PHARMACOPOEIAS AND FORMULARIES

THE BRITISH PHARMACOPOEIA 1958*

BY TEODOR CANBÄCK, STOCKHOLM

The British Pharmacopoeia of 1958 is in many respects a heavy book. It consists of about one thousand pages. It has taken me about four weeks to read it through and it will probably take me another year to get *well* aquainted with it. By the way, is not pharmacopoeia today a she? It appears in a fresh new dress every five years and in between make-ups are applied. The last make-up of the 1953 edition included quite a few new drugs. One of them, phenylbutazone, has already been dropped, the remainder have been included in the 1958 edition.

The official British attitude towards new miracle drugs seems in the past to have been rather more sceptical than for instance the North American attitude. In this edition, however, some of the most modern drugs have received official recognition: acetazolamide, chlorcyclizine hydrochloride, chlorpromazine hydrochloride, erythromycin, hyaluronidase, hydrocortisone and its acetate, lucanthone hydrochloride, neomycin sulphate, noradrenaline acid tartrate, phenoxymethylpenicillin, piperazine adipate and phosphate, polymyxin B sulphate, prednisolone and its acetate, prednisone and its acetate, sodium radioiodide, sodium radiophosphate, etc.

Also included are some older well-known substances such as carbromal, dapsone, dexamphetamine sulphate, mustine hydrochloride, phthalylsulphathiazole, reserpine and solapsone.

An onlooker may wonder if there is not a slight change in the principles of selecting drugs now compared with the situation one or two editions back. A certain broader point of view of the advisability of giving standards for new drugs in an early phase of their life seems now to be prevailing. If this be the case the Commission is, in the reviewer's opinion, to be congratulated as it is,—still in the reviewer's opinion—far more important to have standards for a drug as soon as possible and while its use is still booming, than to discuss at length its merits compared with other drugs. The possibilities of publicising a new drug being what they are today, and the possibilities of stopping the trade with unwanted drugs being what *they* are, standards given for new substances nevertheless have an enormous influence today.

Concerning the attitude towards the chemical tests and assays it is safe to say that many of the historic tests for metals, chloride, sulphate, readily carbonisable substances (with concentrated sulphuric acid) have disappeared. The arsenic test is still there. The assays have in many instances been revised and older extraction methods have been replaced by titration in glacial acetic acid with perchloric acid. Included is also lithium methoxide N/10 for the titration of weak acids. A close comparative study of the 1953 and 1958 editions reveals that the laboratory side of the revision work was a dominating part. It is today a necessity to have access to good laboratory facilities for pharmacopoeial work.

As the multitude of new compounds in certain groups like the sulphonamides, antibiotics, antihistamines, and amines of different types is still increasing the compilers of pharmacopoeias are facing a serious problem: it is becoming more and more difficult to design identification tests for substances within those and similar groups, e.g., tests which really identify the substance. Often only one or

* The Pharmaceutical Press, 17 Bloomsbury Square, London W.C.1. Price 63 shillings.

two out of many hundreds of similar compounds are included in a pharmacopoeia. It is usually not difficult to design a good-looking test for a single substance. The danger is, however, that many of the compounds not included in the pharmacopoeia will give the same result when tested with the official method. This *fact* may lead to remarkable consequences if a case should come up in a court where the substance responded to the official tests but nevertheless was not the official substance. As examples of such substances the barbituric acid derivatives may be cited. Of these pentobarbitone sodium with a m.p. of about 128° for the acid is poorly identified. On the market are a number of substance all called pentobarbitone sodium with m.p. for the acid between 126° and 133°. The *p*-nitrobenzyl derivatives of these substances, however, differ as much as between 140° and 160°. In this case very little harm is done as the different substances probably have about the same action, but the example may illustrate the difficulties in designing adequate tests.

A legal situation of the kind outlined above recently occurred in the U.S.A. in connection with the increased production of Salk vaccine. The manufacturing firm was sued for millions of dollars by more than forty victims or their representatives. The court, however, seems to have decided that the cases against the manufacturer were invalid, as the produced vaccine actually met the official tests although the vaccine contained live virus.

Another general remark about pharmacopoeias is in connexion with the probable free trade market in Europe. The work on the unification of standards and tests cannot longer be looked upon as a game for internationally minded pharmacists, it is today a necessity for the manufacturer of basic drugs. The point cannot be stressed firmly enough that groups which choose to work for themselves play a fast and loose game with the export and import trade of drugs in their country. In this connexion the new British Pharmacopoeia is an excellent example of what can be achieved when common sense is accepted as a basis for the work.

It is out of question to review and discuss all the basic changes which have been made in the standards and the tests. However, a few may be of such general interest that it may be justified to comment upon them. The assay for adrenaline in Lignocaine and Adrenaline Injection is based on the oxidation of adrenaline to adrenochrome by means of ferric ions. The amount of adrenochrome produced is measured spectrophotometrically at 540 mμ. Experience has taught me that this method is definitely unsuitable. It works well as long as there is no destruction of adrenaline but a solution in which the adrenaline is destroyed to 50 per cent still contains 100 per cent adrenaline when assayed by this method. The only chemical method which is acceptable today is one based on the measurement of the fluorescence of a rearrangement product of adrenochrome formed from the adrenaline present.

The monograph on Injections is an excellent one and well worth detailed study. The appendix on Biological Assays and Tests is rewritten and consists with its eight subappendices of no less than fifty-three full pages. Noteworthy is that in the test for pyrogens the rise of temperature is interpreted in such a way that sometimes only three animals are needed; twelve animals will always be enough to ascertain a result.

Concluding this short review it shall be stated that the British Pharmacopoeia of 1958 is an excellent pharmacopoeia worthy of its predecessors. Again we have seen a demonstration of the high standard of British Pharmacy.