THE COMPILATION OF PHARMACOPOEIAS:

INCLUDING A COMPARISON OF THE UNITED
STATES AND THE BRITISH.

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THE tenth revision of the *United States Pharmacopoeia* was completed in 1925, and the new edition came into force on January 1st, 1926.

A revision of the *British Pharmacopoeia* has just been commenced, and therefore it is interesting to compare the new *United States Pharmacopoeia* (U.S.P. X) with the current B.P., which appeared in 1914, in order to see what changes appear desirable in the latter volume.

When comparing the two it is, of course, necessary to remember that the B.P. is twelve years old, and that great advances in therapeutics have occurred since its appearance. On the other hand, it must not be forgotten that the present edition of the B.P. is still, and will continue for a year or two to be, our official guide for the preparation of drugs, and therefore if it is found to be very out of date this fact, whatever be its cause, is a strong argument for making some change that will enable our pharmacopoeia to keep more in touch with existing medical practice.

In considering the merits of any book it is necessary to have a clear idea of the purposes which it is intended to serve. Fortunately these purposes have been defined, since in the preface to the current *British Pharmacopoeia* (p. viii) it is stated that its object is "to afford to the members of the Medical Profession and to those engaged in the preparation of medicines throughout the British Empire one uniform standard and guide whereby the nature and composition of substances to be used in medicine may be ascertained and determined." This statement of aims was amplified by the President of the General Medical Council in his presidential address last November (*BRITISH MEDICAL JOURNAL*, SUPPLEMENT, 1925, vol. ii, p. 185), when he stated that "Any drug, in fact, which is (1) in current use over any considerable area, and (2) requires for the safety of the public that it should be exactly defined, in respect of source, preparation, standard of purity, etc., has a claim to admission."

The primary aim of the pharmacopoeia is, therefore, to fix standards for a certain selected number of drugs. There are several thousand drugs and preparations in use by the medical profession and scores of new compounds are introduced every year; hence it is impossible to fix official standards for every drug used in the treatment of disease throughout the British Empire, since this would need a library rather than a single volume. In point of fact, the present B.P. contains 400 drugs and 400 preparations, whilst the U.S.P. contains 650 drugs and preparations.

A comparison of either pharmacopoeia with the *British Pharmaceutical Codex*, or with Martindale and Westcott's *Extra Pharmacopoeia*, shows at once that the pharmacopoeias contain an account of only a small minority of the drugs used in medicine.

An examination of the pharmacopoeias of other countries proves that there is in practice a general practical agreement that a national pharmacopoeia can only include a selection of the drugs used in medicine. Stress has been laid on this necessity for selection because it is a point that is often ignored, and many arguments regarding the composition of the *British Pharmacopoeia* are based on the completely erroneous assumption that the volume ought to contain an account of all the drugs used in medicine.

Success in the production of a pharmacopoeia depends, therefore, first on a correct selection of the drugs to be included, and secondly on the provision of satisfactory standards for the drugs selected.

The Selection of Drugs.

The selection of drugs is a matter that concerns the medical profession rather than the pharmacists. This fact was recognized in the preparation of this new, tenth, revision of the *United States Pharmacopoeia* (U.S.P. X). The volume is the joint production of the medical profession,

the pharmacists, and the chemists, and the aim has been to prepare "a carefully selected list of medicinal substances of known origin" (p. xlv). The list of selections was drawn up by a subcommittee of sixteen physicians and five pharmacists, and was revised by a committee of twenty-one physicians (pp. ix and x). The choice of drugs was therefore left almost entirely to the physicians.

The principles of selection laid down by the President of the General Medical Council appear perfectly satisfactory, but of the two tests he has mentioned—namely, (a) frequency of use, and (b) necessity for standardization—the latter is obviously the more onerous. The pharmacopoeia is essentially a book of standards, and unless a drug has some action it is difficult to see upon what principle it can be standardized; the lack of a standard for such a drug could not involve any public danger.

It seems obvious that care should be taken to include all drugs with powerful actions which are in medical use, even though they may be used infrequently, and that there is less need for inclusion of such drugs as flavouring agents, carminatives, bitters, etc., since the accurate standardization of these latter is a matter of less importance to the public safety.

There is another factor of an economic nature which ought to be taken into consideration when compiling a pharmacopoeia, and this is that the provision of an official name and an official standard for a drug will often reduce the price of the drug.

Most new drugs are introduced to the medical profession under proprietary names, and it is desirable that the pharmacopoeia should include such drugs as soon as they become firmly established in medical practice. Very frequently such drugs are well known chemical compounds which are sold at a high price under a fancy name, and the medical profession can effect a considerable economy by prescribing these drugs under official names if such names are provided. For this same reason it is desirable that the pharmacopoeia should include as many drugs as possible which have distinctive and peculiar therapeutic actions; so that a medical practitioner, if he so desires, can confine the drugs he uses to pharmacopoeial preparations and thus avoid the expensive proprietary preparations. This last consideration will, of course, tend to swell the size of any pharmacopoeia, and therefore it is very important to avoid as far as possible the inclusion of useless or redundant drugs and preparations.

Any process of selection involves leaving out drugs which are in medical use. This is no great hardship, since the omission of a drug from the pharmacopoeia does not prevent any doctor from prescribing it if he so desires.

Any selection to be defensible must be based on general principles, and I suggest that the two chief principles should be—

(1) The inclusion of all powerful drugs in general use, on the ground that variation in the activity of such drugs is a public danger; and

(2) The inclusion of a sufficient number of drugs to ensure that any medical man wishing to prescribe a drug to produce a particular therapeutic effect should be able to find a drug of the type desired in the pharmacopoeia, and should thus be able to avoid the use of expensive proprietary articles.

In addition, a sufficient number of bases, flavouring agents, etc., must be included to permit the dispensing of standard preparations of uniform quality and appearance.

The selection of drugs should be based primarily on these principles, and after these requirements have been satisfied as many additional drugs can be added as may be considered desirable. This work of selection must be carried through by a committee considering the problem as a whole. For instance, there are between fifty and a hundred compounds which are used as hypnotics. No one would wish all these drugs admitted, but only a committee considering the needs of the pharmacopoeia as a whole can decide what number of hypnotics will form a proper proportion of the volume. Obviously a plebiscite cannot decide a matter of this nature; it can indicate which drugs are most popular, but cannot give any indication as to the number of any one class of drugs that ought to be admitted.

If a pharmacopoeia is to be judged by the proportion it

maintains between the various classes of drugs, and the number of important drugs for which it provides standards, then it must be admitted that the B.P. compares very unfavourably with the U.S.P.

The B.P. describes 400 separate drugs, but of these 40 are bases or colouring matters, 60 are flavouring agents, carminatives, and bitters, and 16 are simple astringents. About 30 more drugs are vegetable purgatives or anthelmintics. Any pharmacopoeia must, of course, contain an adequate representation of all the classes of drugs mentioned, but these numbers seem excessive. Moreover, of the remaining drugs there are a considerable number which have little or no known therapeutic action.

The U.S.P. in its last two revisions has made a determined effort to clear out rubbish, and it has, in this period, removed 432 drugs and preparations, and has added only 108. Thus it has reduced its scope to 650 drugs and preparations, most of which have a well defined therapeutic action. The process has consisted chiefly in deletion of galenicals of doubtful activity, and the insertion of new synthetic compounds. About 80 of the substances discarded, and 22 of the substances added, are in the present *British Pharmacopoeia*.

A more important difference between the two pharmacopoeias is that the U.S.P. contains a large number of potent drugs in general use which are not included in the *British Pharmacopoeia*. The following are a few of the more important drugs which are absent from the *British Pharmacopoeia*, but which appear in the U.S.P.

Class I. Drugs which were known before 1914.—Atophan, barium sulphate, emetine hydrochloride, pituitary extract, nitrous oxide, oxygen, novocain, salvarsan, antidiphtherial serum, antitetanic serum, theocine, small-pox vaccine, sodium veronal.

Class II. Drugs introduced to medicine since 1914.—Neosalvarsan, quinidine, sodium luminal, thyroxin.

The standardization of all these drugs is obviously desirable in the interests of public safety. In most cases the drugs have powerful therapeutic actions, and therefore any variation in their activity is a matter affecting the public safety. In the remaining cases, such as barium sulphate, nitrous oxide, and oxygen, the presence of impurities may be dangerous to life.

The *British Pharmacopoeia* is therefore overloaded with numbers of substances with little or no therapeutic activity, and does not include a considerable number of important drugs. In my opinion about 80 drugs might be deleted from the B.P. without causing the least public inconvenience. Of these 80 drugs only 10 are in the present edition of the U.S.P., and 40 have been deleted at the last two revisions of the U.S.P. On the other hand, there are at least 40 important drugs, nearly all of which are in the present U.S.P., which ought to be added to the B.P.

With regard to the selection of preparations it is very difficult to generalize, as a number of questions have to be considered. Certainly, however, it is undesirable to crowd the pharmacopoeia with a large number of preparations of the same substance. All of these preparations may be excellent, but since the pharmacopoeial space must be regarded as valuable a selection should be made of the most useful.

The U.S.P. has managed to eliminate redundant preparations more successfully than has the B.P. For example, the U.S.P. X contains only seven opium preparations, whereas the B.P. has no fewer than seventeen. Moreover, the U.S.P. saves much space by giving general instructions for the preparation of infusions, decoctions, and extracts.

The U.S.P. X is enabled to save space by the omission of widely used preparations of minor therapeutic importance, because most of these preparations are included in the National Formulary. This latter volume contains prescriptions for a large number of compounds in general use, and is recognized as a legal standard for drugs. Any scheme for the reform of our pharmacopoeia should include the official recognition of some volume of similar scope in this country.

In my opinion about 150 preparations might be deleted from the present B.P. Fewer than 10 of these are in U.S.P. X. Any such process of wholesale deletion would, of course, involve the removal of many drugs widely used by medical men; and, after all, the pharmacopoeia is not

"the Doctors' Bible," nor is it a textbook of therapeutics, but it is a list of official standards for those drugs for which standards are deemed necessary in the public interest. The omission of a drug from the pharmacopoeia does not prevent anyone from using it, but the inclusion of a drug is official recognition of the fact that it is considered sufficiently important to be in a selected list of drugs.

The Standardization of Drugs.

It is impossible to criticize the standards provided for drugs without considering the purposes for which the standards are provided. The standards in the U.S.P. X are legal standards, since the National Food and Drugs Act, 1906, and various State laws make the U.S.P. and the National Formulary the standards for drugs (U.S.P. X, p. x).

The standards of purity, etc., of the B.P. apparently are not intended for legal standards, since it is stated (p. xiv): "In short, the details of procedure in these and other chemical operations are now left to the skill and judgement of pharmacists and of analysts, who are assumed to be fully trained." No attempt, therefore, is made to make the standards foolproof or fraudproof, and in many cases an analytical chemist could, while keeping strictly within the limits of the directions provided, obtain very considerable variations. The *British Pharmacopoeia* is intended to instruct pharmacists how to prepare drugs for physicians. In practice it has been made a presumptive legal standard for other purposes, but it is unfair to blame the B.P. for being unsuited for purposes for which it was not intended.

On the other hand, the B.P. is bound to be the basis of important trade transactions. Drugs, when dispensed as medicines, must comply with the B.P. standards, and hence these standards are bound to form the basis of wholesale transactions. For this reason the standards of purity provided in the B.P. appear to need extensive revision and expansion. With regard to standards designed to measure therapeutic activity, however, there can be no doubt that it is most important that any which are provided by the B.P. should be adequate tests. The inclusion of useless drugs in a pharmacopoeia chiefly injures the reputation of the volume and does little direct harm, and although the omission of an important drug means a failure to provide any official safeguard as regards that drug, yet the provision of an inadequate standard is a far greater peril. It means the legalization of the sale of preparations of widely varying activity.

There are a number of important substances whose activity cannot at present be measured by chemical tests, and therefore require biological standardization. The editors of the U.S.P. recognized this fact in 1916, and laid down compulsory methods of biological assay for pituitary solution and for cannabis indica, and provided optional methods of biological assay for aconite, digitalis, strophanthus, squills, and suprarenal glands. The present U.S.P. has made biological assay compulsory for aconite, cannabis, digitalis, ergot, pituitary extract, strophanthus, and squills, and its regulations imply biological standardization for antitoxic serums, salvarsan, and neosalvarsan. It also provides an optional method of biological assay for the vitamin content of cod-liver oil.

The *British Pharmacopoeia* lays down no requirements regarding biological assay, and in consequence its standards legalize the sale of preparations of active and important drugs of the most widely varying potencies. For example, a tincture of digitalis might satisfy the B.P. requirements, and yet its activity might be anything from zero to more than normal strength.

The passing of the Therapeutic Substances Act, together with the action of the League of Nations in providing international standards for biological assay, will presumably ensure the inclusion of such assays in future editions of our pharmacopoeia. It is regrettable, however, that we should be more than ten years behind the *United States Pharmacopoeia* in adopting this method.

Mistakes in the B.P.

There are a certain number of actual mistakes in the B.P. which are avoided in the U.S.P. For example, the

hypodermic injection of cocaine is of 5 per cent. strength with a dose of 5 to 10 minims. This strength is far greater than necessary, and in consequence the dose is dangerously high.

Again, the methods laid down in the B.P. for the preparation of ergot extracts are such as to risk the loss of the whole of the alkaloids, which are the only active principles in ergot known to produce therapeutic effects when the drug is given by the mouth.

Naturally, the number of such errors is limited, and they can be avoided by simply copying the practice of other pharmacopoeias.

Nomenclature.

A comparison of the U.S.P. and the B.P. shows that the former is superior in nearly every respect, but although this comparison is very flattering to the U.S.P., yet it must not be supposed that this pharmacopoeia is above criticism. It still contains a number of obsolete drugs which might be deleted with advantage, and in the nomenclature chosen for new drugs the results seem in many instances to be rather unfortunate.

Most new drugs are introduced to the medical profession under proprietary names, and they are only adopted into the pharmacopoeia and given official names after they have become established as therapeutic agents, and after their proprietary names have got a firm hold. Obviously it is difficult to replace the general use of these proprietary names by official names, and it would be an obvious advantage were all pharmacopoeias to adopt a common official name. The U.S.P. X seems to have taken especial pains to avoid using any name that has been adopted by the B.P. For example, the chemical compound hexamethylenetetramine became widely known under the name urotropine, and was sold under this name and a dozen other fancy proprietary names for many years. The B.P. 1914 adopted the name hexamine, and the U.S.P. had previously adopted the name hexamethylenamine. Even this divergence was unfortunate, but now the U.S.P. X has rechristened the drug methenamine. Another example is diethyl barbituric acid, which is widely known as veronal. This drug was adopted by the B.P. as barbitone, and the drug has now been admitted to the U.S.P. X under the name barbital.

The only purpose of these official names is to try and replace the proprietary names, and there is no likelihood of this endeavour being successful unless all pharmacopoeias adopt the same name. Medical literature is international, and therefore international names are needed for drugs, and if the pharmacopoeial names are more local than the proprietary names the latter will persist. It is to be hoped that in future official names will be settled by international agreement.

The Editing of the Pharmacopoeias.

A comparison of the new edition of the U.S.P. with the current B.P. shows that the latter needs a very extensive revision if it is to be brought into line with modern medical practice. The difference between the two volumes cannot be accounted for entirely by the twelve years' interval between the dates of their appearance, because the contrast between the U.S.P. IX (1916) and the present B.P. (1914) is almost equally striking. A comparison of the mode of production of the two pharmacopoeias explains very largely the differences to be noted between them.

The U.S.P. was edited by an executive committee elected by a convention at which all interests affected by the pharmacopoeia were represented. The executive committee was divided into fifteen subcommittees which did the detailed work. These subcommittees were composed of experts of all kinds—clinicians, pharmacists, analytical chemists, pharmacologists, and so on. The task of selection of the drugs to be included was left practically entirely to the medical section of the executive committee, but the pharmacopoeia as a whole represents the joint production of the medical profession, the pharmacists, and the chemists.

The *British Pharmacopoeia*, on the other hand, is edited by a committee of members of the General Medical Council, and since the members of this Council are elected mainly to

fulfil the highly important duty of acting as a court of discipline in professional matters for the medical profession, it is only a chance if they happen to be particularly interested in the compilation of a pharmacopoeia.

In the past the editorial committee has been assisted by committees of reference in pharmacy and chemistry. The pharmacists have now declared that they are unwilling to co-operate on the past basis, for the reason that since they have to do a large proportion of the work they ought to have a voice in the editing of the pharmacopoeia.

The production of a satisfactory pharmacopoeia is a public need, and therefore it is to be hoped that some arrangement will be made that will ensure the co-operation of all the interests concerned.

The production of a new edition of the B.P. is so urgently needed that it will be necessary to produce a new volume as quickly as possible, and since most alterations in the pharmacopoeia involve a good deal of careful research work it will probably be necessary to rely in the next edition very largely on information provided by other pharmacopoeias. The expert knowledge available in England is, however, just as good as that in any other country, and it is offensive to national self-respect that we should be content with a parasitic existence, and should not endeavour to supply our quota of knowledge.

In the future some organization ought to be arranged that will ensure continuous research being carried out on pharmacopoeial problems, and a new edition ought to be brought out at least once every ten years. The U.S.P. appears regularly every ten years, and the last edition took five years to prepare. Careful consideration, however, is needed of the exact functions which a pharmacopoeia is intended to fulfil.

The defence of our present pharmacopoeia is that it is not intended as a guide in therapeutics, but that it registers the customs prevailing in the medical profession at the time of its production, and that the standards set forth are merely guides to the pharmacist to enable him to prepare uniform preparations of the type in popular demand by the medical profession. On these assumptions it would be possible to defend almost any pharmacopoeia, however bad. They are not justified in actual practice because it is admitted that a selection of drugs is exercised, and hence the appearance of a drug in the pharmacopoeia is a recognition of its importance.

The pharmacopoeia does not attempt to set limits to therapeutic practice, but it undoubtedly guides it to a certain extent. Under the present arrangement the practitioner knows that the pharmacopoeia is prepared by the leaders of the medical profession, and he does not realize that in selecting drugs they are not guided by their own opinion as to the value of drugs, but merely follow popular custom. Hence the appearance of a drug or preparation in the pharmacopoeia encourages its use, and as its retention is determined simply by the frequency with which it is used a vicious circle is established which checks the progress of therapeutics.

With regard to the standards formulated for drugs, the practitioner naturally believes that the standards for therapeutic efficiency are devised in accordance with the best scientific knowledge available, and does not realize that faulty standards have been defended simply on the ground that the preparations made according to these standards have been accepted by the profession without complaint.

In my opinion a pharmacopoeia ought to be compiled in accordance with the best medical opinion available, and the editors ought not to be afraid to take the responsibility of saying that the drugs included have been selected because they are believed to produce therapeutic actions, and that the preparations have been selected because they are believed to contain the active principles of the drugs in a stable and reliable form. At the same time there should be a clear definition of the purposes for which the standards laid down are suitable.

The assumption of such responsibility would, of course, be a departure from previous custom, but it would result in the production of a volume that would encourage rational therapeutics, and would not be merely a record of obsolescent medical customs.