PHARMACOPOEA INTERNATIONALIS

Some Comments and Criticisms

By R. E. Stuckey

The International Pharmacopœia has now been available since 1951 and sufficient time has elapsed for working comparisions to be made with existing standards and in particular with the Pharmacopœias of Great Britain and of the United States. The recent publication of the British Pharmacopœia 1953 is also of interest in this connection since some of the changes made may well be considered in relation to future editions of the International Pharmacopœia.

Pharmacopœias generally have undergone fairly extensive changes in the years since 1945 and three main trends in particular may be mentioned. Firstly, many new synthetic organic compounds have been introduced and it is in the standards for these compounds that pharmacopœias of different countries will differ; it is to be expected, therefore that there will be difficulty in obtaining agreed standards and methods of testing and in fact those responsible for the International Pharmacopœia may be congratulated on the extent to which agreement has been reached. Secondly, there has been a widespread introduction of newer analytical methods particularly those involving physical instruments; older Pharmacopœias attempted to lay down fairly rigid standards for methods and apparatus but such standardisation with modern instrumental methods is no longer possible and broad directions have to be given leaving the working details to the analyst. Thirdly, there has been a trend towards a rationalisation of the diverse methods used for general analytical testing. This has been reflected in the standardisation of a number of processes in the U.S.P. XIV and in the B.P. 1953 and a number of articles have been published[1] with this object in view. Standardisation or rationalisation of procedures should not be undertaken without good reasons, but in modern analytical practice the application of the many diverse experimental techniques and standards laid down in different pharmacopœias has become a real difficulty. Thus it is not impossible at the present time to find that a pure substance will not pass all the appropriate existing pharmacopœial standards merely, for example, because the melting point may be, say, 205° C. wereas one or other specifications may state that the substance must melt between 202° and 204° C.

The following comments and criticisms are made from a comparison of various pharmacopœias and from practical experience of the processes involved, and are intended to be helpful to those contemplating a revision for future editions of the International Pharmacopœia.

General Processes

Solubilities. The precise definition of the terms "very soluble," "freely soluble" and similar designations is to be welcomed as providing useful information for the reader. In many instances solubilities are

stated as, for example, "soluble in about 300 parts of water," although a few solubilities are given as precise figures, as for morphine hydrochloride —"soluble in 25 parts of water." Presumably such precise solubilities are to be regarded as part of the standards; in most cases such figures, however, are approximate only and have not been determined with a view to being applied as an exact standard. If a solubility is to be regarded as a critical test (and often it is extremely critical) conditions of solution should be given and it would be better to include special directions such as are given, for example, under amylene hydrate for "completeness of solution."

Determination of ultra-violet absorption. This determination should be examined with a view to making it either more, or less, precise. Thus the ultra-violet absorption of desoxycortone acetate is given as "determined in ethanol (95 per cent.) FT, at 240 mμ., not less than 440." The specification given for ethanol FT will not ensure a solvent with an absorption at 240 μu sufficiently low for this test; either a limit of absorption should be imposed for the solvent or, better, general directions should be given, leaving the actual details to the discretion of the analyst. The latter course has been followed to a large extent in the B.P. 1953.

As a minor point, the absorption for ascorbic acid is given as a precise figure, 550 at 245 mμ. Such a requirement is of course unsatisfactory and either a minimum figure or limits should be quoted.

Determination of residue on ignition. Previous comments have been made[2] to the effect that the use of "sulphated ash" would be preferable. The ignition of many substances at a temperature sufficiently low to avoid losses by volatilisation is a tedious process. In addition the limits quoted in individual monographs might well be standardised. There is little point in quoting limits below 0·1 per cent. for solid organic compounds (e.g. nicotinic acid has a limit of 0·05 per cent.); also a figure such as 0·1 per cent. should be practically attainable for most pure organic substances.

Assay of vitamin A. Recent developments have made the revision of this Appendix essential. Since the International Unit of vitamin A (spectrophotometrically standardised) has now been defined there can be no valid reason for the retention of the biological assay. Results obtained from biological assays of say halibut-liver or cod-liver oil would have such wide limits of error that they would be of no practical value, and in view of the chromatographic methods and spectrophotometric correction procedures available the biological assay should be omitted; its inclusion is, in fact, fundamentally unsound.

The limits of error quoted for the correction procedures are too precise; much conflicting evidence has been published on this matter and a more general statement such as is included in the B.P. 1953 might well be given. The assay of cod-liver oil needs reconsideration in the light of the B.P. 1953 and in view of recently published work[3].

Tests for metallic impurities. The same criticism may be levelled against the International Pharmacopœia as has been made of other existing Pharmacopœias. Arsenic and lead tests are included in a more

or less haphazard fashion without reference to the likelihood of their presence. A broad consideration of this problem might well be made for future editions.

Tests for reaction. In numerous monographs, tests are given under the heading "Reaction" and these form part of the standards for a particular substance. It is recommended that only those requirements which are actually limits of acidity or alkalinity be retained as standards. Most of the requirements given under "Reaction" might well be included as part of the Identification section. Thus statements that phenobarbital sodium is alkaline to litmus in 5 per cent. solution, or that an aqueous ascorbic acid solution is acid to litmus are only identification tests.

MONOGRAPHS

Aethisteronum. The residue on ignition, 0·5 per cent., is unnecessarily high; 0·1 per cent. is easily attainable in practice.

Barii sulfas. Future standards for this substance might well include a sedimentation test to limit particle size and the rate of settling of an aqueous suspension.

Bromoformium. It is rather surprising to find this substance included in the International Pharmacopœia in view of adverse comments that have been made about it and in view of its lack of stability. The description of this liquid as "colourless" would exclude most commercial samples after a short storage period.

Diethylstilboestrolum. This substance melts fairly sharply and there should be no necessity for the use of a melting-range with a temperature limit as low as 167° C. Residue on ignition might well be standardised at 0·1 per cent.

Ergometrini maleas. It would be better to use ergometrine maleate as a standard in the assay of this substance rather than ergotamine tartrate. Ergometrine maleate is more readily standardised by its absorption in the ultra-violet region and, in fact, such a process could be considered for the assay of ergometrine maleate.

Potassium salts. A test to limit the presence of sodium salts should be included in future editions since the present tests allow appreciable amounts. A flame photometer test would undoubtedly be the most satisfactory procedure, but if difficulties of description and use are regarded as too great for the inclusion of such a method in an official publication, a simple test such as is used in the B.P. 1953 would suffice.

Methyltestosteronum. The limit for residue on ignition could well be reduced from 0·5 to 0·1 per cent.

Natrii citras. The inclusion of the sulphuric acid test for readily carbonisable substances might well be modified. This test was based on older methods of manufacture of citric acid; in addition it depends to some extent on the strength of the sulphuric acid used. The standardisation of sulphuric acid R at "approximately 96 per cent" is not sufficiently rigid and a sample of pure sodium citrate would, with a strict interpretation of the test, probably fail.

Œstradioli Benzoas, Œstradiolum, Œstronum. The limits for residue

on ignition should be reduced to 0·1 per cent.; the present limit of 0·5 per cent. is unnecessarily high.

Progesteronum. A limit for residue on ignition should be included.

Thiamine Hydrochloridum. The present fluorimetric assay with the possibility of wide limits of error is unsatisfactory for the control of this substance to a purity of "not less than 98·0 per cent." Chemical assays for nitrogen or chlorine content or a spectrophotometric assay would be better.

REFERENCES

1. Maurina and Strong, *Drug Standards*, 1951, **19**, 197.
2. Hersant, *J. Pharm. Pharmacol.*, 1953, **5**, 135.
3. Cama and Morton, *Analyst*, 1953, **78**, 74.

(ABSTRACTS *continued from p. 397*).

produced skin lesions, marked leucopenia and neutropenia and exhaustion of the myeloid elements of the femoral bone marrow. The monkey was more sensitive, repeated daily doses of 5 mg./kg. being invariably fatal and deaths occurred with 2·5 mg./kg., which suggests that pyrimethamine is at least 16 times as toxic as chloroquine or chlorguanide. Toxic effects in the monkey followed two distinct patterns. In one case a dose of 40 mg./kg. was followed by severe chronic convulsions and death. In all other cases there was a slow progressive intoxication characterised by muscular weakness, malaise, anorexia, diarrhœa and bronze pigmentation of the skin. The drug produced a marked leucopenia and agranulocytosis. There was an extreme atrophy of the spleen and the lymph follicles, lesions in the adrenal cortex and kidney calyx. The most striking effects were on the bone marrow which showed a tremendous reduction in cellularity especially in the myeloid elements. It is emphasised that the toxic characteristics of pyrimethamine are wholly unlike those of chloroquine and chlorguanide and the drug presents a serious potential hazard to the human user. It is concluded that the general use of such a toxic drug is not justified until rigidly controlled studies in man demonstrate that it has unique anti-malarial properties conveying a wide margin of safety. G. F. S.

BACTERIOLOGY AND CLINICAL TESTS

Phenylethyl Alcohol, Selective Action of. B. D. Lilley and J. H. Brewer. (*J. Amer. pharm. Ass. Sci. Ed.*, 1953, **42**, 6.) Organisms were grown in infusion broth with and without serum, to which various concentrations of phenylethyl alcohol ($C_6H_5 \cdot CH_2 \cdot CH_2 \cdot OH$) had been added. Phenylethyl alcohol exerted a greater inhibitory effect against Gram-negative than against Gram-positive bacteria and the most useful concentration for use as an aid to the isolation of certain organisms was 0·25 per cent. In plate cultures on agar medium, the separation of *Diplococcus pneumoniæ* II from *Proteus mirabilis* J2, *Streptococcus* C–203 from *P. mirabilis* J2 and *Streptococcus* C–203 from *Pseudomonas æruginosa* K1 was accomplished in the presence of 0·25 per cent. of phenylethyl alcohol. The inhibitor caused changes in colony size and degree of hæmolysis especially when different kinds of blood were used in the agar medium, but organisms retained a recognisable morphology and did not appear to change genetically. Phenylethyl alcohol was applied successfully as an ærosol instead of being incorporated in the medium. G. B.

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of ring structures. Sometimes the atoms of the ring are printed external to the ring itself, e.g., p. 194 benzene, p. 161 coumarone. Furthermore, there is a lack of consistency in presentation, e.g., benzyl acetate is printed as $C_6H_5 \cdot CH_2 \cdot C_2H_3O_2$ (p. 109) whereas ethyl acetate is presented more correctly as $CH_3 \cdot COOC_2H_5$ on p. 385. The section on steroisomerism (p. 596) is particularly weak and somewhat misleading because of attempts at simplification and compression of material. However, these are only minor blemishes. Possibly the presence or absence of certain entries might be questioned. Nevertheless, when it is considered that the editor was faced with the great difficulty of keeping entries and information within the bounds of one volume, and yet giving adequate coverage and detail to keep the book valuable as a reference work, he and his collaborators must be congratulated on the overall result.

This new edition of "Kingzett" certainly fulfils the aims of its first author and founder in being a reliable reference work and a source of interesting and valuable information to layman and expert alike. Its quality will ensure that the book retains its international reputation and its place on the shelves and desks of all those who wish to be acquainted with any aspect of applied chemistry.

A. H. BECKETT.

(ABSTRACTS *continued from p. 404*).

Quaternary Ammonium Compounds with Bactericidal Properties. H. Sturm, E. Konermann, R. Aeschbacher and R. Gradmann. (*Industr. Engng Chem. (Anal.)*, 1953, **45**, 186.) A number of quaternary ammonium compounds derived from such triethanolamine monoalkyl ethers as octyl, dodecyl, hexadecyl and octadecenyl are described. These quaternary ammonium salts dissolve readily in water, forming clear solutions with excellent foaming qualities. The benzyl bromide derivatives crystallise well and are not hygroscopic. They were tested for antibacterial power and the benzyl bromide salt of the triethanolamine monododecyl ether produced the best results. The results of bacteriostasis tests, incompatibility with soap tests and toxicity tests are also given. A. H. B.

Sodium Propionate, Inhibition of Growth of *Streptococcus fæcalis* by. C. H. Hill. (*J. biol. Chem.*, 1952, **199**, 329.) Inclusion of acetate as well as propionate ions in cultures of *Str. fæcalis* causes a complete reversal of the inhibition due to propionate, and it is therefore suggested that the effect of the latter may be to block the synthesis of acetate *via* the oxidative decarboxylation of pyruvate. It is further suggested that this blocking of acetate production may be brought about by combination of propionate with coenzyme A, which is essential for acetate production from pyruvate, as reported for *Clostridium kluyveri* by Stadtman. Pantothenic acid, a constituent of coenzyme A, when added to the medium increases the resistance of the organism to propionate, and the absence of pantothenate did not influence growth in the basal medium, indicating that *Str. fæcalis* must be capable of synthesising pantothenate and coenzyme A. The synthesis of pantothenic acid by *Str. fæcalis* was confirmed by assaying cultures with the medium of Skeggs and Wright (*J. biol. Chem.*, 1944, **156**, 21) with *Lactobacillus arabinosus.* J. B. S.