on the therapeutic efficacy of the constituents, while the main committee preferred to continue a policy based on the extent of use. To this end a survey was made of all the drugs used for medicinal purposes, by determining the extent of use of these in prescriptions, in hospital and retail pharmacies and in drug stores. From the information gained it was decided to include in the National Formulary those items which were used in at least 20 per cent. of the drug stores or which were ingredients in at least one of every 10,000 prescriptions compounded in the United States. What a unique challenge to the advertising agencies!

This method of selection was by no means confined to the U.S.A., and it was practised in this country. From a legislative point of view this collected information was no doubt necessary to ensure that drugs which were commonly used conformed to standards of purity; it may well be that the B.P.C., like the U.S. National Formulary, should undertake this task and follow this policy.

The medical practitioner, however, looked for information where the facts were available in a ready and concise manner. He needed a formulary containing a reasonable selection of therapeutic agents, described in a manner suitable for simple prescribing and administration. The principle of selection should be based on therapeutic efficiency.

The nearest approach to such a publication was provided by the British National Formulary, 1949. This was the combined effort of the medical and pharmaceutical professions and was a commendable attempt to provide a collection of formulæ consistent with therapeutic usefulness and pharmaceutical skill. It contained the essential information about the active ingredients of drugs and their preparations and their official doses. To a limited extent it had been bold. It had excluded two drugs —one, the dangerous and deadly heroin; the other, the inert and innocuous bismuth carbonate. It was obvious, however, that selection even here was too often based on the extent of use rather than on efficacy. It was true that buchu no longer adorned the formulary and that the glycerophosphates were now debarred, but other equally useless and confusing preparations should also have been swept out. Was it necessary to have six bitter-tasting preparations, or was it that mixture of strychnine and iron was masquerading as a potent preparation of iron?

The subject of doses caused much confusion. In Britain there was a curious complex about doses. We were very timid in using adequate doses of drugs. Perhaps this attitude arose from the guidance given by

the B.P., with its range of doses the choice within which, it was careful to point out, must be left to the medical practitioner's own judgment. But why not give him more precise facts to enable him to exercise this? The U.S.P. definition of an average dose gave more guidance.

Let us examine briefly how the compilers of the National Formulary have exercised their judgment regarding the doses of ingredients. Amongst the preparations designed, presumably, for the symptomatic control of diarrhœa there was a mixture with chalk which contained an equivalent of 6 mg. of morphine in each dose, whilst another with kaolin had only 1 mg. of morphine. Were both preparations effective? To render the urine alkaline the maximum B.P. dose of potassium citrate had been used, but only the minimum dose of tincture of hyoscyamus was used in another, similar, preparation. In the mixtures of aspirin and of potassium bromide they had plumped for half the maximum dose. Perhaps this was an attempt to conform with extent of use, but surely the latter preparations were not consistent with the modern knowledge of bromide action?

Frequency of administration was an important factor concerned in building up or maintaining the desirable concentration of a drug in the tissues. The pharmacological principle of this in relation to the action of salicylates was too well known to be elaborated here. In the National Formulary there was a reliable and potent mixture of sodium salicylate. There was now a suggestion to reduce the content of salicylate because of the reported occurrence of dizziness in a few patients. To control these toxic effects, when they arise, all that was required was to direct the patient to take a smaller dose of his medicine. Why spoil an effective remedy when toxic reactions could be adequately controlled in a more rational manner?

The doses of drugs and preparations were described in the metric and imperial systems. The arguments for and against the retention of both could not be discussed here, but there should be a little more consistency in setting out the information. In the section dealing with tablets, the contents of the more recent drugs were given in the metric system, whilst those of the older drugs were given in the imperial system. This promoted confusion.

Forty years ago antitoxins, vaccines and sera were hailed as the therapeutic hope of the future. They found no place in the National Formulary. Could it be that these were no longer regarded as satisfactory therapeutic agents to be used by medical practitioners, or was it that they did not rightly fit into a formulary of drugs?

So much for the nature and content of the Formulary. Let us now consider the arrangement and manner of setting out the information contained in it. So far this had followed the familiar pattern whereby preparations were listed and described in alphabetical order. This might be a convenient system for the pharmacist, but the medical practitioner would derive more information, and that more quickly and easily, by

consulting a book in which preparations were arranged according to the bodily systems on which they predominantly exerted their effects.

Suppose, for example, the practitioner wished to control attacks of asthma in his patient. If he consulted the index of the National Formulary, there was no guidance under ephedrine. He must plough his way through all the possible Latin names of preparations that he knew, and this might range from elixirs on page 27 to tablets on page 79. It would be much more helpful and instructive for him if all the drugs and preparations acting predominantly on the respiratory system were collected together. He would then, probably for the first time, realise that there were available eight or nine effective preparations for the treatment of bronchial spasm.

A pharmacological classification of the constituent preparations would be a more satisfactory method of presenting the valuable information which was contained in the National Formulary. Too much attention should not be paid to the invention or retention of Latin names for preparations; it was much more important to ensure that the facts were readily available.

Dr. Wilson showed, by means of lantern slides, four prescriptions illustrating the tendency of some doctors to prescribe proprietary articles, and to include large numbers of ingredients in their medicines, and concluded: These are perhaps extreme examples of present-day prescribing, but they reflect the confusion which arises from a failure to appreciate just what drugs can and cannot do. Several factors may account for this state of affairs, and one of these may have its origin in the limited scope of the medical curriculum for the teaching of pharmacology and therapeutics; another may be in the flow of enthusiastic but totally unwarranted therapeutic reports from commercial agencies. I should like to suggest, however, that a formulary based on the principles which I have discussed would give immediate and practical guidance to the medical practitioner in designing and in implementing his therapeutic programme.

DISCUSSION

DR. K. R. CAPPER (London) said that it had been suggested that the National Formulary and the formulary section of the British Pharmaceutical Codex should be merged. It should be borne in mind that most of the preparations in the National Formulary were in the British Pharmacopœia or the B.P.C.; out of about 500 preparations in the National Formulary, only about 30 were not in one of those books. The Codex had an important function in setting standards for these preparations and stating methods of assay. These standards were a protection to the pharmacist as well as to the public, because limits of tolerance were given which were based on a knowledge of the conditions in which these preparations were made up and of sampling errors, etc. If it were laid down that every preparation must contain 100 per cent. of what was supposed to be in it, few preparations could possibly comply. The Codex and the N.F. were complementary and should not be amalgamated.

He approved of various hospitals producing supplements to the N.F. in place of their own Pharmacopœias but preparations should not be called after the medical practitioners who were responsible for them. The only way of dealing with Dr. Wilson's suggestion about the therapeutic arrangement of the items would be to produce two formularies, one for the medical profession and one for the pharmacists. The Joint Formulary Committee were at work on the question of flavourings and the difficulties which existed, particularly with children's medicines, were well known.

DR. E. HÖST MADSEN (Denmark) remarked that there had been some criticism of international formularies. This kind of work proceeded very slowly, but it was worth while as, in the end, it was to everyone's gain and the results obtained in individual countries became the property of all countries.

Reference had been made to what should be the object of a pharmacopœia. In the U.S.A. it was intended to be a compilation of the most used formulæ. In Scandinavia they were of the opposite opinion; they thought it should not be a compilation but a guide on a national basis for medical men. They wanted to exclude all formulæ which were no longer regarded as rational and to give as quickly as possible new formulæ in a form which could be recommended. The highest responsibility in the country in medical circles was that of the Pharmacopœia Commission. He was very glad to hear Miss Burr mention the Danish Pharmacopœia, consisting of three volumes. There was also a fourth volume; it gave only shortened formulæ from the Pharmacopœia with indications of how they should be prepared, but with a brief account of their therapeutic uses. It was intended for doctors and could be carried in the pocket. Formerly they had had, as in this country, hospital formularies and formularies issued by the Pharmaceutical Society, but now these were published as one volume by the Pharmacopœia Commission and a new supplement was issued annually. He would recommend that consideration be given to producing a book similar to this fourth volume of the Danish Pharmacopœia.

MR. A. W. BULL (Nottingham) said he would like to take up the theme elaborated by Professor Todd that pharmacy was not accorded the recognition which it deserved as it was regarded as inferior to those sciences which together make up pharmacy in the broader sense of the word. The practising pharmacist could make a very important contribution to formulation. Often a formula could not represent both the therapeutic ideal and the pharmaceutical ideal so that the skill of the formulator then came into play in arriving at the best possible compromise.

In many instances necessary information and data could not be found in the literature, and the details had to be worked out or suitable formula produced by trial and error. An example of the difficulties arising in formulation and the way in which they are overcome would be found in some work done by his colleagues on strong eyedrops of sulphacetamide

B.P.C. The general preamble to the monographs on eyedrops in the Codex states that where possible they should be made approximately isotonic equivalent to a 0·9 per cent. solution of sodium chloride in water. They represented a pharmaceutical ideal but how far was it possible to go towards that ideal? First, was it necessary to have such a high concentration as 30 per cent. of sulphacetamide? The administration of such a high concentration at once stimulated a copious discharge of the lachrymal secretion, which would dilute the effective concentration of the preparation. What in fact was the actual working concentration following that administration? Again what were the tonicities of a solution of this substance of concentrations ranging from 0 to 30 per cent? A 30 per cent. solution was hypertonic. How did it compare with the pharmaceutical ideal of 0·9 per cent. solution of sodium chloride and what was the effect of concentration on the causation of pain to the patient? The boric acid contained in the B.P.C. formula was perhaps to neutralise the solution but the N.F. stated that this substance yielded a very soluble and nearly neutral sodium salt which could be applied to conjunctivae in concentrations of up to 30 per cent. These problems and questions arise from just one preparation and the same question might be asked about many others where it was necessary to compromise between pharmaceutical and therapeutic ideals.

MR. J. W. HADGRAFT (London) said that he would agree with Dr. Wilson on the need for two editions of the formulary. Many remedies remained in the B.P.C. simply because there was a demand for them, such as glycerophosphates which were now thought to be therapeutically inactive. Another problem was the increasing use of proprietary preparations. Now that there was a need for economy in the National Health Service care should be taken to avoid giving official or semi-official recognition to a combination of drugs solely on the ground that there was need for the provision of a less expensive non-proprietary formulation. He thought that Latin even in the writing of prescriptions should be abandoned. The flavouring agents available in the official books were too limited in their type and would appeal rather to the adult palate than to that of a child, and there was a definite need to make medicines more palatable for children. It was desirable to use one system of weights and measures. Not long ago the ludicrous position was reached that formulæ in the National Formulary were based on accurate imperial quantities while in the B.P.C. they were based on accurate metric quantities and accurate percentages, with the result that it was necessary to bring out a special addendum to the National Formulary in order to bring it into line with the B.P.C. He hoped that the metric system would be adopted.

MR. T. D. WHITTET (London) said that at University College Hospital it had been decided, for historical and traditional reasons, to keep their own pharmacopœia. As far as possible they complied with the N.F. and B.P.C. formulæ; in only a few cases did they make a serious alteration. One such case was a mixture which Dr. Wilson had mentioned, mixture of sodium salicylate. Recent research had shown that

many patients could tolerate sodium salicylate without the presence of sodium bicarbonate and, if they could, one got a higher blood level with a similar total dose of salicylate. To bring the hospital pharmacopœia up to date they issued what were known as " therapeutic notes." These comprised a small leaflet giving notes on the more important drugs and which fitted into a space in the back of the pharmacopœia. He would agree with Mr. Grainger in deprecating the outrageous names which were sometimes coined in hospitals. In addition to palatability, suitability and elegance were important properties. Nevertheless unpalatable mixtures are even welcomed by certain patients.

The problem of *p*H in galenicals and injections was very important and needed investigation. In the 1948 B.P. control of *p*H was more frequently applied as compared with the 1932 B.P. He thought it very important indeed to have the proposed new official formulæ tested out practically before use, and preferably stored for some time. There was a need for a laboratory, having a full-time staff, to carry out these investigations either under the aegis of the B.P.C. or the Pharmacopœia Commission. Of the newer solvents available he had found propylene glycol very useful. It was less toxic than glycerin and many substances were more stable in it than in aqueous or alcoholic solution. He had successfully used it for barbiturate elixirs and for injections. A suitable strength was 50 to 60 per cent., and 2 per cent. of benzyl alcohol was added to the injections in case the propylene glycol caused stinging. Ascorbic acid was soluble to about 8 per cent. and much more stable than in aqueous solutions. In this form ascorbic acid was very useful for adding to infants' foods. Calciferol was readily soluble in it and had recently been reported to be 2 or 3 times more active when administered in this way than when in an oily solution.

The sorbitan derivatives (" Crills " and " Tweens ") were very useful in solubilising volatile and fixed oils. Some of them could not be taken internally but others were non-toxic. For example, clear aqueous preparations of vitamin A could be made by using polyoxyethylenesorbitan mono-oleate; they were completely miscible with water and could be made quite palatable. Such emulsions of vitamin A were also stated to be more effective than the oily solutions. Elegant preparations of all the common vitamins were easily prepared by use of propylene glycol and the sorbitan derivatives.

DR. G. E. FOSTER (Dartford) referred to Miss Burr's suggestion of the use of uniform die sizes for tablets. There was some danger in this as the different sizes were useful in differentiating between tablets, particularly those of similar nature. If there were official requirements introduced concerning the sizes of tablets he hoped different die sizes would be used to prevent error.

MR. F. H. OLIVER (Sunderland) said that the therapeutic action of any medicament was due to its pharmacological action and its psychological action, and he thought that the latter aspect of formulation was often forgotten. The ancillary substances which occurred in medicines often contributed largely to the psychological effect, especially in children.

By unsuitable medication it was possible to build up inhibitions which might last the child's lifetime. He welcomed the idea of an edition of the N.F. with the preparations grouped pharmacologically, as this might lead to less rubber stamp prescribing.

MR. V. REED (London) suggested that some formulæ contained far too many ingredients, and also stressed the need for making children's mixtures more palatable.

MR. W. R. HOWARD (Hornchurch) was concerned at the considerable waste of time and effort which went on after a great deal of time and effort had already been devoted by the manufacturer to the careful formulation of his products, a second investigation was conducted by the hospital pharmacist endeavouring to produce an equally elegant and stable preparation. Some of the problems of stability and elegance did not always seem to have received sufficient attention at the time that a formulary was prepared. Problems were met with in large-scale production which did not crop up in *ad hoc* compounding. He therefore suggested that where formulæ contained vehicles or ingredients which were themselves liable to variation (e.g., tragacanth or agar), some latitude should be allowed to the compounder in the use of these materials and the final result should then be controlled by standards laid down in the appropriate publication. The standardisation of size of tablets would inevitably raise the question of the standardisation of formulæ. At the moment, formulæ were very much the subject of art and, fruitful though the field might be for planning, no official body had yet tackled it. The problem would be fraught with many difficulties and would obviously be hedged about with considerations of ready distinguishability for the different doses and similar chemical compounds with markedly different properties.

MR. J. C. HANBURY (Ware) said that, while he agreed that various books of standards performed a most useful function, he thought that if there was any pressure from outside the medical profession to compel medical men to confine themselves to such books, then a grave disservice to the progress of medical science would have been done. He thought that the art of pharmacy was changing rather than disappearing. There was more art, and infinitely more science, in producing some of the modern preparations than some of the rigmaroles of the B.P. 1867 and the like. One had only to think of the problems, both scientific and artistic, in producing satisfactory stable injections of vitamin B_1, and riboflavine and vitamin products of that sort. There was endless scope for pharmaceutical ingenuity in the newer galenicals. The suggestion of a therapeutic index was most valuable. The rôle of the pharmacist in medical science was changing; he must now become more of a pharmacologist and must be trained to do more than merely carry out the wishes of the physician, though the physician must always have the last word. The pharmacist must thoroughly understand the drugs in common use and be in a position to advise the physician on their use and methods of preparation.

MR. A. R. G. CHAMINGS (Horsham) asked what was the criterion of a good drug and who was to decide upon it? It was certainly necessary that any formulary should have a sound pharmacological basis.

MR. R. W. GILLHAM (Leeds) said that non-adherence to standard formulæ in hospitals caused a great deal of unnecessary work. He was sure that slight differences in the doses of various medicines and ointments did not make the slightest difference in effect on the human body, because it was not a volumetric machine. Not everyone realised the problems of transferring small-scale formulations to manufacturing quantities.

PROFESSOR J. P. TODD, in reply, said he hoped his views on the National Formulary had not been misunderstood, but he thought they should guard against the day when all medicaments might have to be bought from a central store. He had not intended to say anything against the International Pharmacopœia. This was a totally different problem from the National Formulary, and he greatly valued and appreciated the work which had been done in connection with it.

MR. H. S. GRAINGER said that he would be very sorry if they were so pedantic as to destroy all sense of tradition and all interest on the part of the medical profession in hospital formularies. He agreed with Mr. Howard that much work was being done in the hospital dispensary which had already been done by manufacturing houses. Nevertheless, ways of keeping down expenses had to be investigated. He would hesitate to limit a practitioner to a particular dose of a drug and in spite of the inconvenience he was encouraged when he saw a young house officer or medical registrar exercising a little individuality and ingenuity in the writing of prescriptions.

MISS M. A. BURR thanked the speakers for being more or less in full agreement with what she had put forward. The co-ordination and extension of pharmaceutical research was very important indeed, and she felt that the Pharmaceutical Society could sponsor something in this connection, which would be of great use in all sections of pharmacy if it were brought into being in the near future.

DR. ANDREW WILSON said that they had been reviewing what had happened over the past 50 years, and he hoped planning for what might take place in the next 50. He hoped that they would go away feeling that the pharmacist must make it his business to know not only the nature and quality of a drug, but also something about how it acted.

THE CHAIRMAN thanked the opening speakers and all who had taken part in the discussion, and the meeting then terminated.