EDITORIAL NOTES

RESEARCH ON PHARMACOPŒIAL PROBLEMS.

(*Continued from p. 183, Feb.* JOUR. A. PH. A.)

THE U. S. P. COMMITTEE ON CHEMICAL RESEARCH.

H. V. ARNY, CHAIRMAN, WITH FRANK R. ELDRED, CHARLES H. LAWALL, W. O. RICHTMANN AND GEORGE D. ROSENGARTEN.

1. Tablets—Standards and Assays. Methods for assaying pharmacopœial substances in tablets and general specifications for tablets should be established.

2. Cinchona Assay. The specific details of the assay call for further study.

3. Colorimetric Assay Methods. A study should be made of standardized colorimetric assays for the accurate determination of minute amounts of alkaloids and other active plant principles in pharmaceutical products, such as:

a. The morphine content of paregoric.

b. The assay of digitalis.

4. Alkaloids. A further study is needed of the physical chemistry in the alkaloidal assay of drugs.

5. Assay of Anthraquinone-bearing Drugs. The colorimetric assay methods for anthraquinone drugs call for further investigation. Other proposed methods should also be studied, with the hope of providing a satisfactory assay.

6. Reconsideration of U. S. P. Chemical Tests in the Light of the Present Knowledge of Hydrogen-Ion Concentration.

7. Electrometric Titration of Drugs Containing Alkaloids. To make this method more useful numerous titrations should be made and curves plotted from the results obtained.

8. Assay of Aloe. A satisfactory method for the assay of aloe is needed. It may involve a new study of aloin and its reactions. No satisfactory process is now available.

9. Assay of Oxgall. No satisfactory process is now available. There is evidence of considerable variation in oxgall as regards the glycocholates and "bile salts." What is meant commercially by "bile salts?"

10. Alkaloidal Assays. A further study should be made of the methods suggested for the improvement of the alkaloidal assays of drugs and their preparations as given in the JOUR. A. PH. A., Vol. 1, p. 29 (1912).

11. Capsicum and Oleoresin of Capsicum. An assay method should be developed which would be more definite than the present organoleptic test.

12. Chloroform Liniment. An assay process should be devised and a maximum and minimum standard adopted.

13. Automatic Devices for Extracting Alkaloids. The methods suggested by the Bureau of Chemistry and claimed to be labor-saving and more accurate than those of the U. S. P. X (see *Ind. Eng. Chem.*, 17, 612 (1925)) should be carefully tested, probably by a commission working on common samples.

14. The Assay of Hyoscyamus and Its Preparations. A further study of this assay (U. S. P. X) is desirable.

15. The Assay of Ipecac and Its Preparations. A further study of this assay (U. S. P. X) is desirable.

16. Indicators for Alkaloidal Assays. Work in the Bureau of Chemistry indicates

that in some instances the indicators specified in the Pharmocopœia for alkaloidal assay do not give the correct neutral points. For example, methyl red and cochineal are not suitable for the cinchona alkaloids. This subject should be given further study.

17. Glycyrrhiza. A comparison of suggested assay methods is desirable, with a view of adopting an official method.

18. The Manufacture of Spirit of Ethyl Nitrite. A study of the methods of manufacture, especially with a view of greater stability, is desirable.

19. The Assay of Sodium Cacodylate. The U. S. P. X assay calls for further study.

20. Differentiating Tests for Strong and Mild Silver Protein. A satisfactory chemical test is desirable. Those suggested should be studied and reported upon.

21. Assay of Alkaloidal Salts. This question should receive the immediate attention of the U. S. P. Research Committee. The majority of the alkaloidal salts of the U. S. P. contain water of crystallization. Many of these hydrated salts lose a portion of their water at relatively low temperatures. A notable example of this type is quinine sulphate, which loses all but about two molecules of water at 50 degrees C. or even lower. In conducting the research on alkaloidal assays these facts will have to be taken into consideration.

Another point that will have to be carefully investigated is the indicators to be used. Methyl red is generally considered the most suitable indicator for alkaloids, yet with some alkaloids it apparently gives low results.

22. Cresol. The U. S. P. X specifications for cresol call for a careful investigation, especially giving consideration to uniformity in their phenol-coefficient.

23. Solubilities. The definition of the meaning of "very soluble," "freely soluble," "soluble," etc., in the U. S. P. X is an advance in the direction of greater definiteness and precision. For practical purposes the degree of solubility conveyed by these terms may suffice, yet there may be instances where the solubility expressed by these terms is too indefinite. "Freely soluble," according to the definition, covers a solubility of from 1 to 10 parts. This is rather a wide range for this degree of solubility.

Such somewhat vague information is not in accordance with the other more precise figures for solubility occurring in the same paragraph. More precise statements of solubility will no doubt be appreciated by the users of the Pharmacopœia.

If it is not possible or practicable to give more precise solubilities instead of the solubilities conveyed by the descriptive terms, it is at least important to ascertain that the solubility of the various U. S. P. products in solvents now designated by "very soluble" or "freely soluble" does fall within the range understood by these terms. The first thing to do would be to classify the chemicals for which the descriptive solubilities are given. This should be undertaken as a collaborative study, a number of laboratories taking part in the investigation.

24. Lactic Acid. There is a need for a study of qualitative tests for lactic acid, with particular reference to testing for lactates in the presence of other organic acids.

25. A Study of the Tests for Caramel Color. There is a need for improvements in the tests for the detection of caramel coloring in liquids where it has been added illegally for the purpose of deception.

26. Solution of Epinephrine Hydrochloride. It is suggested that a dependable formula for the 1 to 1000 solution of epinephrine hydrochloride should be included in the U. S. P., giving the degree of acidity, the amount and nature of preservative, the amount and nature of reducing agent to keep the epinephrine from oxidation, etc. Some manufacturers are adding chlorobutanol or other substances as a preservative. This is not provided for in the U. S. P. X and should either be permitted or excluded by tests. The keeping qualities of the solutions and dilutions therefrom should, of course, be determined by recognized methods of physiological assay.

27. Arsenic Trioxide. A study should be made of its solubility in water, especially as to the influence of its physical form upon its solubility.

28. Potassa Sulphurata. A study should be made of its decomposition on aging and the possibilities of stabilizers being introduced.

29. Ammonium Carbonate. A further study on its composition is desirable, with particular reference to the manufacture of aromatic Spirit of Ammonia.

30. Chlorinated Lime. It is desirable that there should be further study of the condition of its "active chlorine."

31. The Pepsin Assay. This assay calls for further study, providing, if possible, a

more suitable sub-strata than egg white and a more definite end-point.

32. The Assay of Volatile Oils. A study of the U. S. P. X assays for the oils of eucalyptus, lemon and santal has been suggested as desirable.

33. Peppermint Oil. Positive tests should be devised for the exclusion of other peppermint oils which might be used as adulterants.

34. Emetine Hydrochloride. Emetine hydrochloride (U. S. P. X) is defined as containing "variable amounts of water of crystallization" and as losing "not more than 19 per cent (water) upon drying." This makes a very unsatisfactory standard, as it permits two products, one of which is only 81 per cent as active as the other, to be sold under the same designation. It is suggested that the article as found in commerce be investigated, with a view to more closely defining the amount of water the product should contain.

35. Isopropyl Alcohol Test in Whisky. A new test should be devised; that in the U. S. P. X will not indicate certain isopropyl alcohols now on the market which are free from tertiary butyl alcohol.

36. Extract of Malt. The rate of deterioration should be studied and the assay improved, if possible.

37. Microchemical Methods. What Microchemical Methods for the identification or assay of plant constituents are applicable to the Pharmacopœial Texts?

THE U. S. P. COMMITTEE ON PHARMACOGNOSTIC RESEARCH.

EDWIN L. NEWCOMB, CHAIRMAN, WITH W. O. RICHTMANN.

1. Microanalytical Descriptions of Vegetable Drugs. A restudy of all U. S. P. X descriptions and terminology is desirable for the purpose of perfecting the text.

2. U. S. P. Color Standards and Color Nomenclature. This subject is one calling for an extensive investigation, of a collaborative character.

3. Standards for the Degree of Fineness in Powdered Drugs. Further research is needed on the degree of fineness of powdered drugs best suited to yield the maximum of therapeutic values most economically and under varying conditions. This means the preparation of samples of known botanical characteristics, of specific degrees of fineness and coöperation with pharmaceutical and assay groups. Work on percolation has heretofore been done with almost a complete disregard of the actual size of particles and the fundamental principles of osmosis.

4. Organic Foreign Material in Vegetable Drugs. Further research should be conducted on the organic foreign material in vegetable drugs for the purpose of adopting blanket standards for these impurities, as has been done for inorganic foreign material in the U. S. P. X.

5. Vegetable Drug Standards. It would greatly facilitate the work of the next U. S. P. revision if a report could be prepared containing recommended changes to bring about greater uniformity, scientific accuracy and completeness for the vegetable drugs of the Pharmacopœia.

6. Changes during the Drying of Vegetable Drugs. It is desirable to determine the changes which take place in the therapeutic values of certain vegetable drugs from the fresh medicinal plant material to the dried drug. This would be possible through cooperative research with the medicinal men on the Committee who are in a position to carry on clinical work, and also with those who are in a position to carry on assay work. One of our more important specific drugs should be selected for intensive study along these lines.

7. The U. S. P. X Alcohol-Soluble Extractive Method. There seems to be some danger of the U. S. P. X method for alcohol-insoluble extractive giving consistently low results. Gum and balsamic resins contain volatile constituents that will be extracted during the alcohol-extractive determination. When this residue is being dried to constant weight at 110 degrees C., the volatile constituents will pass off, together with a small amount of water that may be present in the drug. In the case of Benzoin the volatile constituents are considered of therapeutic value, and preparations of this drug are often used as inhalants.

In the U. S. P. X method for alcohol-soluble extractives the alcohol-soluble material is dried to constant weight, which, of course, is free from the volatile constituents of the gum resin.

The loss in five samples of Benzoin extractive drug drying at 110 degrees C., as directed by the U. S. P. X, was 2.1, 4.98, 3.4, 2.4 and 3.5 per cent, respectively.

The method should be modified to avoid

this error, possibly through a check against the dry insoluble residue.

THE U. S. P. RESEARCH COMMITTEE ON PHARMACEUTICAL FORMULAS AND PROCESSES.

WILBUR L. SCOVILLE, CHAIRMAN, WITH GEORGE M. BERINGER AND JACOB DINER.

1. Compound Mixture of Glycyrrhiza. It has been reported that rapid decomposition of the ethyl nitrite occurs when using the U. S. P. X formula for this mixture, gas being liberated and all ethyl nitrite being lost within 24 hours. The formula should be studied.

2. Defatting Digitalis Tincture. A test should be developed to prove that it has been defatted. Can some other solvent which is not so inflammable be used, such as carbon tetrachloride?

3. Stability of Pharmaceutical Preparations. This should be studied from the standpoint of two factors:

a. Natural composition.

b. External influences.

4. Deterioration in Drugs Due to Enzymes. A study should be made of glucosidal drugs, with a view of preventing the action of enzymes and the deterioration in the drug during drying, storage or transportation. Drugs suggested for this study are apocynum, convallaria, adonis and chionanthus.

5. Precipitation in Pharmaceutical Galenicals. The causes and prevention should be given further study.

6. The Function and Value of Adjuncts to Menstrua. This is a subject worthy of scientific study in all pharmaceutical preparations.

7. The Extraction of Vegetable and Animal Drugs. The official methods and other methods should be compared and studied and their value determined.

8. The Effect of Hydrogen-Ion concentration upon the Stability of Tinctures, Fluidextracts and Extracts. This is a new field of investigation and seems to promise the solution of some long-standing problems. The following specific illustrations suggest the possibilities:

Tincture of Aconite. The addition of about 2 per cent of acetic acid or 0.1 per cent of hydrochloric acid is suggested. Tincture of Aconite rapidly deteriorates without such an addition.

Tincture of Digitalis. Experiments have been made with tinctures of digitalis adjusted to a variation in hydrogen-ion concentration from p_H 2 to p_H 10. Excess acidity or alkalinity result in rapid deterioration, but no deterioration within two years was noted when the tincture was neutral. As normally made tincture of digitalis is not neutral.

It is doubtful if it is actually known what preparations are stable and what preparations are unstable to-day, and under what conditions those that are unstable deteriorate and to what extent. It is not so long since it was discovered that aconite preparations were unstable, and it does not seem at all improbable that a systematic investigation of the stability of other potent pharmaceutical preparations would bring other surprises. If this investigation could be undertaken in a systematic manner by the various universities and manufacturing laboratories it would be possible before the next revision of the U. S. P. to have rather thorough and complete information on the stability of many drug extracts and the condition under which they should be stored to assure the greatest possible stability.

A tincture of the drug under examination should be prepared by the usual method of extraction and its hydrogen-ion concentration measured. It should then be adjusted by the addition of alkali and acid, respectively, to various hydrogen-ion concentrations, both above and below that naturally encountered. A portion of this material should then be placed in small containers of alkali-free glass so that the periodic examinations may be made. The earlier examinations should be fairly close together, say every three months; later, they can be extended to six-month periods and then to yearly. Preparations should preferably be kept under three conditions:

a. In cold storage.

b. At ordinary room temperature.

c. Under temperature conditions which simulate summer heat.

Another portion of the preparation should be freed from all dissolved air by washing with nitrogen under vacuum and should then be adjusted to various hydrogen-ion concentrations as above directed, bottled under nitrogen or vacuum, but otherwise stored under the several conditions described for the first portion and observed at similar intervals.

Such a study would give definite information on the effect of temperature, air or oxy-

gen and hydrogen-ion concentration on the stability of the preparation when in storage for varying periods of time. Investigations of this character already published on Tincture of Aconite and Tincture of Digitalis indicate the possibilities of such an investigation with other drugs.

9. The Preservation of U. S. P. Drugs and Preparations. Another desirable study is the influence of light upon preparations now directed to be kept in amber-colored bottles. Also the influence of oxidation, hydrolysis, acid-reaction, heat (abnormal), temperature (normal), volatility, etc., the object being to insure better preservation of medicinal preparations and greater reliability. This would be primarily a check upon the present U. S. P. directions for preservation.

The following sub-division is suggested for this study:

a. Oxidation and reduction (ferrous salts, phenols, aldehydes, etc.).
b. Hydrolysis (tannins, sugars, glucosides, acetylsalicylic acid, etc.).
c. Acid and alkaline reactions (pepsin, bismuth, glandular preparations).
d. Catalytic decomposition (H_2O_2, oils, fats, etc.).
e. Light effects (galenicals, some alkaloids, phenols).
f. Exposure effects rather than oxidation [CO_2 absorption, volatility, heat effects (normal changes, efflorescence, deliquescence, etc.)].

10. Tincture of Cantharides and Its Standardization. The extraction of cantharides is difficult, as solvents for cantharidin are few. The best solvent and methods for extraction of cantharides, its preservation and assay are deserving of further study.

11. Solution of Magnesium Citrate. It is claimed by some that the U. S. P. X solution is too acid and also too strong. The entire question should be studied with the coöperation of clinicians. This should include the influence of (*a*) acidity and (*b*) strength on precipitation; the influence of the sugar content on precipitation through hydrolysis, the composition of the crystals which separate, a comparison of various solutions of magnesium citrate from the viewpoint of palatability, permanency and physiologic action.

12. Aromatic Waters. A study of the aromatic waters is desirable from the standpoint of the amount of oil dissolved under different conditions of manufacture, and with particular reference to a definite formula for making these preparations by distillation. (See JOUR. A. PH. A., Vol. 9, p. 878 (1920)).

13. Tincture of Digitalis. It is desirable to investigate the rate of deterioration to be expected in Tincture of Digitalis when prepared by U. S. P. X formula, and also what methods may be adopted to overcome such deterioration. (See also the effect of hydrogen-ion concentration on Tincture of Digitalis, question No. 8.)

14. Ergot. The effect of menstrua on the activity of ergot preparations should be studied.

15. Fluidextract of Cimicifuga. It is suggested that this can be advantageously made with a lower alcoholic menstruum. Various alcoholic strengths should be tried.

16. Extract of Nux Vomica. A study should be made of the relative values of different acids in extracting this drug.

17. Fluidextracts. The fluidextracts of cinchona, ipecac and squill present special problems in extraction, and both menstrua and methods of extraction should be studied.

18. Resins. There is need for the further study of the standardizing and assaying of these products.

19. Tinctures of Cinchona. The two official tinctures need study from the standpoint of extraction, preservation and alkaloidal standard.

20. Extract of Cascara Sagrada. The U. S. P. X basis for standardization is too variable. Some other should be devised; the extractive should be considered and other methods tried.

21. Specific Gravity and Extractive (dry) of Non-Assayed Fluidextracts and Tinctures. It is suggested that extractives should be taken by evaporating 5 cc. of the fluid in a shallow dish until most of the alcohol and water is expelled. Then dry for 3 hours in an oven at 100° C. Report in Gm. per 100 cc.

THE U. S. P. COMMITTEE ON MISCELLANEOUS RESEARCH TOPICS.

A. G. DUMEZ, CHAIRMAN, WITH THEODORE J. BRADLEY.

1. A Study of U. S. P. Nomenclature in the Light of Recommendations from the Second Brussels Conference (1925). Those instances in which the U. S. P. X

is not in harmony with the recommendations of the Brussels Conference (1925) should be pointed out that they may be available for consideration in the next revision.

2. **U. S. P. Tables.** What other tables may be advantageously added to those now in the U. S. P.? If there are any to be recommended they should be prepared now and thoroughly tried in practice.

PERSONAL AND NEWS ITEMS.

Dean Frederick J. Wulling, College of Pharmacy of the University of Minnesota, is chairman of the School Committee of the Safety Bureau of Minneapolis Civic and Commerce Association. He is conducting a series of talks that have special reference to need of safety instruction to children. This work is being done by aid of radio and public lectures.

Ex-President and Mrs. Charles H. LaWall are enjoying a two months' vacation. They left on the first of the month for a trip to California by way of the Panama Canal. It has been many years since the Dean has taken a vacation and he intends to enjoy this one by disconnecting himself, as far as possible, from college and laboratory duties.

I. H. Shurtleff, member of the A. PH. A. since 1875, and, hence, a "fifty-year member," has sent in a $100.00 contribution to the Headquarters Fund and in connection with his letter expressed his appreciation of the work being carried forward.

Editor Hugo Kantrowitz is again arranging for a European trip and invitations are extended to pharmacists and friends to participate in the tour which is to take in interesting points of Germany, Austria, Switzerland and France. The departure of the tourists will be on June 30th and the return about September 1st.

Dean W. F. Gidley, University of Texas, College of Pharmacy, recently spoke before the Rotary Club of Galveston on "Present, Past and Future of the Texas College of Pharmacy."

Al Falkenhainer, of Algona, Iowa, Director of Propaganda, Campaign Committee, A. PH. A. Headquarters Building, for many years Secretary of the Iowa Pharmaceutical Association, is spending part of the winter in Texas with his family. He will soon leave for Belgium where he goes as delegate to the convention of the Rotarians.

The *Druggists' Circular* for March contains interesting sketches of the Presidents of three State pharmaceutical associations, **Clyde Eubanks,** of North Carolina; **Otto C. Kistner,** of Ohio; and **Homer C. Wallace,** of West Virginia.

Prof. Otto Raubenheimer celebrated his sixtieth birthday at his home in Brooklyn, February 4th. The *Apotheker Zeitung* gives a comprehensive sketch of the celebration in which many activities of the well-known pharmacist are briefly but interestingly referred to.

Secretary and Mrs J. G. Noh, of Pennsylvania Association, were among visitors at the office of the AMERICAN PHARMACEUTICAL ASSOCIATION.

Treasurer and Mrs. Charles W. Holton, of the A. PH. A. helped to celebrate Mrs. Charles E. Dohme's 86th birthday; the latter enjoys good health and takes an active interest in affairs.

W. Bruce Philip, former *Chairman* of the House of Delegates, A. PH. A., and Secretary of the Alameda County Pharmaceutical Association, spoke, on January 26th, before the Kiwanis Club of Alameda. He took for his subject "Honesty in Business" and explained to the club members the purpose of the Capper-Kelly bill now pending before Congress, and the necessity of that legislation if the independent retailer, not only in the drug line but in other retail channels, is to survive. Mr. Philip found a deep interest on the part of his hearers, but a meager understanding of the bill and its objects. **Victor L. Schaefer,** Alameda druggist and President of the California Pharmaceutical Association, acted as chairman.

Members will regret to learn of the loss by fire sustained by our fellow-member **John Victor Lee,** pharmacist of Evanston, Ill., last month.

On March 1st, **R. D. Keim** addressed the members of the "Yale Men in Advertising" at the Yale Club, New York, upon the subject of price standardization as opposed to predatory price-cutting. He also spoke before the members of the New York Advertising Club, associated with the Advertising and Selling Course being conducted by that organization.

Dr. Arno Viehoever prepared an interesting pharmaceutical exhibit for the recent meeting of the American Association for the Advancement of Science, with which the AMERICAN PHARMACEUTICAL ASSOCIATION is