PHARMACOPŒIAS AND FORMULARIES

THE PHARMACOPEIA OF THE UNITED STATES OF AMERICA

FIFTEENTH REVISION*

REVIEWED BY FRANK HARTLEY

The publication in July, 1955, by the Board of Trustees of the United States Pharmacopeial Convention of the U.S.P. XV, to become official from 15th December, 1955, inevitably arouses much interest among those concerned with substances and preparations of therapeutic importance. Such interest may lie in the choice of substances and preparations added or deleted by the revision, in the range of information now given, in the techniques adopted for the various standardisations, or in the method of presentation.

In the Fourteenth Revision, 119 substances and preparations were deleted and 202 new substances and preparations were added. Of these 202 items no fewer than 44 have failed to secure inclusion in the U.S.P. XV. In all, 163 articles included in 1950 in the U.S.P. XIV have not been admitted to the U.S.P. XV. There are 242 "new admissions" to the U.S.P. XV.

The selection of substances and preparations for addition and deletion is perhaps the most difficult task of all in the revision of a pharmacopœia. In the words of the preface, "the Pharmacopeia must reflect with fidelity the best practices of medicine and pharmacy in providing standards of purity and potency for drugs of established merit and indispensability. These drugs must constitute, in the words of the first Pharmacopeia, therapeutic agents 'the utility of which is most fully established and best understood'. To this extent, the U.S.P. is a therapeutic guide, the soundness of which is tempered only by that of the judgment of those who select the articles to be included. Yet, by its nature, the process of selection can scarcely be perfect, for no means has been found to ensure, at least by the time of publication, that all drugs included are of equal merit and that no others equally meritorious are omitted. In view of to-day's rapid progress in medical sciences, a varying degree of lag is inevitable".

Many of the additions were clearly to be expected, for example, cortisone acetate, hydrocortisone and its acetate, bacitracin, erythromycin, neomycin sulphate, oxytetracycline and tetracycline, polymixin B sulphate, aminosalicylic acid and its sodium and calcium salts, and isoniazid, diethylcarbamazine citrate, sulphacetamide, sulphamezathine and sulfisoxazole (sulphafurazole). But there are also some surprises. It is surprising to find that in 1955 the following qualified to become "new additions"—calcium pantothenate, dehydrocholic acid, dienoestrol, juniper

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tar, sulphurated potash and white lotion (prepared from zinc sulphate and sulphurated potash) but, perhaps most of all, sulphapyridine, especially as sulphaguanidine, sulphanilamide and sulphathiazole are deleted. Specially interesting additions appear to be protein hydrolysate injection, sterile suspensions of progesterone and testosterone, water-miscible vitamin A, sodium radio-iodide (^{131}I) solution and sodium fluoride (given the category "Dental prophylactic" and Dose—usual—0·7 to 1 part per million in drinking water). Among the deletions are amphetamine and its inhalant, aloin, barbital (barbitone) and its sodium salt and tablets, boric acid ointment, calcium lactate, cascara sagrada tablets, digitalis tincture, ephedrine and its hydrochloride (though the sulphate is retained), ferric ammonium citrate, gentian, neocinchophen, pancreatin and scopolamine hydrobromide tablets.

Interesting innovations are the addition to the monographs of statements of category to "indicate the therapeutic basis of admission of the drug and . . . the best known pharmacologic action of the article or of its active ingredient". As the definition of category is often limited to one word or at most a sentence, the resolution of many definitions of category must have involved much discussion. The reviewer believes, however, that with the increasing number of new substances whose names tax the memory of practitioner and pharmacist alike, the addition of a definition of action, however brief and approximate, cannot fail to be helpful and will diminish the risk of accidental confusion between the names of some drugs used for entirely different purposes. As an example, bethanechol chloride is given as "Category: parasympathomimetic", and benzethonium chloride as "Category: local antibacterial".

Cautionary italicised notes are added to monographs about poisonous substances, as for example, "Caution—Atropine sulfate is very poisonous" and to monographs of substances whose solutions deteriorate, as for example, "Caution—Prepare solutions of Calcium Acetylsalicylate within 24 hours of administration. Under no circumstances use a solution if its color is darker than that of a freshly prepared solution".

Especially interesting also are pages 800–945, prefaced by a separate contents page on "General Tests, Processes and Apparatus". In the section on General Information and Procedures are descriptions of chromatography (on columns and on paper), pharmaceutical preparations (capsules, elixirs, emulsions, extracts, gels, inhalants, lotions, magmas, ointments and ointment bases, pastes, solutions, spirits, sprays, suppositories, suspensions, syrups, tablets, tinctures and aromatic waters), radioactivity and its determination, U.S.P. reference standards, including a list of twenty-four U.S.P. steroid substances now available, spectrophotometry, sterilisation, titrimetry, including titration in non-aqueous solvents, and analysis of vegetable drugs. There follow sections on apparatus for tests and assays, bacteriological tests, biological reagents for clinical tests, including blood grouping and typing serums and thromboplastin, biological tests and assays (including an excellent 15-page section on the design and analysis of biological assays), chemical tests and assays, and physical tests and determinations.

The pyrogen test is an improvement on the previously official test in using summation of rectal temperature rises in groups of rabbits as well as maxima in individual rabbits, but still leaves potential ambiguity in the borderline case, which could be removed without necessarily employing more rabbits, by applying sequential sampling technique. The vitamin B_{12} activity assay continues to be based on the response of *Lactobacillus leichmanii* and the medium still includes centrifugal canned tomato juice, whereas, in this country, we now regard *Ochromonas malhamensis* as more specific in its response and in consequence obtain lower but probably truer potencies.

The Kjeldahl nitrogen determination still adheres to fixed proportions of potassium or sodium sulphate and sulphuric acid for digestion with copper sulphate as catalyst, whereas the B.P. 1953 recognises that greater precision is achieved by adapting the proportions to the nature of the nitrogenous substance being examined.

The weight variation of tablets and of contents of containers of sterile drugs continues to depend on the use of 20 unbroken tablets and 20 containers respectively. A weight variation test for contents of capsules is now added using initially 20 capsules, but if the prescribed limits are exceeded, may be repeated on a further 40 capsules.

For implantation, pellets of desoxycortone acetate and testosterone may be prepared only by compression of the steroid, unlike the B.P. 1953 which recognises fusion as the preferred method. Further, the B.P. 1953 requires pellets to be distributed singly in sterile containers sealed so as to exclude micro-organisms, whereas the U.S.P. XV directs the pellets to be preserved singly in *tight containers*. The general notices define a tight container as capable of tight re-closure, which hardly seems likely to ensure the retention of the sterility of the pellets.

In striking contrast to the British Pharmacopœia, the general notices of the U.S.P. XV state that capsules and tablets may be manufactured with suitable diluents, bulking agents, *colors*, lubricants and adhesives, that "tablets may be coated with harmless ingredients and that capsules, and tablet coatings, may be colored with a pharmacopeial article or a color certified as suitable for coloring drugs under the terms of the Federal Food, Drug and Cosmetic Act". Enteric coatings are permitted and hypodermic tablets continue to be recognised. Buccal and sublingual tablets are permitted to soften but not disintegrate in the disintegration test, which continues to employ the basket-rack assembly with the tablets raised and lowered on a wire mesh through aqueous liquids at about 37° C. Disintegration times of 30 minutes for antihistaminic or barbiturate tablets, of 1 hour for tablets such as carbasone, nicotinamide or penicillin and 2 hours for tablets such as those of ethisterone and ferrous gluconate are permitted.

Substances other than those specified in the monographs are permitted to be added to enhance the permanency or usefulness of the pharmacopœial article or preparation, provided they are non-toxic and harmless in the amounts administered and do not interfere with the therapeutic efficacy or with the tests and assays prescribed. Alcohol denatured by

not more than 10 per cent. by volume of methyl alcohol or acetone may be used in the manufacture of preparations in which alcohol is used as a solvent, provided the finished preparations are identical with those in the monographs and comply with the prescribed standards.

Latin sub-titles which were retained in the U.S.P. XIV have now been omitted and are retained as synonyms only where the Latin stem differs markedly from the English. Apothecary equivalents have been omitted from the statements of dosage and sizes available. It is stated that an intention to retain the equivalents for those drugs still customarily prescribed in apothecary units proved to be a greater source of confusion than outright abandonment. It is also stated that "For those who still use the apothecary measures a table given on the back cover will prove useful". These equivalents are as near to being out of the U.S.P. as is physically possible!

Non-proprietary names recommended for international use by the World Health Organisation are given as synonyms where these differ from those common in the medical literature of the United States. As to identity of the standards of the U.S.P. and of the International Pharmacopœia, it is recognised that small differences may exist, but that there are few instances in which an article conforming to the U.S.P. standards will fail to conform also to those of the Ph.I.

The U.S.P. XV, providing as it does the most up-to-date compilation of modern medicaments and their standards and tests, cannot fail to merit close study. There is much to be learnt from the vast mass of new information which it contains. Not all British readers will agree with all the decisions which have been taken in its compilation. All will, however, appreciate and admire the skill and attention to detail with which Dr. Lloyd C. Miller, Director of Revision, and his team of collaborators have completed their huge task.

(ABSTRACTS *continued from page 788.*)

and concentrations in blood and urine increased with increasing dosages. No toxic effects were observed except for a chill reaction with one lot of the drug. The carrier state was not observed in any patient up to 3 months after treatment.

S. L. W.

Tricyclamol, a New Anticholinergic Agent. A. G. Zupko and L. D. Prokop. (*J. Amer. pharm. Ass., Sci. Ed.*, 1955, **44**, 160.) The degree to which sweating was suppressed in human subjects to whom tricyclamol had been administered was determined by measuring the sweat excreted from several areas of the body. Suppression was greatest on the forehead and dorsum of the hand and least on the upper arm and thigh. Hyperhidrosis was effectively controlled in 76 per cent. of the subjects. The peak effectiveness was reached 60 to 90 minutes after administration of the drug and the duration of the effect was 4½ to 5 hours. The maximum suppression of the parotid salivary output was 26·8 per cent., 60 minutes after the administration of 0·1 g. of tricyclamol. The substance compared favourably with other anticholinergics in regard to anhidrotic and antisialogogic side effects, but some subjective manifestations of parasympathetic inhibition were observed. Low doses were found to inhibit locomotor activity in the rat, but cerebral stimulation was indicated by convulsions when the toxic dose was reached.

G. B.