

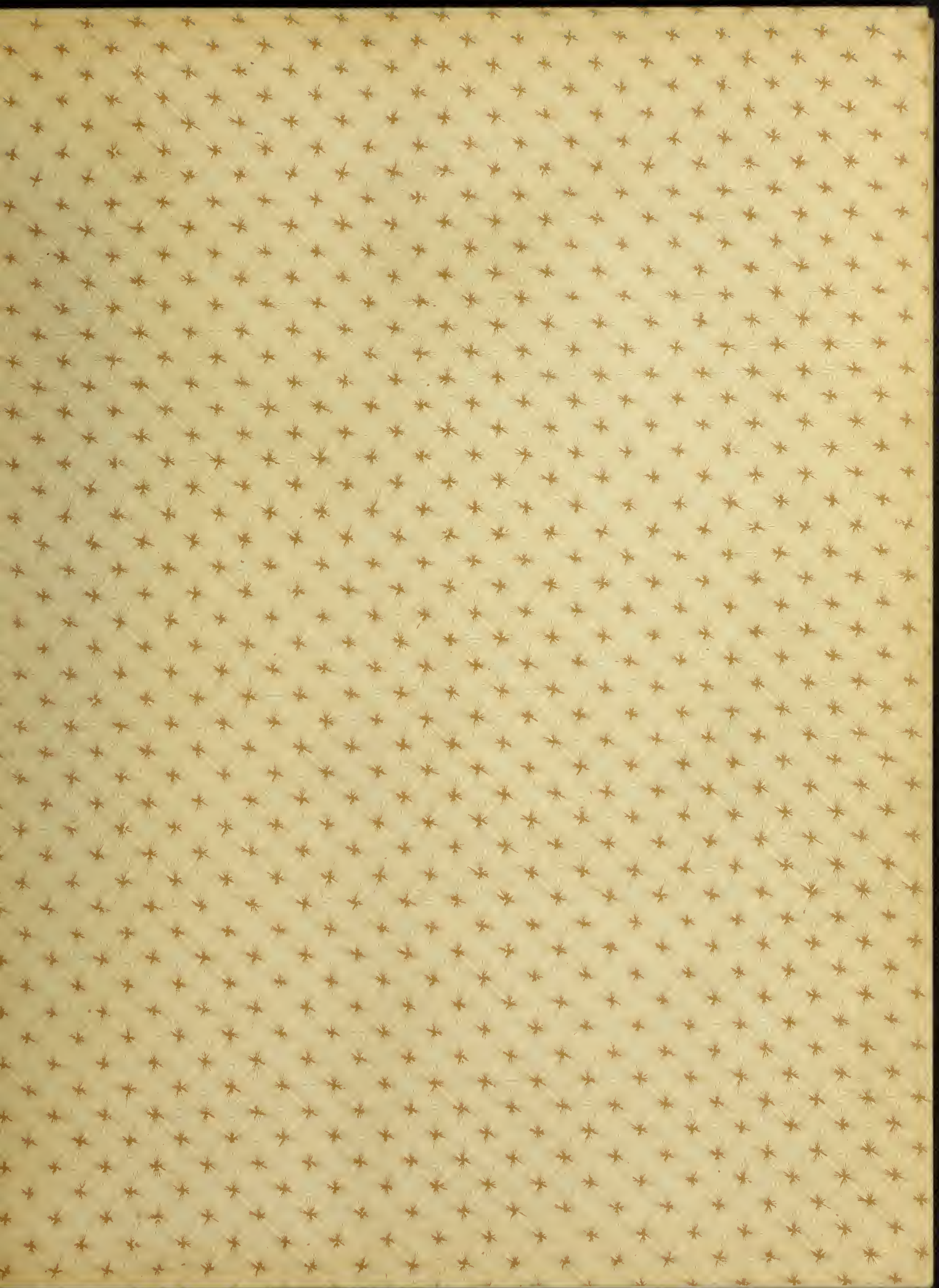
WALTER

Determination of
the Active Principles
of Medicinal Plants

Chemistry
M. S.

1801

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DETERMINATION OF THE ACTIVE
PRINCIPLES OF MEDICINAL
PLANTS.



BY

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THESIS

FOR THE DEGREE OF MASTER OF SCIENCE IN THE
GRADUATE SCHOOL.

UNIVERSITY OF ILLINOIS,

1901.

DETERMINATION OF THE
FRACTION OF MOLECULAR
WEIGHT



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THESIS.

The revision of the Pharmacopoeia of 1900 will in all probability show a marked advance in standards of medicinal drugs. When the last revision, in 1890 was effected, the subject of standardization of galenical drugs was in its infancy, and the committee in consequence, only touched upon the subject. Synthetical products were also then in their infancy, for few of the synthetics had at that time pushed themselves to the front and become generally adopted. The subject of the essential oils was largely a closed chapter, for Wallach was just making his power and his work felt among chemists, and the subject of plant secretions was as yet entirely in a maze of mystery. Nobody knew what these resins and gum resins were and practically nobody wanted to know. Now, we have dispelled the gloom then enveloping us and the pharmaceutical advances during the past ten years far exceed in extent and importance those of the previous two decades combined.

The pharmaceutical chemists have united in work and have applied the methods and theories of pharmacy, and as a result, have evolved from pharmacy's hidden treasure chest, facts of startling beauty and value. They are to-day applying the electrical currents of chemistry's enthusing beauties to the herbs, roots, leaves, gums, etc., of their former shelf bottles and counter drawers, and these are yielding rich treasure, not of noble metals, but of fully as rich hidden treasure. They are bringing to our notice the properties and value of the chemical substances contained in these drugs, and enabling us to formulate which of these are of value as medicinal drugs and which are of no value. Thus, we gradually learn to know what these drugs actually contain and from this, select the ones useful in medicine and discard those of no value. Once we know this and we have, so to speak, the drug in our grasp, and it only becomes necessary to establish what is the proper standard of strength of the drug in these active principles, and decide upon the best method of determining the amount in the drug, i. e. assaying it.

There could be no doubt in anyone's mind that the only correct way to dispense drugs or their preparations is of a uniform medicinal strength. To say that digitalis is digitalis or belladonna is belladonna is old-Pogey, and the standpoint that justifies it is a benighted one or the brain a befogged one.

Belladonna leaves obtained from source A. are not necessarily the same strength as those obtained from source B. or any other source; in fact, the chances are about ten to one that they are entirely different. Some leaves may contain a large

per cent. of atropine while others may be entirely inert. An ounce of leaves A. may kill a man while two ounces of B. may have little effect. What dependence then has any physician to place in a preparation, be it fluid or extract, tincture or what not, if the preparation is merely made from the crude drug without any knowledge of its alkaloidal strength? He may be giving a patient a preparation obtained from one house and be compelled to give big doses to get any effect. He may run out of the preparation and buy some from another house and the same dose as before, would kill the patient. The physician has absolutely no standard on alkaloidal preparations without they be brought up to a regular and uniform standard. Of course, he will get some effect from different makes in all cases, but he may rest sure that the effect will practically vary in most cases unless indeed he happens to get all his prescriptions from the same bottle of the same drug-store. But even when this bottle is refilled, the strength and hence the effect will most likely be different.

Now, it is almost incumbent upon the revision committee to establish a definite standard of strength for all standardizable drugs and require that all like preparations of different makes all conform to one standard of strength. Then, when the drug is purchased, an assay may or may not accompany it; whether or not it does, it should be assayed and its strength established. If it falls below the pharmacal standard, reject it; if above either, take the necessary quantity for making a preparation of standard strength, or make up preparation of regular strength and then assay the finished product and dilute or concentrate to standard strength. Then whenever a doctor prescribes a preparation of an alkaloidal drug, he would get and could depend upon getting identically strong therapeutic effects in all cases. This is a distinct gain for the physician, pharmacist and patient as well. While the work of standardization is now performed by all standard manufacturing houses of physician and pharmaceutical supplies, yet it is not done by majority. The principles and methods of the various houses are held secret.

The physiological effect of drugs has recently been advocated by some as a means of establishing a standard. While this does possess some value in establishing the fact that the drug is not positively inert, it does not, nor cannot possess any value as a means of standardizing, as it is of qualitative not quantitative value. To say that a certain lot of digitalis has been tested physiologically and found to possess therapeutic value is merely to give the drug a label, but not a standard for physiological activity cannot be measured in most cases, if in any case. For instance, to test aconite by the tongue is at best crude, unscientific and unreliable, as far as accuracy is concerned, for tongues, being human, are subject to personal equations and vary just as

eyes, ears and noses do. What may be strong aconite to one tongue may be weak aconite to another. The same holds for digitalis, ergot or any other drug. To say that a certain ergot has been found to act on the organs of a guinea-pig and produce certain results or to constrict its arterioles to a certain extent is no criterion of the efficiency of that ergot as a standard of comparison with others, for the same ergot may affect the same human organs or arterioles much more or less. Physiological activity hence, cannot be used as a standard for drug strength, for its essence is not of a measurable nature and standardization requires, if it requires anything at all, just this very measurable and withall accurately measurable element.

It has been the object of this thesis to present all the information, as regards apparatus, methods and standards used and advanced, up to Jan. 1, 1901, for the standardization of the active principles of medicinal drugs.

APPARATUS.

1. For the simpler assay operations, very little apparatus is required. It is taken for granted that the student possesses the ordinary utensils required for the simpler chemical tests. A few pieces of special apparatus are required and will here be described.

2. Pipettes----Measuring pipettes to deliver a given volume of fluid. Those most frequently used are 1 c.c., 5 c.c., 10 c.c., 25 c.c., and 50 c.c. Then, one should possess one 10 c.c. pipette graduated to twentieths, one 1 c.c. graduated to tenths and others, as required. All forms of pipettes should be carefully tested as soon as received.

3. Measuring flasks----Those of most frequent use are 10, 20, 25, 50, 100, 250, 500, 750, and 1000 c.c.

4. Burettes----For the volumetric work, at least two good burettes are required. 50 c.c. graduated to tenths are most serviceable; also 25 c.c. The use of the float is advised as a much closer reading can be obtained with it, than without. It is not necessary to give direction for testing the various instruments, as the student is already familiar with that line of work.

5. Separating funnels----No piece of apparatus is more frequently used in assay work than the separatory funnel. The volume required generally runs from 50-100 c.c., so, four or six funnels holding 50, 75, and 100 c.c. are needed. They should have short stems and cut off obliquely at the end. The form of Dr. Squibb is by far the best shape. It is often convenient to have a funnel holding 250 c.c. and should be obtained, if possible.

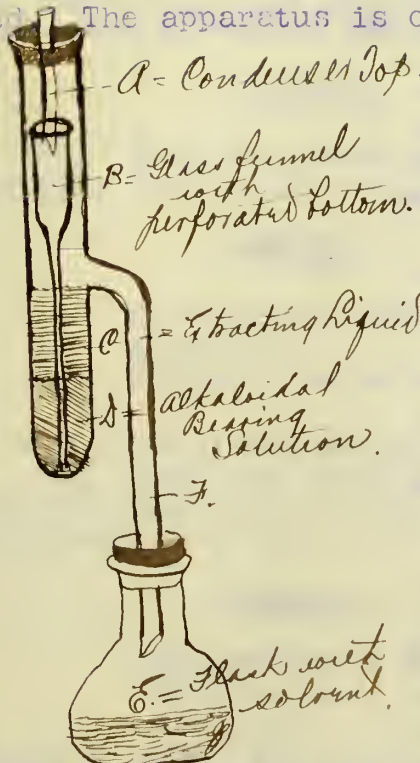
6. Various sizes of glass percolators should be at hand. Those regularly used run from 8-10 inches in length and from 1-2 inches in diameter. Larger ones as well as

smaller ones are frequently called into use.

7. A hot-water funnel is often used to keep a solution hot while filtering. A funnel about 4-6 inches upper diameter answers well.

8. Apparatus for hot repercolation. For the rapid extraction of some powdered drug by volatile solvents, the hot repercolation process at once suggests itself. Various forms of apparatus have been suggested but the Soxhlet tube serves the best. The drug to be exhausted is packed in a glass tube with an opening in the bottom, closed by a plug of glass wool, and the whole inserted in the barrel of the Soxhlet tube. The tube is then securely fastened to an upright condenser (the Hopkins condenser answering very well), and the lower end of the Soxhlet tube fastened to a flask containing the solvent to be used. When heat is applied by means of a water bath, the vapors rise and, striking the cold condenser, fall back into the tube upon the powdered drug. This is continued, the liquid percolating through the drug and rising until the tube is filled to the level of the bend in the siphon tube, when the liquid is drawn off by the automatic action of the siphon being returned to the flask, again volatilized and re-condensed as long as heat is applied. The action goes on regularly and it requires from 2-6 hours for complete extraction of the drug.

9. For the extraction of small quantities of alkaloids from aqueous solution, by the use of immiscible solvents, the apparatus devised by Hulsebosch, and modified by Bosman, is used. The apparatus is often spoken of as the perforator



and is shown in the diagram. The alkaloidal bearing solution, measuring 8-10 c.c., is placed in the bottom of the tube = D. The solvent with which it is to be extracted, is placed in the flask E. Heat from a water bath is then applied and the solvent volatilized and rising through F., strikes at the top the cold condenser, drops back in the form of a liquid into the funnel tube F., open at the bottom, from which it escapes to pass upwards in small drops through the denser liquid from which it is to extract the alkaloid. The liquid will thus pass through the denser liquid, rise and, as soon as it reaches the bend, it flows back into the flask to be volatilized, as before. The

solvent rising from the bottom, pushes that above it, over the bend and thus washes the solution. The lower end of the

funnel tube should be very slightly notched in four or five places with a file, so as to allow the solvent to escape in several directions. If notched on one side only it may happen that precipitated alkaloid on the opposite side may remain undissolved. When starting the apparatus, the acid alkaloidal solution is washed thoroughly with the solvent to remove any coloring matter or other material soluble in the solvent. The liquid is then rendered faintly alkaline by a few drops of ammonia, a new flask and fresh solvent attached and the precipitated alkaloid washed out. The alkaloid can be thus extracted very completely in two or three hours, with a minimum amount of solvent and by a process that is practically automatic. Besides, several different extractions can be conducted at once.

10. If the solvent is heavier than water, like chloroform, a different form of apparatus must be employed. Here, I take a test tube having a small hole in the bottom, and substituting this for the funnel tube in the above apparatus. The liquid, being heavier than water, drops into the test tube through the solution and flows out the bottom of the tube and slowly rises around the tube until it reaches the bend and flows over, as before. Of course, in this case, the liquid to be extracted, floats in the test tube upon the chloroform in the bottom of the tube so no liquid ever gets outside the test tube. To start this form then some chloroform or whatever the extracting liquid, must first be placed in the tube in the perforator, and the alkaloidal solution then added to the tube within the perforator.

11. The mechanical shaker is made frequent use of in alkaloidal work. It may be operated by an electric motor a small water motor, or any other source of power. Ordinary ingenuity will devise a means of accomplishing the desired result, it all depending upon the location.

REAGENTS.

12. Proellins mixture, employed for the extraction of alkaloids from crude drugs.

FORMULA.

Concentrated Ether-----325 c. c.
Alcohol-----25 C. C.
Stronger water of ammonia-----10 c. c.

Mix the alcohol and water of ammonia and add to the ether.

13. Proelline fluid modified; used for alkaloids which are sparingly soluble in ether, in extraction from crude drugs.

FORMULA.

Concentrated Ether-----250 c. c.
Chloroform-----80 c. c.
Alcohol-----25 c. c.
Stronger water of ammonia-----10 c. c.

14. Mayer's solution of Potassium Mercuric Iodide; used for the detection and volumetric estimation of some

4,000,000

- 6.6. *Ammoniumcarbonat* – *Ammoniumcarbonat* wird in der Lebensmittelindustrie als *Lebmittelzusatzstoff* (E 510) verwendet.
- 6.7. *Ammoniumnitrat* – *Ammoniumnitrat* wird in der Landwirtschaft als *Düngemittel* verwendet.
- 6.8. *Ammoniumphosphat* – *Ammoniumphosphat* wird in der Landwirtschaft als *Düngemittel* verwendet.

Abstract

alkaloids. The strength suggested by Prof. Mayer was 1:10 but in regular volumetric work 1:20 is to be preferred, and is the strength used in all subsequent work where Mayer's reagent is referred to.

FORMULA (1:20)

Mercuric Chloride-----6.775 gms.

Potassium Iodide-----25.00 gms.

Distilled Water qs.-----1 Litre.

Dissolve the mercuric chloride and the potassium iodide separately in about 400 c. cm., mix the solution and add distilled water q. 1000 c. cm.

15. Wagner's Reagent, Iodine in Potassium Iodide solution. Used a great deal in Qualitative tests for alkaloids and employed by Prof. Prescott and others in the volumetric determination of atropine and morphine.

FORMULA.

Iodine-----12.66 gms.

Potassium Iodide-----32.00 gms.

Distilled Water Qs.-----1 Litre.

16. Potassium; Bismuthic iodide prepared by dissolving iodide of Bismuth and iodide of Potassium in water. It yields even in very dilute solutions, precipitates which are very sparingly soluble, and resemble orange sulphide of antimony in color. It should not, however, be forgotten that albuminous and other similar substances are also precipitated by this reagent.

17. Schomonschein's Reagent, Sodium Phosphomolybdate; yields with most alkaloids yellowish precipitates which are in certain instances readily produced, and assume a bluish or greenish color. The reagent is prepared as follows:- Precipitate a solution of sodium phosphate with ammonium molybdate in excess, in presence of nitric acid. Wash the precipitate with water containing nitric acid, and dissolve in a hot solution of sodium carbonate. Evaporate to dryness and ignite gently to free from any ammonium salts. Moisten the residue with nitric acid and ignite gently. Dissolve the residue thus treated in ten times its weight of a mixture of nitric acid (sp. gr. 1.42) one volume and distilled water thirteen volumes. A simpler mode of preparing this reagent is as follows: Dissolve 2.16 gm. of molybdic acid in a slight excess of solution of caustic soda, boil for some time to expell traces of ammonia, and then add 0.358 gm. of crystallized sodium phosphate.

18. Scheibler's reagent, Sodium Phosphotungstate:- This is prepared thus:- Dissolve 100 parts sodium phosphate, in 500 c. c. water and add qs. nitric acid to give it a faint acid reaction. This reagent, as well as Somenschein's reagent, may be employed same as Mayer's reagent, for volumetric estimation of alkaloids.

Valsar's Reagent, Mercuric potassium iodide.

19. Mercuric iodide-----45.4 gms.

Potassium iodide-----33.2 "

Distilled Water qs.-----1 Litre.

Mercuric chloride, 5% solution: Picric Acid, saturated

(19:11) ADDENDUM

1. The first of these is the fact that the
 2. second of these is the fact that the
 3. third of these is the fact that the
 4. fourth of these is the fact that the
 5. fifth of these is the fact that the
 6. sixth of these is the fact that the
 7. seventh of these is the fact that the
 8. eighth of these is the fact that the
 9. ninth of these is the fact that the
 10. tenth of these is the fact that the

aqueous solution. Tannic Acid 5% solution.

20. Froedhe's Reagent, prepared fresh as required, by dissolving by aid of heat, one milligramme of molybdate in 1 c. c. of concentrated sulphuric acid, to be used as soon as cold.

21. Picric Acid solution which gives yellowish precipitates.

22. Tannic Acid solution which unites with the alkaloids to form greyish- yellow or greenish-brown colored precipitates.

23. Mercuric Chloride solution yields white precipitates with the alkaloids which are not very sparingly soluble. It possesses value in that it does not precipitate ammonical salts.

24. The standardized solution of iodine dissolved in water with iodide of potassium to be about decinormal strength (12.653 gms. of free iodine in 1000 c. c.) The solution may be made as the volumetric test solution of iodine of the U. S. P., and used with the exact decinormal factor of iodine, if preferred.

25. A solution of sodium thiosulphate, of about decinormal strength, standardized to a known ratio with the iodine solution. The volumetric test solution of sodium thiosulphate of the U. S. P., may be used.

26. The starch test solution of the U. S. P.

27. Chinoidine Iodosulphate, employed by Dr. De Vrij for the estimation of quinine. Heat together on a water bath, one part of chinoidine and two parts of benzol. Decant the clear solution and agitate with an excess of dilute sulphuric acid. To the acid solution contained in a vessel, add slowly with continuous stirring a solution of one part of iodine and two parts of potassium iodide in fifty parts of water. The precipitate of Chinoidine iodosulphate subsides on warming, and it is to be washed repeatedly with water of decantation. Dissolve one part of this precipitate in six parts of strong alcohol by aid of a water bath, heat and allow the solution to cool. Decant from the deposit, evaporate and dissolve the residue in five times its weight of cold alcohol. This solution constitutes the reagent.

1. The first of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

2. The second of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

3. The third of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

4. The fourth of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

5. The fifth of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

6. The sixth of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

7. The seventh of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

8. The eighth of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

9. The ninth of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

10. The tenth of these is the fact that the United States has a large and growing population of Negroes. This is a fact which is well known to all who are interested in the progress of the race. It is a fact which is well known to all who are interested in the progress of the race.

28. For the Alkalimetric estimation of alkaloids, we should have normal and decinormal solutions of sulphuric acid. Hydrochloric acid and potassium or sodium hydrate n and n are frequently used in delicate titrations but 25 100 they can be prepared as required.

29. Indicators: Various indicators are employed in alkaloidal assay work, chief among them being, Brazil wood, Cochineal, Methyl, Orange, Haematoxylin and Phenalthalein. Iodeosin is another indicator, regarded by some of superior merit.

General Methods of Assay of Crude Drugs.

30. Selection and preparation of the sample. It is necessary in the first instance to secure a fair average sample of the drug. A handful of the drug should be taken from several parts of the package or bale in order to insure such an average. If the drug consists of large pieces, valuable in quality, select a few representative pieces. Take from each of these, a good section and reduce all of them to a coarse powder. Mix well and take a small quantity, about 50-60 grammes and reduce it all to a powder of desired fineness. In general, the finer the powder the better, as the extraction is much quicker and more perfect. The average fineness desired is No. 60 to 80. When the drug consists of seeds, leaves, etc., nearly uniform in quality, it suffices to reduce to a coarse powder, at first about 300 to 350 grammes, taken from different parts of the package, as already explained, and then reduce 50 grammes to the uniform powder.

31. If the drug requires to be dried before grinding, the loss in weight during the operation must be noted and the requisite correction made in the results. Of course such a correction could not be exact but only approximate, as some drugs are hygroscopic, gaining weight in damp weather, and losing again during dry weather. The only value of an assay of the drug, should be when the drug is in the condition to be used, as it may vary as much as 5% in moisture at different times. The only ideal and true method is to assay the dried drug and thus give for a basis, the thoroughly dried drug as a positive invariable quantity. In practice, we deal with the variable, hygroscopic drug and so must be content with practical not ideal results. Of course, in case of a drug not to be used at once, particularly if it is to go into the market with a guaranteed assay, the moisture of the drug should be determined and reported as an essential part of the assay.

32. Methods for exhausting the drug:- The methods for exhausting of the drugs group themselves into four processes, each of which may have, in a particular instance its advantages.

a. The drug in No. 60-80 powder is placed in a bottle or flask, with a measured or weighed quantity of the chosen menstrum sufficient to insure complete exhaustion, at least, eight or ten times the weight of the drug, securely corked, and allowed to macerate therein with frequent or continuous agitation for several hours, at least; and in some cases, from one to two days. Any mechanical shaking device is very convenient as the flasks can be fastened therein and removed when operation or extraction is deemed complete. This method is not the best for all, as in majority of cases the extraction is not complete. Besides, it

10. For the determination of the amount of active ingredient in a sample, the following method is recommended: Weigh a sample of the drug, and determine the amount of active ingredient by the method described in the monograph. The result is expressed in terms of the amount of active ingredient in the sample.

11. If the drug requires to be dried before use, the loss in weight during the operation must be noted and the percentage correction made in the results. Of course, such a correction could not be made for only a few samples, as some drugs are hygroscopic, gaining weight in air, and losing weight during the operation. The only value of an assay of the drug, should be that it is in the condition to be used, as it may vary as much as 5% in moisture at different times. The only assay method is to assay the dried drug and then give for basis, the percentage which there is a relative increase in weight. In practice, we deal with the variable, and the active ingredient is constant with practical not local variance. Of course, in case of a drug not to be used at once, particularly if it is to be used in the market with a guaranteed assay, the moisture of the drug should be determined and reported as an essential part of the assay.

12. Method for assaying the drug: The method for assaying of the drug group themselves into four processes, and of which we have, in a particular instance, the following:

1. The drug is 50-60 percent is placed in a mortar or flask, with a measured or weighed quantity of the drug, as mentioned in the monograph to insure complete dissolution, at least, eight or ten times the weight of the drug, should be added, and allowed to macerate for several hours, at least, and is continuously agitated for several hours, at least, and is some cases, from one to two days. For mechanical stirring device is very convenient as the flask can be rotated therein and removed when necessary or rotation is desired complete. This method is not the best for all, as in some it causes the extraction to not complete. Indeed, it

takes longer time than other methods.

b. Percolation:- The principle of Percolation is as follows:- When a powder placed in a cylindrical vessel, with a porous diaphragm below, is treated from above with a liquid capable of dissolving a portion of its substance, that portion of the fluid first in contact, in passing downward, exercises its solvent power on the successive layers of the powder until saturated, and is impelled downward by the compelled force of its own gravity, and that of the column of liquid, above it, minus the capillary force with which the powder tends to retain it. The details of the process are hardly necessary here, as they are too long to give and, besides, every chemist and pharmacist is well acquainted with the process. (However, for details, consult Remington's Practice Pharmacy, 3rd Ed. p. 262-282). This process, when properly conducted, assures a more complete exhaustion of the drug. The operation, however, consumes more of the operator's time and requires more attention.

c. Boiling, with several successive portions of the chosen solvent. This requires far more time than some of the other methods and besides, heat sometimes affects parts of the alkaloids.

c. Hot Repercolation:- This is by far the neatest and most efficient means of extraction. The Soxhlet Extraction apparatus (par. 8), is the best form. It enables us to use a minimum amount of solvent and very little time to watch it and the extraction is always complete. When once set in operation, the action is automatic, so that the method after all is economical of time, particularly where the assaying is required to be made frequently.

33. Choice of Solvents:- The choice of solvents depends upon the nature of the drug under examination? In the majority of cases the active principle desired is an alkaloid, present in the form of salt soluble in water or in alcohol. Here, again, we find trouble. If we extract with water, we extract gums, starchy matter and various constituents which hinder our subsequent work. While alcohol is to be preferred, it must be remembered that it extracts resins of various kinds, coloring matters and a great deal of inert matter. Nevertheless, alcohol is the better solvent and the stronger the alcohol, the better the result. One thing against it is that it does not penetrate the drug as well as water, so in some cases, it is advantageous to moisten the drug with water, pack it and then extract with the alcohol. The immiscible solvents are very good for extracting the alkaloids from various drugs and do not extract much inert matter. Acidulated water and acidulated alcohol are sometimes employed.

34. E. Landin uses kerosene as a solvent and claims good results, especially in the extraction of the alkaloids of Cincona Bark.

7
35. Another method consists in mixing the drug with milk of lime, magnesia or sodium carbonate, thoroughly moistening it and then drying. Then, extracting with alcohol or wood spirit to exhaustion. This method works very well with some drugs, especially with those heavy in alkaloids. It does not extract much inert matter and the alkaloids are easily separated from the residue in a state of medium purity. The method is, however, open to the following object-

1. The method is, however, open to the following objections:-
It does not extract much heavy matter and the alcohol is
with some trace, especially with some heavy in alcohol.
or good weight is obtained. This method with some
boiling is and less drying. Thus, extracted with alcohol
with of this, remains of sodium carbonate, especially the
alkali separated from the residue in a state of sodium
salt. The method is, however, open to the following objections:-

(1) The liability of decomposition of some of the more sensitive alkaloids, due to the long exposure in contact with the alkali. (2) The long time required to make the extraction. This latter objection may be obviated by subjecting the drug, after drying, to hot repercolation, using chloroform, ether or petroleum ether as solvents.

36. Alkaline solvents:- Various forms and modifications besides the original Prollins Mixture, have been suggested for alkaline extraction of the alkaloids from the crude drugs. The original Prollins Mixture (12) is, however, generally used for this method of extraction. The ammonia sets free the alkaloids which are immediately dissolved by the ether. The object of modifications to the above formula arise from some alkaloids not being freely soluble in ether, hence, the employment of varied proportions of ether and chloroform. These different mixtures of varied quantities of the constituents of Prollins Mixture extract the alkaloids by maceration, and, in a comparatively short time, especially when aided by the mechanical shaker. It is ordinarily claimed ten to twelve hours, but frequently three to four hours are all that is necessary. In some cases the alkaloid which is taken up in the first hour or so, will begin to crystallize out of the solvent within half a day, so that it will not do to leave it on the drug more than four hours.

37. Keller has modified the procedure by employing a measured volume of the solvent and then adding a certain quantity of water of ammonia which is supposed to be absorbed by the drug without affecting the volume of the solvent. After the required time for maceration has passed, water is added to the mixture to be absorbed by the drug, causing it to lump and collect in small balls and thus leave the solvent free and can be poured off perfectly clear. It is quite evident, however, when ether alone is used as the solvent, that there will be a partial solution of the fluids in one another, so that there may be a slight diminution in the ether volume, from what it was at the beginning and so, an aliquot part might show a higher proportion of alkaloid than normal; yet this is in all probability obviated by errors arising from other causes and the small diminution of volume need not be considered. However, when absolutely correct results are desired, we may proceed as suggested by Mr. W. Puckner by exhaustion of the residue of the drug by the percolation with the appropriate solvent and so obtain any alkaloid yet remaining in the drug.

38. General Methods of Estimation of Alkaloids in Crude Drugs. Dragendorff Method (2):- Moisten the finely powdered drug with twice its weight of water, containing from one to three per cent, of sulphuric acid. Macerate in a well stoppered bottle for 24 hours, and then add enough alcohol to make up a volume of 10 c.c. of solvent for each gm. of drug used. Macerate again, for three days, shaking frequently. Filter the solution from an aliquot part of the filtrate the alkaloid may be estimated by any good method, but it is best to drive off the alcohol by evaporation on a water bath, and then estimate the alkaloid in the aqueous solution re-

maining by titration with Mayer's reagent. The method, while consuming little time, is now rarely used save for a few drugs notably ipecac.

39. Method of Losch:- (3):- Exhaust the drug (one part) by maceration with ten parts of alcohol acidulated with hydrochloric acid. Filter and evaporate to one third its original volume. Filter again when cold, and evaporate to consistency of soft extract. Exhaust this with two parts of water acidulated with sulphuric acid, filter, add saturated solution of six parts of alum, warm the mixture, add ammonia in slight excess and evaporate to dryness on the water bath. Pulverize the residue and exhaust with chloroform, ether or anhydrous alcohol. The alkaloid thus obtained is crude and may be either purified and weighed or dissolved in acid and estimated volumetrically. The method is needlessly cumbersome, but is suggestive. An iron alum, or, simply ferric chloride may be advantageously substituted for the alum, or at least for a portion of it; and sodium bicarbonate may be employed in place of the ammonia. Nevertheless, it is not the best method available and in no way is it adapted to the separation of volatile alkaloids.

40. Method of Mayer (4):- Place in a tared flask 15 grams of the drug in coarse powder with 120 grams water and 30 grams of dilute sulphuric acid (10%). Having placed a small funnel in the neck of the flask, heat six or eight hours on the water bath, add water to make up the loss by evaporation and then set aside for two hours in a cool place; filter, and of the filtrate, take an aliquot part. It is assumed that air-dried seeds and bark will yield about 80% of extractive; roots and rhizomes, air-dried about 40%. The amount of fluid therefore, corresponding with 10 grams of drug will be, in the first case, 108; in the second case, 104; in the third, 108 grams. The portion of fluid weighed out for the assay is to be evaporated at a gentle heat, one half its volume, 25 or, if much coloring matter is present, 30 grams of finely pulverized litharge added; then, after half an hour, 5 grams of lead carbonate is to be added and the mixture brought to complete dryness by continued application of a gentle heat. Rub the residue to a powder, introduce into a flask and exhaust by maceration with an appropriate solvent, either absolute alcohol, ether, chloroform, etc. It is impossible to filter free from some finely divided lead carbonate, which must be allowed to subside and the clear fluid decanted or removed by a pipette. On evaporation of this solution, the alkaloid is generally pure enough for weighing. Nevertheless, for accurate results, it may be estimated by titration after weighing.

41. If the drug contains a volatile alkaloid the acid solution (above) must be evaporated to a small volume and a mixture of thoroughly dried litharge and terra alba added. After the lapse of an hour, a further addition of lead carbonate is made in sufficient quantity to absorb all sensible moisture, and the dry powder thus obtained is to be exhausted at once with absolute alcohol. If the extract is colorless, it may be neutralized with hydrochloric or oxalic acids and dried, but if colored, it is to be neutralized

with sulphuric acid. Some water added, the alcohol evaporated off, the liquid rendered alkaline with caustic soda and shaken out with ether at once.

42. The foregoing are about the best methods in use previous to 1831, when Prollins (5) proposed an improved method for the assay of cinchona bark, and from this, gradually evolved the many good methods now in use.

43. The method of Dieterich which is still used by some chemists in Germany, consists in mixing the drug with calcium hydrate and a little water, drying, powdering and extracting by hot repercolation with ether. The residue of impure alkaloid, remaining on evaporating the ether, is dissolved in alcohol and titrated with centinormal hydrochloric acid.

44. Method of Schweissinger (6):- Ten grams of the fineles cut dry herb (aconite, belladonna etc.) are put into a flask with 200 c.c. of water containing 1 c.c. diluted sulphuric acid, securely corked and digested in a warm place over night, occasionally shaking the mixture. It is then allowed to cool, strained, and the residue pressed. Of the strained liquid, 160 c.c. corresponding with 8 grams of the drug, are evaporated on the water bath under constant stirring, at a temperature of about 65 degrees C., until reduced to about 20 grams. This solution is then poured in a thin stream, into 30 c.c. of strong alcohol, the volume made up to 100 c.c., the mixture well shaken and allowed to rest until the sediment is well deposited. Of the filtered alcoholic solution, 50 c.c. equal to 4 grams of the drug, are measured out, evaporated to 100 c.c., transferred to a separatory funnel, 1 c.c. of ammonia water and 40 c.c. of a mixture of chloroform 3 volumes, and ether 5 volumes, added, the whole shaken together gently, to avoid emulsionizing, for some time and allowed to separate. Finally, 20 c.c. of the ether chloroform mixture are measured out, evaporated in a capsule and titrated with centinormal acid using cochineal as an indicator.

45. Method of Grandval and Lajour (7) :- Make a mixture of ether 8 c. c., alcohol 3c. c., and water of ammonia 2 c. c. With this, moisten 10 grammes of the drug and pack in a miniature percolator, which may consist of the barrel of a small glass syringe. A little absorbent cotton is placed beneath the drug in the percolator and another portion above it. The drug is then exhausted by slow percolation with ether, about 100 c. c. being required. Make sure that the drug is exhausted by evaporation of a few drops of the percolate on a watch glass and adding a drop of centinormal sulphuric acid and a drop of Mayer's reagent.

46. Introduce the ether into a separator, and 5 c. c. of normal sulphuric acid, shake together, let separate and draw off the acid solution into a suitable container. Wash the ether several times with 4 c. c. distilled water, adding this to the acid solution. Then place the acid solution in a second separator, make alkaline with caustic soda and shake out with ether. Then, by evaporating, we have the alkaloid ready for weighing.

47. Method 2-- 100 grammes of the finely powdered drug are well triturated with 100 grammes of basic lead acetate, then exhausted by percolation with water, which must be continued as long as the percolate gives any precipitate with Mayer's reagent. Most of the inorganic acids present, remain as insoluble lead compounds, together with much of the coloring and extractive matter and a large portion of the proteids. Dilute sulphuric acid is added to the solution in slight excess, and the lead sulphate filtered out; the alkaloids are then precipitated in the filtrate by Mayer's reagent, variable amounts of albumin and coloring and extractive matters also coming down. After standing some time, the precipitate is collected and treated by one of the following two processes:- (1) Potassium cyanide, a little caustic soda, and ether (or any other appropriate solvent) are well shaken with the precipitate. The ethereal solution is caused to separate from the emulsion produced by the addition of a little olive-oil and finally made alkaline with caustic soda and shaken out with ether. (2) The precipitate by Mayer's reagent is digested in a flask with a slight excess of sodium sulphide, after which the alkaloid is extracted precisely as in method (1). The second process is that to which the authors give preference. Liquid alkaloids, except sparteine, they claim, cannot well be separated by this method, which is unsatisfactory also as applied to belladonna and other drugs containing atropine.

48. Method of Keller (8);- Dry the drug completely at a slow temperature, preferably in a desiccator over sulphuric acid. Reduce to, at least, a No. 80 powder. For the assay, use from 10 to 20 grammes of the drug, depending upon the amount of contained alkaloid. As a general rule, 20 grammes are used as the sample. Introduce this into a suitable container, and add a mixture of ether 100 grammes and chloroform 25 grammes. Shake the mixture well and

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macerate for five or ten minutes, shake once more, add 10 grammes of water of ammonia, 10%, and shake immediately and vigorously so that the powdered drug shall be uniformly moistened. Shake occasionally during half an hour, then add a sufficient quantity of water (20-40 c. c.), to cause the drug powder to agglutinate. Pour off of the clear ethereal fluid, 100 grammes, representing 16 grammes of the drug. It frequently happens that the full 100 gms. cannot be obtained. In such a case, weigh the fluid obtained, care be taken to avoid loss by evaporation and to calculate the quantity of drug it represents, (The relative proportion of ether and chloroform should not exceed 25 or 30 per cent, by weight of the mixture).

49. In case the fluid drawn off is turbid, it should be left at rest in a well stoppered flask or bottle until it becomes quite clear, after which, the requisite quantity is to be poured off. Place the ethereal fluid in a separator and wash out the alkaloid it contains, with 5% hydrochloric acid, using three portions of 20 c. c., 15 c. c., respectively. From the mixed acid solutions, the alkaloid is removed by shaking out with ether and chloroform, after rendering alkaline with ammonia. Three washings should be conducted, adding the ether mixture the first time before rendering the liquids alkaline. In all about 100 c. c. of the solvent should be used. The fluid is removed to a tared Erlenmeyer flask of about 200 c. c. capacity, the solvent recovered by distillation, and the vapors of ether and chloroform removed from the flask by a light current of air from a bellows, the flask dried to constant weight and weight taken. The alkaloid is generally quite pure, but, for safety, after weighing, it may be titrated with standard acid. Dissolve in 5 to 10 c. c. of neutral absolute alcohol, add water to the beginning of turbidity, then a few drops of haematoxylin indicator, and finally from a burette $\frac{n}{10}$ or $\frac{n}{20}$ hydrochloric acid, until the color changes. Then, calculate the quantity of alkaloid present. (88)

50. In case of drugs like ergot and nux vomica, which contain a considerable quantity of oil, it is advisable to treat the drug with ether by percolation, before attempting to extract the alkaloid. The ether may, by this previous washing, extract notable quantities of the alkaloid, hence the extract should always be washed and shaken with acidulated water, which is then tested for alkaloid. If it is found to be present, it must be removed by the usual method and added to the quantity of alkaloid extracted in the subsequent assay process.

51. Method of K. Schwickerath (9);- Twenty grammes powdered drug are digested in 150 c. c. of a weak Prollins mixture (Conc't ammonia water 30%, 10 c. c., Alcohol 70 c. c., Ether 920 c. c.), for twelve hours, shaking frequently. For the latter purpose, the most serviceable thing is some form of agitator run by power. The drug may be moistened with water to advantage, at the beginning of the operation, or water is added after the maceration. Filter off through cotton, 75 c. c. of the ethereal fluid, corresponding to 10 grammes of the drug, place in a shallow glass vessel, add 8 c. c. of distilled water and 2 to 3 c. c. of dilute sulphuric acid 2.5%, and set aside in a moderately warm place, permitting the alcohol and ether to evaporate.

The chlorophyll, fat, wax, etc., are hereupon deposited in small adhering particles on the sides of the dish, while the alkaloid goes into solution in the acidulated water. The acid solution is now filtered through a very small filter into a separatory funnel or preferably into a perforator (See par 9). The waxy residue in the dish is treated with 1 c. c. dilute acid and a little ether which is again allowed to evaporate and the aqueous solution passed through the filter and added to the acid solution. This may be repeated once more if deemed necessary. The alkaloid is then recovered from the solution by treatment with an alkali and the appropriate solvent, the perforator method being preferred.

52. Use of the Bosman-Schwickerath Perforator;- Introduce into the perforator (see par 9), the acid solution from which the alkaloid is to be extracted; this liquid should not occupy the extractor more than half way from bottom to first side or overflow tube. Place, in the acid solution, a small piece of filter paper and lightly insert just below the level of the overflow tube and above the zone for the aqueous liquid, a ring of absorbent cotton, to prevent carrying over of droplets of the aqueous fluid. Now place in the flask, 30 c. c. petroleum, connect the flask to the perforator and apply heat from a water bath, so regulated that the ether bubbling through the liquid and rising and overflowing will be returned in a fine stream. This process of previous washing removes all fatty and waxy matter and should proceed about one hour.

53. Now disconnect the apparatus, pour out the petroleum ether in the flask and ether remaining in the perforator, into the bottle for ether, to be recovered. Now place in the flask, 30 c. c. of the chosen solvent, add to the acid solution in the perforator, enough ammonia or preferably sodium carbonate to render the liquid distinctly alkaline, reconnect the apparatus and apply water bath heat as before. The washing this time, should be continued from two to three hours. It often happens, if there is a very large amount of alkaloids present, that a small portion may remain undissolved, which will generally be plainly seen. In such cases, it is heat to disconnect the apparatus, add drop by drop of hydrochloric acid to strong acid reaction, thus dissolving the remaining alkaloid, again render the solution alkaline, and continue the extraction an hour, or until the whole of the alkaloid is dissolved. Make sure of this by testing a drop of this solution, after acidulating, with Mayer's reagent (which may, however, possibly produce a turbidity due to something beside alkaloid). Finally, transfer the ether in the flask to a tared beaker rinse the ether which remained in the extraction apparatus, and which is easily poured off by tilting the apparatus, add this washing of flask to this ether in the beaker, evaporate the dryness, dry and weigh. The result can then be verified, if desired, by dissolving the alkaloid and titrating with standard acid using cochineal, as indicator.

54. The great advantage of the perforator method is that a number of assays can be progressing at once, under the supervision of a single operator and, while the perforator works automatically, the chemist may devote himself to

other labors. The extraction of alkaloids is also accomplished with a minimum amount of costly solvent.

55. Method of J. U. Lloyd (10) :- To examine a drug qualitatively for alkaloids. Percolate the powdered or ground drug with the appropriate solvent or, if the proper menstruum is unknown, with various solvents, alcohol and hydro-alcohol, and use the percolates, as directed in (56). It will be best to abstract the iron magma first with chloroform, as herein suggested, and then with sulphuric ether, evaporating the liquids separately and treating the residues severally with chloroform, as later directed. If it is desirable to obtain the alkaloid in considerable amount, after demonstrating the presence of an alkaloid, the percolate may be concentrated by evaporation and used in increased proportion; but with many evanescent alkaloids, as hereafter described, more or less may disappear during the operation. This method, Prof. Lloyd states, gives excellent results and, by means of which, he has found alkaloids in plants that heretofore failed to yield them.

56. Assay of percolate or fluid extract:- Pour 5 c. c. of the fluid into a flat bottomed porcelain mortar of about one pint capacity, and thicken it to the consistence of a stiff magma, by means of a sufficient quantity of a mixture of equal parts of dry hydrate of iron and bicarbonate of sodium. Exhaust this magma by trituration with 20 c. c. chloroform, decant the chloroform and repeat the washings three times with successive portions, each of 10 c. c. chloroform, decanting them severally with ordinary care, most alkaloids (of fluid extracts, for which this method is commended), may usually be extracted by a skillful manipulator, by means of two of the portions of chloroform; but in order to guard against imperfect work, four washings are directed and pains must be taken to perform the washings thoroughly if the examination be quantitative. In some cases, the amount of chloroform may be increased to advantage. With cinchona, for example, the factor must be increased or the chloroform washings extended, because of the slight solubility of cinchonine. If an alkaloid is not soluble in chloroform, and is soluble in ether, use that solvent instead, and proceed, as heretofore directed.

57. This treatment will liberate the alkaloid from its combination, and practically transfer it to the chloroform together with the fats, various resinous bodies and most of the chlorophyll. Tannates, mineral salts, most vegetable acids and coloring matters are left in the residue. If the iron magma does not separate clearly when triturated with the chloroform, so that the chloroform is transparent traces of it pass into the chloroformate alkaloidal solution. This is (excepting guarana), immaterial, however, as the subsequent manipulation separates it completely. (In case of Guarana, the residue obtained at this stage is practically pure caffeine. Express its weight in grammes and multiply by 20 to get the per centage).

58. Notes 1 on Lloyd's method;- The operator must diligently wash all parts of the magma with the chloroform which can be readily, effectually and quickly accomplished by ordinary care and the use of a good spatula in scraping the sides of the mortar. The spatula should be about a

four inch blade, thin, slender and supple, so that they will curve easily and hug the sides of the mortar. Ordinary, blunt, stiff spatulas are cumbersome and impracticable. After each portion of chloroform has been decanted and, before the succeeding portion is added, the magma should be scraped into the bottom of the mortar. If this part of the process is properly accomplished, the alkaloid to the limit of error in manipulation, will have been transferred from the magma to the chloroform, and the formation of emulsions avoided. If the magma becomes friable when the first portion of chloroform is added, then mixes with and absorbs the chloroform (as will be the case if the fluid extract be strongly alcoholic), add to the mixture, after the preliminary trituration, from 2 to 5 c. c. water; or better, the necessary quantity of a mixture of equal parts glucose and water, being careful to use as little as possible. The magma will then separate sharply from the chloroform (as it should), thus favoring the approximate abstraction of the alkaloid and preventing any considerable amount of chloroform from remaining in the magma, and holding its proportion of alkaloid therein. The mortar should be capacious, preferably the flat porcelain style, all porcelain pestle, and possessed of a good lip. It seems that some well informed analysts are lamentably awkward in exclusively pharmacal manipulations; and it appears as though the skilled use of the mortar and pestle has become to be practically a lost art with some talented assayists. It may be remarked that beginners in assaying always use too small a mortar.

59. Notes on the 2nd step:- Gradually pour the foregoing chloroform solution into an evaporating basin (or a flask connected with a condenser, if it is proposed to recover the chloroform), on a water or steam bath, continuing to add the chloroform solution as the solution evaporates. It is not best to attempt too great economy in assay work but prefer to evaporate the chloroform at as low a temperature as possible, in an open dish. It is always best to use a flat-bottomed evaporating dish with a good lip, the object being to spread the alkaloidal residue in an even thin film over the bottom of the flask or dish, so that while the acid water subsequently added need not be in large amount, it will thoroughly permeate it and extract the alkaloid. If a round bottomed evaporator is used, the residue in some cases may be too thick for absolute extraction.

60. Notes on 3rd step:- Then, after the chloroform has evaporated, pour upon the residue, enough dilute solution of sulphuric acid (one part acid to fifty water) to cover the residual film, agitating gently (until the residue is permeated) and then carefully decant the liquid into the bottom of a small wetted filter that is set in a small funnel in the upper neck to a separatory funnel of about 8% capacity and contain 10 c. c. chloroform. Filtration will be rapid, especially if a straight funnel be employed. Now again, cover the residue in the dish with acid water, warm it as before, and again filter through the same paper pouring the liquid this time, around the inside of the top of the paper. Repeat the operation, stirring the residue (if any remains) in the acid water well, the last time, by

means of a glass rod. Such resins, essential and fixed oils as well as chlorophyll, as pass into the chloroform and are mechanically mixed with the water, are left in the wetted filter by this operation. It has been found out by many experiments, that in most cases the alkaloid is nearly all extracted by contact with the first acid water, and completely by the second; but in order to avoid any loss, a third extraction is advised. Usually, excepting nux vomica and very oily drugs, the undissolved residue is considerable. If the work has been properly performed to this point, the alkaloid, practically free from such impurities as can follow into the alkaline chloroform, will now have been transferred to the mixed acid water.

61. Notes on the 4th step:- Quickly cool the acid liquid, make it alkaline with ammonia, and rotate it immediately, not by shaking, but by a circling rotating motion, with three portions of chloroform of 10 c. c. each, drawing them separately into a tared dish and heated on a water bath. The dish, here again, should be flat, so that the alkaloidal residue may be thin and easily dried to constant weight, without forming a skin over a soft under portion (which prevents evaporation); and for this object, with experienced assayists and sensitive balances, the analyses of small amounts of fluid extracts are preferable. Under such conditions, the residue practically reaches constant weight as soon as the chloroform evaporates. When the last portions of the chloroform have evaporated, cool the dish in desiccator, cover and weigh at once. This alkaloidal residual is obtained from chloroform, and if that liquid is enveloped in the residuum, the best way to bring it to constant weight is to heat it in a drying oven. Even here, chloroform is extremely hard to get rid of and long and high heat are often necessary to drive off the last traces. In this connection, do not forget that desiccators, either lime, sulphuric acid or calcium chloride, are dryers of aqueous residues and that they have no affinities for, and do not abstract chloroform vapors. (A great many assayists prefer to work large amounts. However, it is evident that with good manipulation and accurate balances, there is less risk of error in the manipulation of 5 c. c. fluid extract, than with amounts large enough to necessitate previous evaporation, or subsequent trouble and uncertainty in bringing the residue to constant weight. With such drugs as nux vomica and cinchona, possessed of a large amount of stable alkaloids, no necessity exists for working large amounts, especially with cinchona, in which the alkaloid cinchonine is so insoluble in chloroform and ether. With such as ipecac and aconite, possessed of evanescent alkaloids that are prone to disappear during manipulation, too great care cannot be observed in shorting the process and avoiding the destructive action of heat and chemical manipulation. Some of these alkaloids wear out rapidly, and under no case, should an assay be attempted and interrupted. Finish the work at once and without delay). The weight of the residue expresses in grammes and multiplied by 20 gives the practical alkaloidal per centage of the fluid extract.

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62. Method of A. B. Lyons:- Pour into a four oz. prescription vial, 10 grammes of the drug in moderately fine powder. Pour in carefully, exactly 100 c.c. of Prollins fluid (12), cork securely and shake vigorously several times at intervals of a minute or two. Place in a mechanical shaker for four hours, or else shake frequently during that time. At the end of that time, decant into a measuring flask, exactly 50 c.c. of the clear fluid, transfer to a shallow capsule or evaporating dish and set in a warm place (or expose to current of air) until the ether has nearly all evaporated. Then add 5 c.c. of highly dilute sulphuric acid (1%) and 10 c.c. of fresh ether. Stir to dissolve in the ether, all the oily and waxy matter that may have separated, and to insure combination of all alkaloid with acid, evaporate the ether completely together with any alcohol that may remain.

63. Filter the aqueous fluid through a very small filter, into a 1 oz. prescription vial, which should have a square shoulder and a good lip (or else filter at once into a perforator and finish the process by method of Carl Schwickerath). Treat the residue in the capsule with 3 c.c. of water slightly acidulated and 5 to 10 c.c. ether, stir well together, evaporate off the ether, and pass the aqueous fluid through the same filter as first solution into a vial (or else perforator). Test a small drop of this fluid with Mayer's reagent, on a mirror. If it contains more than a trace of alkaloid, repeat the washing of the residue once more, with 2 c.c. of water and 5 c.c. of ether. This should not often be necessary, but the filter may be washed finally, with a few drops of water.

64. We have now, an aqueous solution, containing all the alkaloids from 5 grammes of the drug. In this, for rough approximate work, we may estimate the alkaloid by the titration with Mayer's reagent, when this is applicable, or by other volumetric processes, as by Wagner's reagent, but in exact work, the alkaloid must be extracted and weighed, or titrated with standard acid and this consumes hardly more time than a direct titration of the acid fluid.

65. The procedure for extracting the alkaloid is as follows:- Pour into a vial containing the acid solution, 15 c.c. of ether, shake well, let separate, pour into a second similar vial, containing 3 c.c. of slightly acidulated water. Shake together, let separate completely, and pour off the ether into a container for waste ether. (Rarely a second washing of the ether with water may remove traces of alkaloid and it is always best to take this precaution). Repeat the double washings of the contents of No. 1 and No. 2, with one or two successive portions of fresh ether (15 c.c.) until all traces of chlorophyll and waxy matter are removed; the ether is to be poured off each time as closely as possible, without loss.

66. Now add to No. 2, two or three drops of water of ammonia (10%) and 20 c.c. of ether, shake immediately fifteen seconds and let separate. (Make sure that the ammonia is in excess, by treating the vapor in the vial with red litmus paper, which must not be allowed to touch the neck of the vial. If the paper is not made blue, add more ammonia and repeat the shaking). Pour off the ether into No. 1, add water of ammonia in excess, perhaps 10 drops,

10. Method of A. I. Linné:—Four tubes were used, each containing 10 c.c. of the same mixture as in the above, but in which the amount of the various acids was varied as follows:—

(1) 10 c.c. of the same mixture as in the above, but in which the amount of the various acids was varied as follows:—

(2) 10 c.c. of the same mixture as in the above, but in which the amount of the various acids was varied as follows:—

(3) 10 c.c. of the same mixture as in the above, but in which the amount of the various acids was varied as follows:—

(4) 10 c.c. of the same mixture as in the above, but in which the amount of the various acids was varied as follows:—

[illegible][illegible]

65. The procedure for extracting the alkaloid is as follows:- Pour into a vessel containing the solid mixture 10 c.c. of ether, shake well, let separate, pour off the ether and mix into a solution 2 c.c. of slightly ammoniacal water. Shake thoroughly, let separate completely, and pour off the ether into a beaker for waste ether. (Repeat several washings of the ether with water and throw away the ether and it is almost best to leave this as a waste product.)

Report the double analysis of the contents of the () and (), with one or two suggestive portions of () (c.c.) until all traces of color disappear and removed; the other is to be poured off once time as usual.

as complete, without loss.

No. 1, and water of ammonia in water. The water of ammonia and repeat the washing. Throw out the water and of the vessel. If the paper is not made pink, this may be done again, which must not be allowed to come in contact with the vessel, or treating the vapor in the vessel with fresh water and let evaporate. (Make sure that the water is removed (10%) and 20% of water, which immediately will be removed in 2, 2, and 3, and 4, and 5, and 6, and 7, and 8, and 9, and 10, and 11, and 12, and 13, and 14, and 15, and 16, and 17, and 18, and 19, and 20, and 21, and 22, and 23, and 24, and 25, and 26, and 27, and 28, and 29, and 30, and 31, and 32, and 33, and 34, and 35, and 36, and 37, and 38, and 39, and 40, and 41, and 42, and 43, and 44, and 45, and 46, and 47, and 48, and 49, and 50, and 51, and 52, and 53, and 54, and 55, and 56, and 57, and 58, and 59, and 60, and 61, and 62, and 63, and 64, and 65, and 66, and 67, and 68, and 69, and 70, and 71, and 72, and 73, and 74, and 75, and 76, and 77, and 78, and 79, and 80, and 81, and 82, and 83, and 84, and 85, and 86, and 87, and 88, and 89, and 90, and 91, and 92, and 93, and 94, and 95, and 96, and 97, and 98, and 99, and 100, and 101, and 102, and 103, and 104, and 105, and 106, and 107, and 108, and 109, and 110, and 111, and 112, and 113, 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and 669, and 670, and 671, and 672, and 673, and 674, and 675, and 676, and 677, and 678, and 679, and 680, and 681, and 682, and 683, and 684, and 6

and immediately shake vigorously 30 seconds. Let separate, return the ether to No. 2, but shake this only once and then let stand several minutes, so that the ether will separate completely from the watery fluid. Now add to No. 1, 15 c.c. of fresh ether, shake well together and let separate. The ether is now to be decanted carefully from No. 2 into a tared beaker, to be replaced by that from No. 1.

67. A third portion of ether, passed in succession through No. 1 and No. 2, will generally extract all the alkaloid if it is one freely soluble in ether (If not, it is better to use a mixture of 15 c.c. ether, and 5 c.c. chloroform for the first washing to be followed generally with pure ether for the subsequent washings). In any case, test the residual aqueous solution in No. 1, which should be generally quite clear, by placing a drop of it on a mirror, adding acid in excess and then a drop of Mayer's reagent. There should not be produced, more than a faint cloud, although traces of alkaloid will often be found even after five or six washings.

68. Evaporate the ethereal solution on the water bath to constant weight. If chloroform has been used in the extraction, redissolve the residue once or twice in alcohol and evaporate to expel persistently adhering traces of chloroform. Weigh the residue. The weight of the alkaloid in decigrammes multiplied by two, or the weight in centigrammes divided by five, will be the percentage of total alkaloids contained in the drug.

69. After weighing the crude alkaloid, dissolve it in 5 c.c. alcohol, add 5 c.c. of No. 1-25 hydrochloric acid and 25 c.c. distilled water. Be sure that the alcohol and water contain no traces of acid or of alkali; add 2 drops of Brazil wood indicator (or haematoxylin or cochineal) and titrate back with No. 1-25 alkali. The amount of alkali consumed must be subtracted from 5 c.c. to give the acid equivalent of the alkali present. In case of alkaloids having only feeble alkalinity, the alkalimetric test is, of course, superfluous.

70. For rapid work, in the case of alkaloids that admit of determination by alkalimetry, the assay may be abbreviated by evaporating the original ethereal extract (50 c.c.) to dryness, taking up with 10 c.c. acid free ether, evaporating once more, adding 10 c.c. of acid free ether, together with 5 c.c. of No. 1-25 acid, evaporating off the ether and titrating back with N 1-25 alkali, as described in the last paragraph. The alkaloid can be afterwards recovered from the solution in the usual way if this is desired.

71. Short assay process #2- Dr. Lyons:- Put into a 4 oz. prescription vial, 12 grammes (this quantity is suitable in the case of drugs containing less than 0.8 percent. of alkaloid. If there be as much as 1 percent., 10 grammes of drugs is sufficient, if five percent., not more than 4 grammes of drug should be used) of the drug in fine powder. Pour in exactly 100 c.c. of a mixture of ether eight volumes and chloroform one volume, cork securely and shake well. After 10 minutes, shake once more, add 5 c.c. water of ammonia (10%), cork and immediately shake vigorously, repeating this several times at an interval of a minute or two. Place in the mechanical shaker four hours, or else shake at frequent intervals (once in five or ten minutes) during that period, then, if the drug does not settle

promptly leaving a clear supernatant liquid, add water sufficient to cause it to aggregate into lumps on shaking (from 15 to 25 c.c. generally suffice). In any case, decant exactly 50 c.c. of the clear ethereal fluid into a measuring flask, and thereafter follow the instructions given under Assay Process, No. 1. (62 et seq.)

72. Instead of evaporating the ethereal fluid, it is practicable to wash out from it, the alkaloid, in the following manner; transfer the fluid to a separator, add about 2 1/2 c.c. of dilute hydrochloric acid (10%) and shake together. Make sure that the acid is in excess, best by adding a drop of some indicator, add more acid if necessary, and water enough to make up 5 c.c. in all of aqueous fluid. Shake together 30 to 60 seconds and let separate. Draw off the acid fluid into a one ounce prescription vial, treat the ethereal fluid with four or five successive portions (3 c.c.) of slightly acidulated water until all the alkaloid is removed. Test a small drop each time after the second washing, on a mirror, with Mayer's reagent. Add the first portion of the contents of the vial (No.1), put the next two or three washings into a second vial (No.2) and the last into a third vial.

73. To recover the alkaloid, add first to No. 3, a drop of water of ammonia and 5 c.c. of chloroform mixed with 15 c.c. of ether: shake, let separate and decant the ethereal fluid into No. 2; add 2 or 3 drops (excess) of water of ammonia, shake, let separate and decant into No. 1; add excess of water of ammonia (perhaps ten drops, but make sure that the ammonia is in excess by testing the vapor in the bottle with red litmus paper), shake together well for 30 seconds or more, let separate and decant into No. 3, which now contains little but water; shake together once, let stand fully two minutes for complete separation and decant into a tared beaker. Put into No. 2, 20 c.c. ether, which is to be passed in succession through No. 1 and No. 3, in the same manner as before, and follow this with one or two additional portions of ether, 15 c.c. each until assured that the whole of the alkaloid is removed.

74. Finally evaporate the solvent at a water bath heat and dry to constant weight, as in process No. (68) and (69) (The details of the process have been given quite minutely for the benefit of beginners). The object of the final washing in vial No. 3 is to avoid the possibility of carrying over with the alkaloid any of the aqueous mixture of vial No. 1, which is heavily charged with a salt of ammonia.

75. Short assay process No. 3- Lyons:- This differs from Process No. 2 only in using, for extracting of the drug, light petroleum (petroleum benzin) instead of a mixture of chloroform and ether. A benzin, having a boiling point of 80 degrees C. is generally suitable and even to be preferred to that having a lower boiling point. In particular assays it will be found advantageous no doubt, to use even a less volatile hydrocarbon oil, but this has not yet been experimented upon fully. It will be found best, generally, where petroleum benzin is used, to follow the procedure of (72) unless emulsification occurs, and in this, his experience is not common.

76. Short Assay Process No. 4- Lyons:- Proceed exactly as in process No. 2, but use, for extraction of the

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drug, a mixture of chloroform one volume, and ether four volumes.

77. Some modifications of the above processes suggest themselves, as likely to be of service, although not yet fully tested in practice. These involve the use in the first stage of the process, of some agent to fix organic acids and other compounds which go into solution in ether and chloroform. Ferric Chloride or lead acetate suggest themselves; possibly litharge might answer the purpose. The first may be used in the following way. Treat the drug in the beginning, with an ethereal mixture, 100 c.c., containing 0.2 to 0.5 gramme of ferric chloride, agitate frequently or continually during one hour, then add excess of water of ammonia and continue the process in the regular way. Or, the drug may be moistened in the beginning with an aqueous solution of lead acetate or of ferric chloride and, after an hour, treated with ether (ether, chloroform or other solvent) and ammonia in excess in the usual way.

78. Method of Lyman F. Kebler (11), A modification of that of Keller. Place 10 grammes of the powdered drug in a 250 c.c. flask, add 25 grammes chloroform and 75 grammes of ether, cork the flask securely, agitate the flask for several minutes, add ten grammes of water of ammonia (10%), and agitate frequently during one hour. On adding 5 grammes more of water of ammonia, the suspended power agglutinates into a lump, the liquid becomes clear after standing a few minutes, and can be poured off almost completely; 50 grammes of the clear fluid are taken for the assay and treated by one of the following methods.

79. Process 1:- Place the ethereal fluid in a beaker, evaporate on the water bath, add 10 c.c. ether and evaporate once more. Dissolve the residue in 15 c.c. alcohol, add water to slight permanent turbidity, haematoxylin, Brazil wood or cochineal as indicator, and a measured quantity of volumetric acid; titrate back with centinormal alkali.

80. Process 2:- Transfer the ethereal fluid to a separator, treat at once with 20 c.c. of acidulated water, after thorough agitation and complete separation, remove the aqueous solution to a second separator. Repeat the above operation twice with 15 c.c. of acidulated water and add to first washing. Wash out the alkaloid from the aqueous liquid, after adding ammonia in excess, with three portions of a mixture of chloroform three volumes, ether one volume. The ether-chloroform is then evaporated off in a tared beaker, the residue twice dissolved in 8 c.c. ether to carry off the last traces of chloroform, dried on water bath to constant weight and accurately weighed. It may then still be dissolved in alcohol and titrated with standard acid and alkali. The first procedure yields naturally a somewhat higher figure.

81. Method of Prescott and Gordin (12):- One to four grammes of the finely powdered drug is weighed into a low, wide-mouthed vessel with a round bottom, holding 8 or 10 ounces and having a well fitted cork, such as a screw top ointment jar (an ordinary tea-cup fitted with a specie cork answers well.) The powder is rubbed up with a small pestle to a fine paste, by adding a little of a solvent mixture, composed of stronger water of ammonia and alcohol, each 5 c.c., chloroform 10 c.c., and ether 20 c.c. Then a few

1.0.0. chloroform 10.0.0. and ether 20.0.0. Then a few drops of dilute water of ammonia and alcohol are added to the mixture. The mixture is then allowed to stand for 24 hours. The mixture is then filtered and the filtrate is evaporated to dryness. The residue is then weighed and the weight is compared with the weight of the original sample. The difference is the weight of the chloroform. The first procedure yields a fairly accurate result.

2. Method of Frenkel and Gerson (1911). - One gram of the finely powdered drug is weighed into a 100-cc. glass-stoppered vessel with a round bottom, closed with a stopper and having a well fitted cork, with an extra hole in the stopper for the insertion of a glass tube. The powder is packed in with a small amount of water. The vessel is then sealed with a small amount of wax. The vessel is then heated in a water bath at 100°C. for 24 hours. The vessel is then cooled and the stopper is removed. The mixture is then filtered and the filtrate is evaporated to dryness. The residue is then weighed and the weight is compared with the weight of the original sample. The difference is the weight of the chloroform. The first procedure yields a fairly accurate result.

more cubic centimeters of this mixture are added, so as to have the drug well covered with the liquid, using in all, about five times the amount of the drug taken. The vessel is corked with the pestle inside and is set away for about four or five hours, taking care to agitate by circular movement, very frequently, during that interval. After that time, the cover is removed and the vessel kept in a current of air, stirring frequently until all odor of ammonia has disappeared. With a good draught and frequent stirrings the powder will be almost perfectly dry in about two hours. The vessel is then put in a vacuum desiccator over sulphuric acid for about four or five hours.

82. An amount of powdered sodium chloride, equal to about five or six times the amount of drug employed, is then carefully mixed in, with use of the pestle and the whole thrown into a small percolator, one provided with a glass stop cork and having a plug of cotton at the bottom. The vessel is then cleaned out several times with small quantities of sodium chloride and the cleanings added to the percolator. The mixture in the percolator is then covered with a piece of cotton which is pressed down with a piece of glass and a suitable menstruum, usually chloroform, is poured slowly into the percolator until the menstruum reaches the stopcork. The latter is then closed, the percolator covered and set away for five or six hours. After that time, the stop-cork is opened and the drug exhausted with the menstruum, until 10 drops of the percolate evaporated on the water bath on a watch crystal, and the residue taken up in a few drops of acidulated water; the solution shows no turbidity whatever on adding a few drops of Wagner's reagent. When finished, the percolate, which is received in a flat evaporating dish, is placed in a good draught, at a temperature of about 30 degrees C. When the liquid is reduced to a very small volume, ten c.c. acidulated water, (if an alkalimetric assay is intended, the acidulated water in the operation should be standardized and taken in definite quantities), are added, and then a few cubic centimeters of ether or petroleum ether, so as to have an ethereal liquid cover the aqueous solution, (if the menstruum is all evaporated off, it will be sometimes difficult to dissolve out the alkaloids with acidulated water. If chloroform be used, coming below the aqueous layer, it evaporates too slowly), when the whole is stirred with a glass rod until all the ethereal liquid is driven off. The liquid is then filtered and the evaporating dish and filter washed several times with acidulated water. In this way, is obtained a colorless solution of the alkaloid, which can be worked up for any method of assay.

83. The iodometric Method:- In the periodide method of assay, the final alkaloidal solution obtained, whether by methods (81) and (82), by Dr. Lyon's methods, or by any other method, this final solution representing a definite quantity of the drug to be assayed, is poured slowly, and with constant stirring, into a flask holding 100 c.c. in which has been previously added 20 or 30 c.c. of a standardized solution of iodine and 1 or 2 c.c. of dilute hydrochloric acid (U.S.P.); (except in case of morphine, an excess of acid is not hurtful and even promotes the separation of the periodide. Hydrochloric acid is to be preferred

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to sulphuric acid). The flask is then filled up with distilled water to 100 c.c., stoppered, and well shaken until the periodide has separated out. The supernatant liquid is to be perfectly transparent but of a red iodine color. Fifty c.c. are then filtered off and in this portion, the excess of iodine determined by titration with standard sodium thiosulphate. The amount of iodine consumed, multiplied by a suitable factor, gives the amount of alkaloid present in the quantity of drug taken.

84. In the case of several alkaloids being present in the drug, a mean iodometric factor can be deducted in the same way as is done in alkalimetric assay. It is to be noticed that, should there be no precipitate with iodine, but only a slight turbidity, then the drug is extremely poor and a much larger amount must be taken for the assay. On the other hand, should the supernatant liquid, after adding the alkaloidal solution to the iodopotassium iodide solution and separating the periodide by shaking, have very little color or be almost colorless, then it is certain that the drug is very rich, and either a smaller quantity of the drug or a larger quantity of the iodine solution must be employed in the assay.

85. All assays should be made in duplicate. The careful operator will always provide for verification of his results, by some form of duplicate assay. In most cases, it is not necessary to make two, wholly independent assays, although that is the most satisfactory procedure. In the assay of a crude drug, we more often make a single weighing of the drug, which is exhausted by some appropriate solvent and the solution made up to a definite volume. Of this, we then take for assay, two aliquot parts, following preferably different methods of treatment. A method of assay which in itself gives only approximate results, as for example a titration with Mayer's reagent, furnishes valuable confirmation of results reached by more scientific and exact methods and such a duplicate may be all that the operator has the time to carry out.

86. Estimation of Alkaloids by Alkalimetry. The alkaloidal residues obtained by extraction with immiscible solvents and commonly weighed as total alkaloids, are never quite free from foreign substances. With reasonable care in manipulation, they are generally so nearly pure that we shall make no serious error in accepting their weight as practically that of the alkaloid itself, and when the amount of alkaloid is large, as in cinchona bark, the gravimetric estimation is close enough for the professional chemist. When the quantity of alkaloid, however, is very small, the error is often considerable; impurities may constitute from ten to fifty percent. of the alkaloidal residue. We must therefore, have some check upon the results obtained by weighing, and this, in the majority of cases, is supplied in the alkaline reaction of the uncombined alkaloids. The most of them can be determined with great exactness, by titrating with standard acid.

87. Unfortunately, in drug assays, the residue generally contains two or more alkaloids, having different equivalent values, so that even alkalimetry does not give us the definite, exact result we desire. It enables us, however, to check our gravimetric result and, in most cases, the

limit of error is not greater than five percent of the entire amount, as against a possible thirty or even fifty percent. of the entire amount in the gravimetric method. It must not be understood that errors as large as this, are common where gravimetric methods are followed; it is sufficient that even with reasonably careful work, they are possible, and hence the operator should always control his work, when practicable, by alkalimetry. The beginner must remember, however, that in experienced hands, the alkali-metric process admits large possibilities of error.

88. Direct titration with standard acid:- Dissolve the alkaloid in ether, chloroform, or other immiscible solvent (10 c.c.), put the solution into a stoppered vial of clear glass, add water (5 c.c.) colored with methyl orange (A. H. Allen) or other suitable indicator. Add the standard acid (N-25, hydrochloric acid) little by little, at last, a drop at a time, shaking after each addition. The end reaction is sharply marked by change of color in the aqueous fluid.

89. Residual titration with Iodeosin as indicator:- Dissolve the alkaloidal residue in a little acid free ether containing iodeosin (2 milligrammes to litre) add an accurately measured quantity of standard acid N-25, in excess of what is required to neutralize, transfer to a stoppered vial or flask of clear glass, and titrate with alkali N-25, shaking the container well, after each addition. As soon as the alkali is in excess, the iodeosin is taken up in the aqueous solution, imparting a red color to it. The indicator is not suitable for titration of quinine, but answers well for most of the alkaloids.

90. The ordinary procedure:- (1) Dissolve the alkaloidal residue in 10 c.c. of acid free ether, add water 10 c.c., and a drop of indicator, preferably, Brazil wood, cochineal or haematoxylin; add from a burette hydrochloric acid N-25, until after stirring well, it is in decided excess. Allow the ether to evaporate. It should leave scarcely any residue. If there is any appreciable residue, pour the acid solution into a clean beaker, treat the residue with 5 c.c. fresh ether and 1 c.c. of acid N-25, evaporate off the ether and add the acid contents to the solution in the second beaker. Now, titrate back with N-25 alkali until the color of the solution changes permanently, that is, so that the original color does not return within 20 or 30 seconds. Subtract the quantity of alkali used from the total acid taken, and calculate the quantity of alkaloid by the tables following in (93). Note that the relative strength of acid and alkali must be fixed under conditions similar to those of actual titration and with use of the same indicator.

91. Alternative Method (2):- Dissolve the alkaloidal residue completely in 5 c.c. acid free alcohol, add 10 c.c. N-25 hydrochloric acid or such a quantity as shall be more than sufficient to neutralize all the alkaloid. (The weight of the alkaloidal residue, already determined, will indicate the quantity required); Add 40 c.c. water, two drops of indicator, and titrate back with N-25 alkali. It is important that the solution contain not more than one fifth its volume of alcohol, as a larger proportion will interfere with the sensitiveness of the indicator, partic-

and reaction is sharply marked by a change of color from yellow to red.

well for most of the aldehyde.

When the solution is poured into water, a red color is given. The color is not suitable for detection of aldehyde, but it is

useful in the detection of aldehyde. The color is given by the

aldehyde, and it is not given by the aldehyde.

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aldehyde, and it is not given by the aldehyde.

10. The ordinary procedure:- (1) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (2) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (3) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (4) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (5) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (6) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (7) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (8) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (9) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless. (10) Dissolve the solid in 10 c.c. of water, add a drop of indicator, previously prepared, and titrate with 0.1 N. sodium hydroxide solution. The end-point is reached when the color changes from pink to colorless.

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ularly haematoxylin. One plan is to add excess of standard sulphuric acid and evaporate off most of the alcohol before titrating. There is, however, possibility of loss of some delicate alkaloids, from the action of an excess of sulphuric acid, during the evaporation.

92. Make sure in all cases, when an alkaloidal solution is evaporated to dryness previous to titration, that there is no possibility that it be reached by acid vapors, also, that the heat to which it is subjected be not sufficient to cause chemical changes in the alkaloid. It is advisable, indeed, of the more unstable alkaloids, to avoid any application of heat exceeding about 45 degrees C. It is impossible that in driving off chloroform the solvent itself may become decomposed, furnishing acid to vitiate the result. In any case, if the titration gives results much lower than the weighing, we should suspect some sources of error affecting the former rather than the latter, and a duplicate experiment should be made, avoiding, as far as possible, the above mentioned dangers.

93. Determination of Alkaloids in Salts by Alkalimetry. While to most indicators, alkaloids are alkaline in reaction, they are nearly all neutral towards phenolphthalein. Consequently, when a solution containing an alkaloidal salt is titrated with standard alkali, in presence of this indicator, the whole of the acid appears by the titration, as free acid. If a solution containing an alkaloidal salt together with excess of acid, is divided into two equal portions, and these are titrated with standard alkali, using in one case, Brazil wood, haematoxylin or cochineal, and in the other, phenolphthalein, we shall get different results, the difference representing the quantity of alkaloid present in one half the solution. We may thus determine the amount of alkaloid even though it has been partially neutralized through accident or carelessness. The method is not applicable in the case of atropine, narcotine, coniine, colchicine, caffeine and some other alkaloids. It is important that the standard alkali used for the titration be free from carbonate.

94. Normal equivalents of the more important alkaloids. The following table is useful in interpreting the results of titration.

Table on the next page.

Table.

Aconitine-----	647	25.9	1.294	0.518	0.431	0.259
Atropine-----	289	11.6	0.578	0.231	0.193	0.116
Berberine-----	335	13.4	0.670	0.268	0.223	0.134
Brucine-----	393	15.7	0.786	0.314	0.262	0.157
Cinchonine-----	293	11.7	0.586	0.234	0.195	0.117
Cinchona Alkaloids--	314	12.6	0.628	0.251	0.209	0.126
Cocaine-----	303	12.1	0.606	0.242	0.202	0.121
Coniine-----	127	5.1	0.254	0.102	0.085	0.051
Emetine-----	254	10.2	0.508	0.203	0.169	0.102
Gelsemine-----	408	16.3	0.816	0.326	0.272	0.163
Hydrastine-----	397	15.9	0.794	0.318	0.265	0.159
Morphine-----	284	11.4	0.568	0.228	0.190	0.114
Nux Vomica Alkaloids	363	14.5	0.726	0.290	0.242	0.145
Physostigmine-----	275	11.0	0.550	0.220	0.183	0.110
Pelocarpine-----	208	8.3	0.416	0.166	0.139	0.083
Quinine-----	323	12.9	0.646	0.258	0.215	0.129
Strychnine-----	233	13.3	0.666	0.266	0.222	0.133
Veratrum Alkaloids--	687	27.5	1.374	0.550	0.458	0.275

Also aconite root and leaves, but results are without value.
 Also belladonna root and leaves; Hyoscyamus and stramonium
 leaves and seed.

Also ipecac

Also yellow jesamine

Only feebly alkaline; with ordinary indicators, titration
 not satisfactory.

Also jaborandi

95. Kjeldahl's Iodometric Method for alkaloids:- Another plan for the exact determination of alkaloids, based upon their power of neutralizing acids, has been proposed by Christensen (13). It is a modification of Kjeldahl's iodometric method of estimating free ammonia. The alkaloid or alkaloidal residue is dissolved in an excess of sulphuric acid, N-25, an excess of neutral solution of potassium iodide (1-15) and of one of potassium iodate (1:25) is then added, whereupon iodine is liberated in quantity exactly proportional to the free acid remaining. If the solution is then titrated with a solution of sodium thiosulphate N-25, then the quantity of this solution deducted from the quantity of standard acid taken, the remainder will be the quantity of acid N-25, consumed in neutralizing the alkali. It is a pretty method but seems to have no advantage over the simple alkalimetric process.

96. Volumetric Estimation as Chloride;- Another procedure may be adopted for determination of alkaloids which form strong combinations with acids, and which are not too easily decomposed by excess of acid. The alkaloid in the ethereal solution may be super-saturated with an ethereal solution of hydrochloric acid, evaporated by a gentle heat, the residue taken up with alcohol once or twice, and dried again to drive off completely excess of acid, and the residue dissolved in distilled water and tritrated with silver nitrate standard solution N-100 to determine the chlorine and thus indirectly the quantity of alkaloid present.

97. The method of Gordin and Prescott (14):- Messrs. Gordin and Prescott observe that while from a theoretical point of view, one of the best methods of estimating the alkaloids is undoubtedly the alkalimetric estimation of their basicity, the weakness of their basicity is often so great as to cause acids combined with them to react upon most indicators and particularly phenolphthalein, as if the acids were free. The end reaction, unlike that with sulphuric or hydrochloric acids and standard alkali, is therefore indefinite and of little practical value. A simple improvement of the method however, makes it possible to estimate all alkaloids capable of forming salts with as much sharpness as is obtained in inorganic alkalimetric analysis, and admits of the use of phenolphthalein as indicator in all cases where carbonates, etc. are absent. This consists in taking up the alkaloid in an excess of standardized mineral acid; then precipitating the alkaloid with a slight excess of some delicate reagent like Mayer's or Wagner's making up the mixture to a definite volume and filtering off one half of this after the precipitate has formed completely. In this filtrate, the excess can then be

accurately determined by the use of standard alkali and phenolphthalein as indicator. In case Wagner's reagent is used, the filtrate must first be decolorized with sodium thiosulphate. Whatever the composition of the precipitate may be as regard to mercury and iodine, the alkaloid always falls as a salt and therefore takes up an amount of acid which is equivalent to the combining weight. Hence, on deducting the excess of acid as determined alkalimetrically from the total quantity of acid employed, the amount combined with the alkaloid is at once ascertained and from this, the amount of alkaloid is readily calculated. In order to obtain the best results, the acid and alkali should be standardized for each alkaloid, by a weighed quantity of that alkaloid, and proceeding as above described.

98. Acidimetric Titration with Ammoniacal Cupric Oxide (15); E. Falières has employed an ammoniacal solution of cupric oxide, with advantage, for the acidimetric titration of alkaloids. The method is based upon the fact that as soon as the last trace of uncombined acid is saturated, a distinct turbidity is produced in a solution of the alkaloid, prepared by dissolving 0.10 Gm. in 20 c.c. n sulphuric acid. The reagent is prepared by dissolving 10 Gm. of cupric sulphate in about 500 c.c. of water, adding ammonia until the initial precipitate is redissolved, and then enough distilled water to make 1000 c.c. The test is made in a glass vessel placed against a black background, the standard copper solution being then run in until a permanent turbidity results. In the case of cinchona, the total alkaloid may be determined in the first extraction, since the accompanying impurities do not affect the appearance of the cupric oxide precipitate.

99. Gravimetric Estimation of Individual Alkaloids; For exact gravimetric determination of individual alkaloids, the precipitates produced by gold and platinum chlorides are well adapted. When these precipitates are ignited, the residue consists of metallic gold or platinum as the case may be. In general, the procedure is like that for determining potassa as a platinum compound. The alkaloid solution is evaporated with a slight excess of hydrochloric acid and an excess of the reagent nearly to dryness; the crystalline precipitate is washed with a little water or with dilute spirit, care being taken to remove all excess of reagent and all mineral salts, the residue ignited and weighed, best in a Gooch crucible.

100. The following table gives (a) the weight of the respective residue of gold or platinum corresponding with one hundred parts of the pure precipitate (16); (b) the factor of which to reduce from the weight of the residue, the alkaloid it represents (For example, a res-

idue of 27 Milligrammes of gold in an atropine estimation would correspond with a precipitate of the double chloride of gold and atropine weighing 27×100 divided by 31.37 milligrammes or with pure atropine weighing 27×1.46 - 45.4 milligrammes.

Table of gold and platinum equivalents found on the next page.

241
2

There are 25 milligrams of gold in an average medium-
sized gold nugget and a piece of gold of the same size
contains 25 milligrams of gold and silver. The gold is
by 25.7 milligrams of gold and silver is weighed
25.7-25.8 milligrams.
Index of gold and silver equivalence found in
the next page.

Table.

Atropine-----	31.37	1.46	-----	----
Berberine-----	29.16	1.70	18.11	3.43
Brucine-----	-----	----	16.52	4.03
Caffeine-----	37.02	0.98	24.58	1.99
Cinchonine-----	-----	----	27.36	1.50
Cocaine-----	30.68	1.54	-----	----
Codeine-----	-----	----	19.11	3.06
Coniine-----	-----	----	29.38	1.30
Emetine-----	-----	----	29.70	1.30
Gelsemine(Gerrard)-----	36.90	1.04	16.70	2.09
Gelsemine(Thompson)-----	29.80	1.63	18.58	3.30
Hyoscyamine-----	34.60	----	-----	----
Morphine-----	-----	----	19.51	2.92
Nicotine-----	-----	----	34.25	0.62
Pelocarpine-----	35.50	1.06	23.6	2.13
Piperine-----	-----	----	12.70	5.85
Quinine-----	40.00	0.82	26.26	1.66
Strychnine-----	29.15	1.69	18.16	3.42
Theobromine-----	-----	----	25.55	1.85
Veratrine-----	21.01	3.01	-----	----

Chemical	Conc.	Temp.	Time	Yield
Acetone	1.00	25.0	1.00	1.00
Benzene	1.00	25.0	1.00	1.00
Chloroform	1.00	25.0	1.00	1.00
Dichloromethane	1.00	25.0	1.00	1.00
Ethanol	1.00	25.0	1.00	1.00
Hexane	1.00	25.0	1.00	1.00
Methanol	1.00	25.0	1.00	1.00
Nitrobenzene	1.00	25.0	1.00	1.00
Phenol	1.00	25.0	1.00	1.00
Pyridine	1.00	25.0	1.00	1.00
Toluene	1.00	25.0	1.00	1.00
Water	1.00	25.0	1.00	1.00

101. Volumetric Estimation of Alkaloids by Mayer's Reagent:- Most alkaloids are very completely precipitated from acid aqueous solutions, by the solution of potassio-mercuric iodide, known as Mayer's Reagent. The precipitates are more or less soluble in alcohol, ether, acetic acid, solutions of iodides and so in an excess of the reagent. In alkaline solutions, ammonia also is precipitated. The fluid therefore is to be tested for alkaloids by this reagent, must be slightly acid in reaction, and must be nearly free from alcohol and other fluids similar in their solvent action to alcohol. The presence in the solution, of certain salts, notably of iodides, has a marked influence upon the final result.

102. If Mayer's reagent is added little by little to an acid solution of an alkaloid, the first portions will produce a heavy precipitate, but soon a point will be reached where a drop of the reagent only produces a faint cloud in the solution. It may be still necessary to add a considerable quantity, ten or twenty drops, of the reagent before the point is reached, when a further addition produces no effect, and it will then be found, in the case of most alkaloids, that a large excess of the reagent has been added, so that addition of fresh alkaloidal solution causes a heavy precipitate. The excess will constitute a certain proportion of the fluid at the end of the titration; hence, the most dilute the solution titrated, the larger the quantity of reagent required to complete the precipitation.

103. We cannot, therefore, fix for each alkaloid, a definite invariable titration equivalent. We find, moreover, that the degree of acidity of the alkaloidal solution, the manner of adding the reagent, any variation, in short, in the mode of procedure is liable to influence the result materially, so that quantitative determinations of an alkaloid by titration with Mayer's reagent are of value only when carried out under certain laid down conditions. We find, further, that at best, there is a provoking variability in the composition of the precipitates, so that even when we collect and weigh these, we obtain only approximate results.

104. In spite of these drawbacks, a good many alkaloids can be determined with reasonable exactness, by titrating with Mayer's reagent, and no doubt, in the hands of an experienced person, the method will be undertaken with more confidence and will actually give better results than alkalimetry. For certain alkaloids, it is true, it is worthless, for some others, too troublesome to be recommended; the same may be said of the alkalimetric method; in either case, we are to prove all methods and hold fast to that which is good.

101. The following relation of solubility...
102. It is known that the addition of a little...
103. We cannot therefore, for each...
104. In spite of these...
105. It is...
106. It is...
107. It is...
108. It is...
109. It is...
110. It is...
111. It is...
112. It is...
113. It is...
114. It is...
115. It is...
116. It is...
117. It is...
118. It is...
119. It is...
120. It is...

Mayer's reagent is very good in rough valuations of ipecac and of colchicum, and in the determinations of strychnine and berberine. Besides this, it is useful in determining rapidly, whether or not a given tincture or fluid extract is deficient in alkaloid.

105. Method of Titration with Mayer's Reagent. Put the solution (10 or 20 c.c.) to be titrated, which should contain as nearly as possible, 0.5 per cent. of alkaloid, into a small cylindrical measuring glass, or a roughly graduated test tube and note its volume. Run into it from a burette, Mayer's reagent, N-20, 15 drops, or, if you have an idea of the quantity of reagent you are likely to require, use one half of that quantity. Filter into second test tube, selecting a filter which will hold the whole of the fluid at the end of the titration, but not much more.

106. When the fluid has nearly all run through, set the funnel in test tube No.1 and add to the filtrate two drops of Mayer's reagent from the burette; if this produces a dense precipitate, as it should, add 10 or even 15 drops of the reagent, return to the filter, using the fluid that has filtered meanwhile, into No.1 to rinse No.2, returning all to the filter. Proceed in this way until the precipitate begins to be scanty, when the quantity of reagent added at once must be reduced accordingly, until finally it becomes a single drop. As the end of the precipitation is neared, allow nearly the whole of the liquid to pass through the filter before adding more reagent, and filter twice if necessary, to secure a perfectly clear fluid.

107. The reaction is taken to be complete, when the addition of a single drop, or at most, two, of reagent does not produce at once a turbidity in the fluid. It will often happen that one or two drops will produce a faint cloud, which disappears as it mixes with the rest of the fluid. If a larger quantity of reagent be added, a permanent turbidity, or even a precipitate, is produced, but this should be ignored. Uniformity of practice in fixing the end point of the reaction is, of course, indispensable. The operator should practice with solutions containing a known quantity of alkaloid, and so determine its equivalent as modified by his personal equation. If, at the close of a titration, it appears that the original solution was stronger or weaker than that recommended above (0.2 to 0.5%), a new solution should be made, and of a strength approximately of 0.5 per cent. and the titration repeated with this solution.

108. Hereth's Method (17), of titrating with Mayer's reagent consumes rather less time than that given above, and is carried out as follows:— Knowing

[illegible][illegible][illegible]

104. Bessie's letter (17) of 1894, which
Bessie's mother received from her in 1894
and is dated as follows: - Bessie

approximately the alkaloidal strength of the solution to be examined, provide half a dozen or more test tubes or vials, into each of which measure 10 c.c. of the solution. To the first, add a quantity of Mayer's reagent which is believed to be a little less than enough for the precipitation (make sure that such is the case, before proceeding further, by filtering and testing the solution with more of the reagent). To the second portion, add a quantity of reagent 5% greater; to the 3rd, a quantity 10% greater and so on. Let the tubes stand eight hours, then test a portion of the clear supernatant liquid from each, by a drop of the reagent. Amongst them, there will be some that will react strongly, others that do not react at all. The first one that fails to react, obviously, has received of the reagent, a little more than enough, and the amount of additional precipitate in the one preceding it in the series, will enable us to fix quite accurately the point at which precipitation would have ceased, had the titration been carried on in the usual manner.

109. If this method is to be adopted, it will be necessary, of course, to fix the value of the equivalent for each alkaloid empirically, by experiments carried out in the same manner, which would differ more or less, from those based on the ordinary procedure.

110. Gravimetric Determination by Mayer's Reagent. Results somewhat more exact and uniform may be obtained in the use of Mayer's reagent, if we collect and weigh the precipitate instead of depending upon the quantity of reagent consumed. The error would rarely be over 5 per cent. of the total weight, not an ideal exactitude of result, it is true, and yet close enough to give useful information. The reagent must be added in slight excess, and time given for complete reaction and separation of the precipitate; in the ordinary routine, say two hours. The precipitate is to be then collected upon a pair of mutually counterpoised filters, washed with the smallest practicable quantity of water, applied so as to wash the filters especially. When the filters have drained, press first between folds of filter paper, to remove most of the water, then dry at 100 degrees C. to a constant weight and weigh, or, after the precipitate is washed and drained, it may be dissolved in strong alcohol, evaporated in a tared vessel and weighed.

111. Titration of Tinctures, etc., with Mayer's reagent:- It is sometimes recommended to titrate directly with Mayer's reagent solutions prepared from tinctures or fluid extracts, by acidulating, evaporating off the spirit and diluting, if necessary, with water. Such a procedure may enable us to detect any notable

[illegible]

209. It will be noted in the foregoing, it will be necessary, of course, to the value of the evidence for each affidavit submitted, by a person or persons, one of the many persons, which would either have to be first shown to be a reliable person.

110. Gravimetric Determination of Water in Hydrocarbons: Results obtained from these analyses are given in the table. In the case of the hydrocarbons, it was found that the gravimetric method of determining water was not of sufficient accuracy. The error would vary from 0.1 to 0.2 per cent. of the total water, and in these cases the gravimetric method is not reliable enough to give the information. The results are given in the table. The results are given for complete reaction and for reaction of the hydrocarbons in the ordinary reaction, and are given. The gravimetric method is not reliable enough to give a pair of completely unhydrolyzed fibers, washed with the smallest possible quantity of water, applied to the water in the fibers. When the fibers are washed with the fibers, the first between 100 and 150 per cent. to remove most of the water, then dry at 100 degrees C. to a constant weight and weigh on after the reaction. This is washed and dried, it is determined by the gravimetric method, and the results are given in the table.

...the ... of ...
...the ... of ...
...the ... of ...

deficiency of active principles, but is liable to be misleading, since other substances besides alkaloids are precipitated by Mayer's reagent. Solutions prepared with strong alcohol or with ethereal solvents are less likely to contain such substances (albuminoids) but in general titration with Mayer's reagent should be practiced only on solutions so prepared that they can contain little besides alkaloidal salts.

112. It must be admitted, however, that direct titration, applied to galenical preparations, does not correctly indicate in most cases, their relative medicinal strength, and a titration and standardization at all.

113. Where several alkaloids are present in the drug, as is often the case, the titration method, whether with Mayer's reagent or with standard acid, can only be of limited application, unless preceded by a separation of the alkaloids. It may, however, sometimes serve, when the total alkaloid has been determined, to indicate the relative proportion of the constituents, if there are but two, as in *nux vomica*, and after all a standard based upon total alkaloid may be as rationally fixed by titration as by weighing.

114. Precipitation equivalents of Mayer's reagent: Only by experimental method can the correct precipitation equivalents of the several alkaloids be determined for practical purposes. If solutions are always made so as to contain very nearly 0.5 per cent. of the alkaloid and the titration is made in solutions always containing the same proportion of free acid, there should be with most alkaloids, but little variation in the titration equivalent and it is with these conditions in view that the accompanying table has been tabulated by Prof. Lyons and the column of "Practical Equivalents" should be used where the titration is conducted in the manner described above (105) and what follows. Dragendorff's figures are also given based upon titrations conducted in a somewhat different manner.

115. When the solution contains much less than 0.5% of alkaloids, closer figures will be obtained by using the "Corrected Equivalents" of the table after having deducted from the quantity of Mayer's reagent used, a correction which consists of a certain per cent. of the whole volume of fluid at the end of the titration. Thus, a titration of cocaine, suppose the volume before titrating to be 12 c.c., and that 5.25 c.c. of Mayer's reagent 1-20 have been required for complete precipitation. Then, at the end of the titration, the volume of fluid was 12- 5.25- 17.25 c.c. The correction by the table is 8% of this or 1.38 c.c. Subtract this from 5.25 and we have 3.87 c.c. as our corrected figure for quantity or the table after having deducted from the quantity of

Mayer's reagent used, a correction which consists of a certain per cent of the whole volume of fluid at the end of the titration. Thus a titration of cocaine, suppose the volume before titrating to be 12 c.c., and that 5.25 c.c. of Mayer's reagent 1-20 have been required for complete precipitation. Then, at the end of the titration, the volume of fluid was 12 plus 5.25 equal 17.25 c.c. The correction by the table is 13% of this or 1.38 c.c. Subtract this from 5.25 and we have 3.87 c.c. as our corrected figure for quantity of Mayer's reagent consumed. This, according to the corrected equivalent of the table (.0098), indicates the presence of .033 Grms. cocaine in the solution, instead of .0405, the figure we should have deduced by the use of the column of Practical Equivalents.

116. A second titration should be made, if time and material permit, with a solution concentrated so that 8 c.c. contain as much alkaloid as the 12 c.c. used in the first titration. In this case, if it were a question of concentration by evaporation of the aqueous solution, it would be better to abide by the figure already obtained, rather than expose the alkaloid to risk of destroying it, - a principle to be borne in mind in all operations in which we deal with chemical compounds so unstable as many of the alkaloids.

117. The last column in the table, based upon experimental data, is to facilitate calculations where the alkaloid is to be determined by the weight of the precipitate produced by Mayer's reagent. Multiply the weight by the mean value of the factor, to find approximately the weight of the alkaloid contained in the precipitate. Thus, a precipitate from a brucine solution weighs 93 milligrammes; the factor is stated to be 0.465 to 0.500. The mean of these is 0.4825. The quantity of alkaloid is therefore about 45 mg., or somewhere between 43.2 and 46.8 mg.

118. The reason why titration with Mayer's reagent is unsatisfactory is, in most cases, that the end of the reaction is not sharply defined, precipitation continuing long after the reagent is in excess. Better results could, no doubt, be obtained were there any simple method of determining the excess of the reagent after precipitation ceases. A plan suggested by Prof. Lyons and one he has employed with some satisfaction, consists in adding to the solution at first an excess of Mayer's reagent, filtering and adding to the clear filtrate, after the precipitate has completely drained on the filter, 5 c.c. of a solution of strychnine containing nine milligrammes to the c.c., titrating the excess of strychnine and so ascertaining the excess of Mayer's reagent present.

TABLE ON THE NEXT PAGE.

TITRATION EQUIVALENTS OF MAYER'S REAGENT N.1-20

Name of Results.

Alkaloid.

Aconitine----	Good	0.01350	0.0141	-----	-----	0.526-0.555
Atropine-----	Unsatis- factory	0.00625	0.0077	5%	0.0088	0.488-0.461
Berberine----	Good	0.02063	0.0263	-----	-----	0.500-0.520
Brucine-----	Fair	0.00985	0.0125	3%	0.0139	0.465-0.500
Chelidone--	-----	0.0084	-----	-----	-----	-----
Cinchonidine-	Unsatis- factory	-----	0.0070	-----	-----	0.266-0.303
Cinchonine---	Fair	-----	0.0071	-----	-----	0.290-0.300
Cinchonine---	Unsatis- factory	-----	0.0090	-----	-----	-----
Cocaine-----	Fair	-----	0.0078	8%	0.0098	0.406
Colchicine---	Fair	0.01580	0.0109	8 1-2	0.0149	0.625
Coniine-----	Unsatis- factory	0.00625	-----	-----	-----	-----
Emetine-----	Good	0.00945	0.0106	3%	0.0116	0.390
Gelsemine----	Fair	-----	0.0096	7%	0.0120	0.500-0.540
Hydrastine---	Fair	-----	-----	-----	-----	0.476-0.500
Hyoscyamine--	Unsatis- factory	0.00698	0.0116	-----	-----	0.400-0.454
Morphine-----	Unsatis- factory	-----	0.0128	-----	-----	0.478-0.526
Nepalline----	-----	0.01940	-----	-----	-----	-----
Nicotine-----	-----	0.00203	-----	-----	-----	-----
Pelocarpine--	Unsatis- factory	-----	0.0055	-----	-----	-----
Physostigmine	-----	0.00688	-----	-----	-----	-----
Quinine-----	Unsatis- factory	-----	0.0056	-----	-----	0.299-0.323
Sabadilline--	-----	0.01870	-----	-----	-----	-----
Sabatrine----	-----	0.01670	-----	-----	-----	-----
Sanguinarine-	Fair	0.00743	-----	-----	-----	-----
Strychnine---	Good	0.00835	0.0091	2 1-2	0.0102	0.363-0.385
Veratrine----	Fair	0.01480	-----	-----	-----	-----
neutral-nearly neutral solution must contain 3% sulphuric acid.						

120. Volumetric Determination of Alkaloids by Wagner's Reagent:- Although Wagner's Reagent precipitates the alkaloids very completely from their aqueous solutions, chemists generally, until quite recently, have entertained the impression that the precipitates are of too variable composition to make them available in quantitative work. The researches of Dr. Prescott and his co-laborers in laboratory work, during the past two or three years, have proved that this impression was not well grounded; that in case of certain alkaloids, if not of all, conditions of precipitation can be easily secured, which will give us compounds of perfectly definite and constant composition, and that it is easy to determine the iodine in these, by single volumetric tests.

121. Volumetric Estimation by Wagner's Reagent:- Prescott and Gordin (18), give the following general method of determining alkaloids by residual titration, after precipitating with Wagner's reagent in excess; To 10 c.c. of decinormal iodine solution (U. S. P.) diluted with a little water, add 1 c.c. of the acidulated alkaloidal solution and shake the mixture well for a few minutes. Should the precipitate separate out very quickly, leaving the fluid light yellow or greenish, the quantity of alkaloid is too large and the work must be repeated, using a more dilute alkaloidal solution, so that the solution, after separation of the precipitate, shall remain of a dark red color.

122. Having thus approximately ascertained the quantity of alkaloidal solution to use in the assay, repeat the experiment, using 25 c.c. of the decinormal iodine solution, until the and shaking, after addition of the accurately measured dilute alkaloidal solution, until the supernatant liquid is perfectly transparent, and of a dark red iodine color. (The iodine solution must be largely in excess throughout the work, hence, it will not do to add more of the reagent if it be found that the quantity used, was insufficient. The process in such a case, must be repeated from the beginning). An aliquot part of the liquid is filtered off and the excess of iodine in it determined by titration with decinormal sodium thiosulphate (U. S. P.). Subtract the number of c.c. used, from 25, to find the quantity of decinormal iodine solution required to precipitate the alkaloid. The following factors have been established experimentally. Each c.c. of the decinormal iodine consumed, corresponds with atropine, 3.6048 mg.; strychnine 5.5555 mg.; brucine, 6.5530 mg.; morphine, 9.4794 mg.; caffeine, 4.85 mg. (19)

123. Other volumetric processes that may be sometimes serviceable, depend upon the use of standard solutions of some of the other precipitants of alkaloids. Thus, coniine which is very imperfectly precipitated by Mayer's reagent, may be titrated with Sonnenschein's reagent (sodium phosphomolybdate), and this, indeed, admits of quite extended use. With our improved methods, however, of extracting the alkaloids directly from the drug and obtaining them thus in a pure form, these indirect methods of procedure have mostly fallen into disuse.

124. Better results, than those given by Mayer's reagent, are claimed and, no doubt, justly, by Mr. Thresh (20), from the use of a solution of potassium and bismuth iodine (16). The solution is to be used exactly as Mayer's reagent is, being added to the acidulated (Hce or other acid) aqueous solution, until it ceases to give a distinct precipitate. The precipitates separate promptly and the end of the titration is more sharply defined than with Mayer's reagent.

The following are the quantities of the several alkaloids named, which correspond with 1 c.c. of the reagent.

Aconitine-----	.00280	%	Atropine-----	.00388
Apomorphine-----	.00425	%		.00400
Berberine-----	.00206	%	Brucine-----	.00457
Caffeine-----	.00358	%		.00463
Cinchonidiene-----	.00253	%	Codeine-----	.00404
Cinchonine-----	.00272	%		.00428
Emetine-----	.00253	%	Narceine-----	.00416
Morphine-----	.00404	%		.00437
Quinidine-----	.00290	%	Theine-----	.00433
Quinine-----	.00273	%		.00448
Struchnine-----	.00496	%		

Special Methods of Separating Alkaloids in a State of Purity.

125. Scheibler's Process:- Precipitate the aqueous solution with phosphotungstic acid, collect the bulky precipitate, wash with water containing some phosphotungstic acid and ammonia. Rinse the washed precipitate into a flask, add caustic baryta or potassium carbonate to alkaline reaction and distill to obtain any volatile alkaloid. If the alkaloid is a fixed one, treat the precipitate with caustic baryta or lime and dissolve out the alkaloid with chloroform.

126. Wagner's method:- (21) Acidulate the aqueous solution with sulphuric acid and precipitate the alkaloid with excess of Wagner's reagent. Collect the precipitate, dissolve it in a solution of sodium thiosulphate (hyposulphite), filter, precipitate once more with excess of the Wagner's Reagent, dissolve the precipitate in excess of aqueous sulphuric acid, evaporate to dryness on the water bath, keeping the sulphurous acid in excess, until the hydriodic acid is all expelled. The alkaloid is left finally in the form of a sulphate.

127. Kippenberger's Method (22):- Precipitate the slightly acidulated aqueous solution with an iodine solution containing 12.7 grammes of iodine and 60 grammes of potassium iodide to the litre. Collect the precipitate on an asbestos filter, wash thoroughly with cold water, dissolve in a small quantity of purified acetone, dilute with water and shake with light petroleum (boiling point 30-50 degrees C.) first with addition of caustic alkali, then after rendering acid with hydrochloric acid. Draw off the aqueous solution, evaporate off the acetone at a gentle heat, add a few drops of sodium thiosulphate, to remove free iodine, finally, render the solution alkaline with sodium carbonate or with ammonia and shake out in the usual way with chloroform or other necessary solvent.

128. By Mayer's reagent, T. B. Groves (23), directs to collect the precipitate, wash slightly, suspend in water, add solution of silver nitrate (or lead of acetate) sufficient to decompose the precipitates. Excess of the reagent can easily be shown by testing a drop of the filtered fluid with solution of potassium chromate. The aqueous solution, after filtration, is to be rendered alkaline and shaken out with immiscible solvents. Prescott (24) directs to titrate the washed iodo-mercurate precipitate with stannous chloride solution and caustic potash added to strong alkaline reaction and then extract with an appropriate solvent. (If potassium carbonate be substituted for caustic alkali, strong alcohol may be used as the solvent).

129. Another plan suggested by Prescott, is to dissolve with iodo-mercurate precipitate in alcohol, adding acid, if necessary, and precipitating the mercury with hydrogen sulphide gas. The filtrate can be freed from iodine if this be desired, after expelling the excess of hydrogen sulphide, by adding excess of silver nitrate, filtering, adding hydrochloric acid to precipitate excess of silver and filtering again, the alkaloid, now being in the form of chloride.

130. By Phosphomolybdate of Sodium:- Exhaust the drug with acidulated water, make nearly neutral and precipitate the solution with solution of lead subacetate in slight excess; precipitate excess of lead from the filtered solution with sulphuric acid, cautiously added, partially neutralized with soda, filter, concentrate by evaporation; precipitate with sodium phosphomolybdate in slight excess, collect the precipitate, wash with a little water containing phosphomolybdic and nitric acid; mix the moist precipitate with excess of carbonate of calcium or barium, or with calcium or barium hydrate, dry at water bath heat and extract the alkaloid, which is now free, with alcohol or other appropriate solvent.

131. By Tannin:- Prepare an aqueous solution in the manner just described; neutralize accurately with solution of soda, add solution of tannin cautiously, avoiding excess and preserving the neutrality of the solution by successive additions of soda solution. (The following alkaloid require for complete precipitation, presence of an excess of acid;--aconitine, physostigmine, veratrine; and some others may be precipitated without loss from an acid solution, but this is the exception.) Collect the precipitates, wash slightly with water, mix with finely powdered litharge, or preferably with precipitated lead hydrate, or with zinc oxide and a little water. Heat on the water bath, with frequent stirring and renewal of evaporated water until the tannin is wholly removed, so that a portion of the mixture shaken with alcohol and filtered, yields a filtrate which does not darken in color, upon addition of ferric chloride. Dry the mixture, powder and extract the alkaloid with alcohol.

132. Separation of Alkaloids from one another by Solvents.

The comprehensive scheme of Prof. Dragendorff, (25), which will follow, will be of assistance in case it is desired to separate one alkaloid from another. The alkaloids,

being in aqueous solution containing free acid, shake with successive portions of petroleum benzin. Besides volatile and fixed oils, camphors, etc., the solvent will remove (a) crystalline, capsicine, peperine (in part) and picric acid, (in part); (b)-- Amorphous, certain constituents of black hellebore and products of decomposition of aconitine, and (c) Volatile, phenol.

133. Shake the still acid fluid, with several successive portions of benzol. This will remove absinthin, cantharidin, cascarillin, caryophyllin, cubebin, digitalin, elaterin, populin, santonin, and the alkaloids, caffeine, colchicine, with traces also of berberine, delphinine, physostigmine, and veratrine: Also, remnants of piperine and of picric acid.

134. Treat the acid fluid next with chloroform, in the same manner. This solvent will remove convallamarin (in part), digitalin, helleborein, picrotoxin, saponin (in part), senegin (in part), smilacin and syringin, with the alkaloids cinchonine, jervine, narceine, (in part), papaverine, theobromine, and traces of brucine, delphinine, narcotine, physostigmine, and veratrine, also, remnants of some of the substances imperfectly removed by benzol.

135. Next, shake the solution once more with petroleum benzin to remove traces of chloroform, reject this portion, add ammonia to alkaline reaction and shake with fresh portions of petroleum--benzin, which will now remove (a) fixed alkaloids, brucine (partly), cocaine, emetine, quinine, sabadilline, strychnine, veratrine; (b) volatile alkaloids, aniline, coniine, lobeline, nicotine, sarracenine, sparteine and trimethylamine.

136. Shake the solution next, with benzol, which removes the remnant (generally considerable) of the fixed alkaloids partly taken up by the benzin, also aconitine, atropine, cinchonine, cinchonidine, codeine, lyoscyamine, napelline, nepaline, thebaine, with remnants of brucine, delphinine, narcotine, physostigmine, and veratrine.

137. From the solution, chloroform will remove morphine (in part) with the remainder of the cinchonine, narceine and papaverine, and A glylic Alcohol in turn will remove salicin, solanine, and remnants of convallamarin, saponin, senegin, morphine and narceine. The fluid of powdered glass will still yield to chloroform curarine.

138. On Acetic as a Substitute for Ethyl Alcohol in extracting the active principles of some officinal Drugs. by E. R. Squibb. (20)

In the proposed substitution of acetic acid for alcohol as a menstruum for extracting and a vehicle for preserving administering the active principles of drugs in medicine, the very first question is as to the therapeutic equivalency. That is, if the presence of the necessary amount of acetic acid in fluid extracts, etc., can be shown to be therapeutically objectionable, or more objectionable than the necessary amount of alcohol, then it is not proper to make the substitution.

139. But acetic acid has been used for the extraction of cantherides, colchicum, ipecac, opium, squill, etc., without developing any known therapeutical objections, and in a limited experience in the extraction of spices, and of some drugs for veterinary use, it gives extracts practically identical with those of alcohol. The acid has universally accepted food value, not only as a hydrocarbon, but as a mild acidulous aid in primary processes of digestion, but, in the small quantities that would be present in the doses of fluid extracts, it would be practically inert, or at least, as nearly inert as the alcohol which it would replace.

140. Its properties and value as an antiseptic, detergent and preservative are well known, but, whether it would be present in sufficient proportion to preserve such preparations from change during a long time, has not yet been determined. Dr. Squibb has preserved samples for two years without change, these being the oldest samples on hand.

141. Fluid extracts made with acetic acid menstrea are much more loaded with inert extractive matter than when made with alcoholic; and this is a disadvantage, but hardly hurtful, nor more than an inconvenience occasionally.

142. In compounding prescriptions, the acetic acid menstruum has a slight general advantage over alcohol in the amount of precipitation on dilution and on mixing, and in the character of the precipitates, these being more soluble, and containing less resin and fat and probably less of the active principle. In administration, there are similar slight advantages over alcohol in that the dilutions with water at the moment of taking the doses are less muddy and unsightly, while the acidulous taste is less disagreeable.

143. From these considerations and from all that is yet known, it is claimed that there are no serious therapeutical or administrative objections to a more extended and more general trial of this proposed substitution.

144. The chief, though possibly not the only reason for a careful consideration of this proposed substitution is economy in the use of alcohol by the use of cheaper solvent. The alcohol of the U. S. Pharmacopolia 91% by weight costs about \$2.40 per gallon of 6 lbs. 13- ounces avoirdupois, or, say, 35- cts. per avoirdupois pound or, say, 77- cts. per 1000 Gm.

145. The acetic acid of the U. S. P., 36% costs about 10 cts. per pound, or say, 22 cts. per 1000 Gm. When diluted to a strength of 10%, which is the strength most frequently required as a menstruum, the cost is less than 3 cts

per pound, as against 18 cts, per pound of diluted alcohol of the U. S. P., with which this 10 per cent. acid corresponds-- The alcoholic menstruum costing six times as much to accomplish the same extraction.

146 In order to measure with a fair degree of accuracy the comparative capacity of alcohol and acetic acid for extracting the active principles of drugs, parallel extraction of the same drug were made under the same conditions and at the same time.

147. Nux Vomica and cinchona, being two drugs difficult to extract, were used in the work. The drugs were in No. 60 powder for the alcoholic extraction and moderately coarse for the acid. The repercolation process was used for the extractions, and siphon percolators, and these were so managed that the mass of solid contents was kept entirely filled with the menstruum, as indicated by a stratum on top of the mass and the percolate rising in the well tube to near the level of the menstruum on top. This mass in saturation, was allowed to stand covered for 48 hours, when the siphon was put in place and started, being held so high as to draw only from the upper part of the well tube, and at the rate of dropping so slow as to yield two to three fractions of 100 c. c. each, in the 24 hours.

148. The results of all the work showed that the acetic acid extracted the drug in a much less time than the alcohol and obtained a higher per cent of extractive. Then, by the substitution of acetic acid for alcohol, one half the cost of grinding, and five-sixths of the cost of menstruum are saved, an equivalent product being obtained in larger quantity. While acetic acid has not been given much show in regular fluid extracts, it is now employed to fair extent in preparations for veterinary use.

149. Assay of Galenical Preparations:- Fluid extracts; To ascertain the alkaloidal strength of the fluid extract, we may generally adopt one of the following general methods of which, some, as (a) or (f), are recommended for usual routine; some, as (b) or (j), are of only limited utility. (a) (Prof. Lyons). Add ammonia and shake directly with an immiscible solvent, wash the alkaloid from this into acid water, separate, add ammonia and shake out once more with the appropriate solvent. (b)- Dilute the fluid largely with water, add excess of lead subacetate and filter; Add sulphuric acid drop by drop to precipitate excess of lead, filter once more, concentrate, if necessary, after rendering nearly neutral, add ammonia and shake out with chloroform. (c) (27) Add to the fluid extract, ferric chloride in excess, then sodium bicarbonate sufficient to produce a stiff magna. Triturate this with successive portions of chloroform until the whole of the alkaloid is removed. This may be sufficiently pure for weighing, but usually requires to be washed out with acid water and extracted from this once more by adding alkali and shaking out with appropriate solvent. (d) (28) Dilute fluid extract with equal volume of water to which Q. S. dilute acid have been added. Evaporate off alcohol on water bath, cool and filter; use liquid either for gravimetric or perforator method. (e) (29) Add to the fluid extract, ten to twenty times its volume of

weak Prollins Mixture and shake together for some time. Pour off an aliquot part of the ethereal fluid and treat as in the assay of a drug by Prollins Mixture. See (160).

(f) (30) Mix the fluid extract with oak saw-dust, dry at a low temperature, treat the residue exactly like a crude drug, with Prollins Mixture, etc. See p. (159). (g)

Evaporate off the alcohol at a low temperature, add plaster of paris mixed with a little sodium bicarbonate, allow the mixture to set and harden; When sufficiently dry, pulverize and extract the alkaloid by hot repercolation, or else by simple maceration, with ether, petroleum ether and chloroform (mixed), or other appropriate solvent. The alkaloid must be purified as in process (C). (31) Extract the alkaloid directly from the fluid extract, by adding caustic soda, and shaking out repeatedly with ether, remove traces of aqueous fluid containing alkali by addition of plaster of paris; the ethereal solution is then titrated directly with centinormal acid, using lodeosin as an indicator.

The method is not applicable if chlorophyll, fixed oils or salts of ammonia are present. See (165) and (167). (1).

Add a little water and a few drops of dilute acid, evaporate to nearly dryness, make up to suitable volume and titrate with Mayer's reagent. (j).

Pour the fluid extract into nine times its volume of water containing acid, filter, precipitate the alkaloid from an aliquot part of the filtrate, by adding ammonia, collect on a tared filter, wash, dry and weigh, or else, after drying, dissolve in an appropriate solvent. Evaporate and weigh. (k). Introduce the fluid extract without previous treatment into a perforator, render acid and wash thoroughly with petroleum ether, then render alkaline and extract the alkaloid with an appropriate solvent.

(l). Add to the fluid extract, a few drops of acetic acid, then an equal volume of water, evaporate at a temperature not exceeding 50° C., to expell alcohol, remove chlorophyll etc., by repeated washing with petroleum ether, recovering from this any alkaloid that may have been taken up, by treating with a little dilute acid; Mix the acid solutions, wash once with chloroform, unless the alkaloid is one taken up by that solvent from acid solutions, in which case use ether, make alkaline and remove alkaloid with chloroform or other appropriate solvent.

(m). Put into a two-ounce vial, one gram of freshly slaked lime, add 5 c. c. of fluid extract and immediately 45 c. c. alcohol, shake well for a minute or two to insure complete solution of the alkaloid, filter, render faintly acid with sulphuric acid and filter once more, evaporate off the alcohol to obtain an aqueous solution comparatively free from inert matter, from which the alkaloid may be extracted, after washing once or twice with ether, by rendering alkaline and washing out in the usual way.

150. Routine of Process 149 (a). practiced by Prof. Lyons. The details will vary somewhat, according to the solvent chosen. The following is the method as used.:- Measure into a one-ounce prescription vial, having a square shoulder and a good lip, exactly 5 c. c. of a mixture of chloroform one volume, ether three volumes. (Use pure ether preferably whenever that solvent can be relied upon

to extract the alkaloid). Add water of ammonia 10% five drops and immediately shake together, observing whether there is any tendency to emulsionize, in which case, let the shaking be gentle. Continue the shaking 30 seconds and then let separate and pour off the ethereal fluid into a second vial containing 3 c. c. water and 1 drop water of ammonia, add to No. 1, 20 c. c. pure ether; if the contents of the vial seem inclined to become syrupy, add 1 c. c. dilute alcohol, but this is not often necessary. Shake both bottles a few seconds and then let separate. After 2 minutes 9 longer, if necessary) pour off the ethereal fluid of No. 2 into a third vial; that from No. 1 into No. 2: Add c. c. fresh ether again to No. 1, which should remove the last traces of the alkaloid, but this must be ascertained by testing a drop of the residual fluid after acidifying with Mayer's reagent.

151. Pour into vial No. 3, three c. c. per cent hydrochloric acid shake well 30 seconds, let separate and pour off the ethereal fluid into a fourth vial containing 2 c. c. water acidulated with hydrochloric acid. The ether which has been added to No. 1, is passed in succession through the series in regular order, and finally through a fifth containing 2 c. c. of water, before being finally rejected. The result will be that we have in No. 1 and No. 2, nothing of value, in No. 3 nearly all the alkaloid in acid solution in No. 4, an acid fluid containing a little alkaloid and in No. 5, water with possibly traces of alkaloid. Now, add to No. 4, twenty c. c. of chloroform-ether, (pure ether, if this will answer the purpose) and a few drops water of ammonia, shake well, let separate and transfer the ethereal fluid to No. 3. Also, add to No. 3, water of ammonia, in excess (15 drops or more), shake 30 seconds, making sure the ammonia is in excess (test the vapor with red litmus paper), let separate and transfer the ethereal fluid to No. 5, to which a drop or two of water of ammonia has been previously added.

152. Wash the contents of the vials No. 4 and No. 3 (in this order) in succession with two or three fresh portions of ether, making sure that all the alkaloid is extracted. Pass the ether in each case, finally into No. 5, which serves merely as a wash bottle, and from this, after complete separation into a tared beaker, in which it is evaporated to dryness on the water bath and finally weighed. Where chloroform has been used as a solvent, redissolve the residue in alcohol and evaporate again, to expell the last traces of chloroform. Finally the residue may be dissolved in ether, or in alcohol and the alkaloid in it, titrate with standard acid.

153. The above process has been given in minute detail because Prof. Lyon claims it always gives satisfactory results. Emulsionizing is not liable to occur, while the ether-chloroform removes the alkaloids almost as certainly as the pure chloroform does. It may be necessary sometimes, to carry through the entire process with ether-chloroform, or to vary it by using pure chloroform (10 c. c.) in the first washing, adding immediately, ether enough (20 to 25 c. c.) to bring it to the surface. Petroleum-ether may be used in the case of a few drugs. A mixture of chloroform and petroleum-ether may prove as generally useful a

[illegible]

1. The first of the three is the fact that the Government has been unable to secure the necessary funds to carry out its policy of maintaining the value of the dollar at its present level. This is due to the fact that the Government has been unable to secure the necessary funds to carry out its policy of maintaining the value of the dollar at its present level.

38 solvent as that above recommended. Whatever solvent is used, the routine of process will be the same.

THE HISTORY OF THE
CITY OF BOSTON

FROM THE FIRST SETTLEMENT
TO THE PRESENT TIME
BY
JOSEPH NEALE
OF BOSTON
IN TWO VOLUMES
VOL. I.
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154. Abbreviated Process:- If the operator is willing to depend upon the alkalimetric test alone, the above process (151) and (152) may be abbreviated as follows. Proceed as before, up to the point where the ethereal solution is treated with acid. Instead of decanting into a third vial collect the several portions of ethereal solution in a beaker, evaporate by gentle heat to dryness and determine the alkaloid by alkalimetry. (90) or (91). Subsequent separation and weighing of the alkaloid may be made, if desired.

155. The acid solutions contained in vials No. 3 and No. 4 (151), can be transferred to a perforator, rendered alkaline, and the alkaloid extracted (52 and 53), without any preliminary washing with petroleum-ether.

156. Routine Alternative Process (149 a). If the solvent has a higher specific gravity than the fluid - extract (e.g. pure chloroform), a plan differing in detail must be adopted as follows:- Put into a small separator, 10 c.c. of the fluid extract (a smaller quantity, if it is rich in alkaloid), add a few drops of water of ammonia and 20 c.c. chloroform, agitate carefully, add a little water (3 to 8 c.c.) agitate once more, let separate and draw off the chloroform into a second separator containing 5 c.c. water to which has been added a few drops of dilute sulphuric acid (1:5), agitate and, when the chloroform has separated, draw it off into a 3rd separator containing 5 c.c. acidulated water. Agitate and separate the chloroform which should now contain no traces of alkaloid (prove this by evaporating a few drops on a watch crystal, adding a small drop acidulated water and testing with Mayer's reagent). Treat the contents of separator No. 1 with 10 c.c. fresh chloroform, which is to be passed through the series in succession, and the same process repeated as long as alkaloid is taken up from No. 1.

157. When the exhausted chloroform has been removed (it is to be preserved for redistillation), put into separator No. 3, 15 c.c. fresh chloroform and a few drops of ammonia, shake together and draw off both and aqueous fluid into No. 2; add more ammonia, if necessary, to make alkaline. Shake together, let separate and draw off the chloroform into No. 3, in which has been placed 5 c.c. of water. Wash out the contents of No. 2 with several additional portions of chloroform, passing each through No. 3, and finally into a tared beaker. Evaporate of the chloroform, dry moderately on water bath, take up the residue with acid free alcohol, dry completely and weigh. Finally, determine the alkaloid by titration with standard acid (90) and (91). Of course, the modifications described in (154) and (155) are equally applicable to this alternative process.

158. Detail of process of Prof. J. U. Lloyd:- In a flat bottomed porcelain mortar with a good lip, mix 5 c.c. of the fluid extract with 1c.c. solution perchloride of iron, add an equal mixture of dry ferric hydrate and sodium bicarbonate, with constant stirring, until a stiff magma results. Abstract the magma by repeated titration with chloroform using first 20 c.c. and then three portions of 10 c.c. each making up, in all, exactly 50 c.c. Divide into two equal portions. The first portion is placed in a separator

with spherical bulb and extracted with three successive portions (10 c.c.) of 2% sulphuric acid. Collect the acid solutions in a second separator, make alkaline with ammonia, wash out the alkaloid, by rotating better than shaking, with three successive portions of chloroform (10 c.c.) Evaporate the chloroform in a tared dish to constant weight and dry and weigh. (The second portion of the original chloroformic extract may be used for an independent acidimetric determination.)

159. Detail of Process of F. A. Thompson. (149 f.) Place in a capsule, 5 to 7 grammes of oak saw-dust and pour gradually into this, 10 c.c. of the fluid extract. (If it contains more than 1% alkaloid, dilute with 50% alcohol to reduce it to approximately that strength, and take 10 c.c. of the diluted extract, nothing of course, exactly how much this represents of the original extract). Mix thoroughly with the saw-dust, which must be in sufficient quantity to absorb the fluid pretty well, dry at a temperature not exceeding 45 degrees C., transfer to a 4 oz. prescription vial, add 100 c.c. of modified Prollins mixture (13), shake frequently during 15 or 20 minutes, pour off exactly 50 c.c. of the ethereal fluid and complete the assay exactly as described in (62) or (72). This method is certainly to be preferred to that of Steiglitz (149 e) in which there is some difficulty in deciding just what quantity of the ethereal fluid should be taken as an aliquot part (e.g. one half) of the fluid extract taken.

160. Prof. Lyons states that he has sometimes adopted a plan similar to that of Steiglitz, for rapid approximate work, as follows: To 5 c.c., of the fluid extract, add 5 c.c. of ammoniated alcohol (alcohol nine volumes, stronger ammonia one volume), followed immediately by 45 c.c. ether, shake well two or three minutes, let separate and pour off the whole of the ether which may be assumed to contain 95% of the alkaloid present, and is to be treated as in the ordinary assay, by Prollins mixture (72). The plan of (150) et seq. is preferable in that it does not consume so much time.

161. Other absorbents besides saw-dust, have been employed; absorbent cotton by some infusorial earth, absorbent paper, vegetable fiber in the form of twine cut in short pieces, etc. The saw-dust seems to fill the requirement best of all for reasons that need not be enumerated. Care must be taken however, in selecting a saw-dust, using one containing as little tannin as possible and one as free as possible from soluble matter, particularly of a resinous nature. Hence, pine saw-dust is not to be used unless first extracted with alcohol. Well washed saw-dust from hard-wood of any kind (even oak) is good. It should not, however, be too fine. Filter paper is liable to soften and mat together, but if cut in small pieces and used in quantity sufficient to absorb the mixture without being too much softened, it answers a good purpose, as does the chopped string or rope. Sand or broken glass cannot be recommended; pumice-stone broken into fragments about size of hemp-seed, is better, and is to be preferred to infusorial earth.

162. It is possible to combine the use of ferric chloride (Lloyd), or of lead acetate with that of saw-dust or other absorbent. The ferric chloride is to be added to the fluid extract before it is mixed with the solvent. It may be necessary to add a little more ammonia than that contained in the pröllins mixture. There must be enough to decompose both alkaloidal salts and the iron or lead compound.

163. Absorbent cotton is used by F. B. Raynale, in the following manner:- Pack somewhat firmly in the bottom of a four ounce round shouldered, wide-mouthed, prescription vial, two grams of absorbent cotton. Into the center of this, place by means of a pipette, 10 c.c. (or a smaller quantity, if rich in alkaloid) of the fluid extract. When this is completely absorbed by the cotton, add a 100 c.c. of Pröllins mixture modified (13) and shake occasionally during half an hour. Then take out an aliquot part of the ethereal fluid and treat as in (62) or (72).

164. Kebler, as a routine process, adds to 12 c.c. of the fluid extract, 12 c.c. of water, adds 30 grams chloroform, 90 grams ether, shakes, adds ammonia in excess, shake frequently during 30 minutes, then takes 50 grams, equivalent to 5 c.c. of the fluid extract and extracts the alkaloids in the usual way.

165. Routine of process of J. Katz. (149 h). Put into a separator, 10 c.c. of the fluid extract (25 c.c. of the tincture) which should contain about 50% (by volume) of alcohol, add 1 c.c. of a 33% solution of sodium hydrate and 50 c.c. of ether and shake well five minutes and let separate. Draw off the aqueous fluid into a two ounce vial, add to the contents of separator, 3 c.c. of water, shake, let separate and draw off the water into the vial, shake out the contents of the vial twice with ether containing 10% of alcohol (25 c.c. each time). The first portion is shaken into a second vial with 1.5 c.c. of water and then decanted into a flask to which has been transferred the ether from the separator. The ether is then deprived of traces of alkaline water by shaking with plaster of paris (2 or 3 grams) and is then filtered into a glass stoppered flask containing 50 c.c. of distilled water. The second portion of alcoholic ether is washed like the first, with 1.5 c.c. water and then used to wash the flask containing the plaster of paris, and the filter previously used, being finally mixed with the rest of the ether. The alkaloid is then titrated with centinormal acid using as an indicator, three drops of an alcoholic solution of iodeosin 1:250.

166. The method is recommended by its author on account of dispensing wholly with the application of heat. The weak point in it is the possibility that ammoniacal salts may be present in the tincture and so make it assay high in alkaloid. The ethereal solution can be evaporated surely without harming the alkaloid, unless it be a volatile one, and the titration after evaporation of the solvent, would be much more conclusive, although this modification deprives the process of its one unique feature.

167. Tinctures containing chlorophyll, fat or fatty acids, must be deprived of these before extracting (as above) with ether, (the latter would otherwise appear in the result,

as alkaloid). They are removed by mixing the tincture with water acidulated with sulphuric acid, shaking with talcum during several hours and filtering. The filtrate may be further washed once with petroleum-ether to remove the last traces of these objectionable bodies.

168. If the alkaloid is one not easily soluble in ether, it is necessary to use, as a solvent, a mixture of chloroform and ether. Three portions of the solvent are used, of respectively 30, 15, and 15 c.c., but these are washed, not with pure water but with a 30% solution of sodium chloride, since with pure water, emulsification is liable to occur.

169. Tinctures, wines and elixirs are to be treated in general like fluid extracts, but the volume of fluid may be generally reduced considerable with advantage, by evaporation at a low temperature, as a preliminary step.

170. Syrups may in some cases be assayed by adding alkali and shaking out repeatedly with chloroform, ether being added to facilitate separation, but in many cases it is necessary to dilute the syrup, precipitate the alkaloid with Wagner's reagent and recover it from the precipitate (126).

171. Solid extracts are to be converted into fluid extracts by dissolving in dilute alcohol where that is practicable. In many cases, they cannot be dissolved as a whole and in such cases, special procedure must be used to obtain a solution. If the dilute alcohol yields a turbid mixture having only minute suspended particles of undissolved matter, we may simply add saw-dust, dry and proceed according to (159).

172. If the extract is an aqueous one, heavily loaded with gummy matter, we may exhaust it with alcohol according to the following procedure:- Treat 2 grams of the extract in a beaker with 5 c.c. dilute alcohol, add 15 c.c. strong alcohol to precipitate the gum, stir until the gummy matter separates, decant into a flask or vial, re-dissolve the gum in 3-5 c.c. water, add alcohol, drop by drop to the point of incipient precipitation; then add 10 c.c. strong alcohol to re-precipitate the gum. Repeat this process once more, if necessary; (test the gummy residue for alkaloid, by Mayer's reagent). The united alcohol solutions may now be concentrated by evaporation to obtain a solution suitable for extraction of the alkaloid.

173. In the case of alcoholic extracts heavily loaded with chlorophyll, fat or resinous matter, the following method will be found a good one. Soften the extract by warming in a beaker with a little dilute alcohol. Add to the syrupy extract a few drops of dilute sulphuric acid and treat with successive portions (5-10 c.c.) of ether, pouring these off into a separator until the most of the chlorophyll, etc., has been taken up. Pour into the separator 3 c.c. water with five drops of 10% sulphuric acid, shake, let separate, draw off the acid fluid into the capsule containing the residue of the extract, which will now be almost wholly soluble in water. Remove the solution to separatory funnel, wash once or twice with fresh ether to remove any chlorophyll still remaining, separate, render alkaline and shake out with ether or some appropriate solvent.

174. Method of L. Vuittalie (32) :- Dissolve 3 grams of the extract in exactly 20 c.c. of water containing 5 drops of 10% sulphuric acid, add 10 c.c. solution of lead acetate (10%), allow the precipitate to settle and filter the solution. Measure off 16 c.c. of the filtrate into a separatory funnel and add 40 c.c. of a mixture of ether 25 volumes, chloroform 4 volumes and water of ammonia one volume. Shake well for a minute or two, make up the ether-chloroform layer to its original volume of 40 c.c., shake again for one minute and let separate. Evaporate 25 c.c. of the clear ethereal solution, representing one gram of the original extract, and determine the alkaloid in the residue by alkalimetry (30).

Method of E. Dieterich (33) :- Mix two grams of the extract (1 gram in case of nux vomica) with 3 c.c. of water, add 10 grams coarsely powdered lime forming a crumbly mass which is introduced into a displacement apparatus and extracted with ether, of which 30 grams may be used. The re-percolation is continued from 30 to 45 minutes in case of aconite, belladonna and henbane; an hour and a half in case of nux vomica. The ethereal solution of the alkaloid is transferred to a tared dish or beaker, the last portion being rinsed out with a little fresh ether, 1 c.c. of distilled water is added, and the ether evaporated at a temperature not exceeding 30 degrees C. taking care to avoid proximity of volatile acids like hydrochloric, nitric or acetic. The residue, weighing 1.5 grams, is dissolved in 0.5 c.c. alcohol, sp. gr. 0.892, 10 c.c. of distilled water added, and the solution titrated with centinormal acid, using rosolic acid as indicator.

176. The method just described has been justly criticized owing to the liability of loss of alkaloid from the action of lime. It certainly has no advantage over the other processes given.

177. Method of H. Beckurts. (34) The original process consisted in dissolving, 2.5 grams, in a mixture of alcohol 3 c.c. and water 6 c.c., adding 1 c.c. water of ammonia and shaking out with three successive portions of 20, 10 and 10 c.c. chloroform and determining the alkaloid by alkalimetry. In the case of extracts containing chlorophyll, he now advises the following procedure: (5) Dissolve 5 grams of the extract in 50 c.c. of alcohol, sp. gr. 0.892, adding baryta water to make up volume to 150 c.c. allow to deposit, filter, and precipitate excess of baryta by carbon dioxide. Filter evaporate 75 c.c. of the filtrate (equivalent to 2.5 grams of the extract) to a syrup, dissolve in a mixture of 6 c.c. water and 3 c.c. alcohol and 1 c.c. water of ammonia; shake out with chloroform as above and determine the alkaloid by alkalimetry.

178. Method of O. Schweissinger and G. Sarnow (36):- Dissolve 2 grams of the extract in 8 c.c. water of ammonia, shake out with 40 c.c. of a mixture of chloroform 3 volumes and ether 5 volumes. Let separate and, after half an hour pour off exactly 20 c.c. of the chloroform ether, corresponding with one gram of the extract; evaporate and determine alkaloid by alkalimetry. Obviously the method cannot be used

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without modification in examining extracts containing chlorophyll. Otherwise it has the advantage of rapidity of execution.

179. H. M. Gordin (37) states that from a theoretical point of view one of the best, if not the best method of estimating alkaloids, is undoubtedly the alkalimetric estimation of their basicity. The only drawback to this method has always been the fact that owing to this basicity being very weak, the acid combined with the alkaloid, reacts with regard to most indicators and particularly phenolphthalein as if it were free. A large number of indicators have been proposed in order to make the end reaction sharp and distinct; but any one has had experience in the alkalimetric estimation of alkaloids knows well that in no case is the end reaction sharp and distinct, as it is for example in titrating sulphuric or hydrochloric acids with standard alkali. This indefiniteness of the end reaction makes a theoretically faultless method of very little practical value. The following simple improvement makes it possible to estimate all salt-forming alkaloids with as much sharpness as is obtained in inorganic alkalimetric analysis and admits of the use of phenolphthalein as indicator in all cases where carbonates, etc. are absent. This improvement consists in precipitating the alkaloid after it has been taken up with an excess of standardized mineral acid, by a slight excess of some delicate reagent like Mayer's or Wagner's. Whatever the composition of the precipitate as regards mercury or iodine, will be, the alkaloid always separates as a salt and therefore takes up an amount of acid which is equivalent to the combining weight of the base. Making up the mixture to a certain volume, shaking until the precipitate separates out, filtering off half, discolorizing with solution of sodium thiosulphate in case of Wagner's reagent, the excess of the acid can be accurately determined by the aid of standard alkali, using phenolphthalein as indicator. The alkaloid having been removed, the estimation can be carried out with the same sharpness as is obtained in ordinary alkalimetric analysis.

180. In order to obtain very good results, the acid and alkali should be standardized for each alkaloid, by a weighed out sample of that alkaloid and proceeding as above; otherwise, the results will always be a little too high. This is due to the fact that in the presence of organic matter some iodine of the potassium iodide of the reagent is set free and an equivalent amount of acid disappears. This can be proven by dissolving some alkaloid in acidulated water, adding a little potassium iodide and letting stand 3 or 4 hours. If the liquid be then tested with starch, the presence of free iodine can be easily shown. Another advantage of this method is that by precipitating the alkaloid, a good deal of foreign matter which generally accompanies alkaloids when these are obtained from extract or tinctures, will also be thrown out, the excess of acid remaining in the filtrate.

181. Method of Prescott and Gordin. (38) The final alkaloidal solution obtained by whatever mode of extraction, but always representing a definite quantity of drugs to be assayed, is poured slowly and with constant stirring into a flask holding 100 c.c., in which has been previously drawn

20 to 30 c.c. of the standardized solution of iodine and 1 or 2 c.c. of dilute hydrochloric acid (U. S. P.). The flask is then filled up to 100 c.c., stoppered, and well shaken until the periodide has separated out. The supernatant liquid is to be perfectly transparent, but of a red color. Fifty c.c. are then filtered off, and in this portion the excess of iodine determined by means of standard sodium thiosulphate. The amount of iodine consumed, multiplied by the proper factor, gives the amount of alkaloid present in the quantity of drug taken.

182. For accurate, expedient and cheap assaying of fluid extracts, Nagelvoort (39) recommends the following:- Weigh into a porcelain or other small dish, 3 grams of the fluid extract, add 5 c.c. water and expell the alcohol, transfer to a medicine bottle of about 100 c.c. capacity, add 60 c.c. pure ether, and make alkaline by adding small quantities at a time, of a 5 or 10% solution caustic soda, verifying the alkalinity by litmus paper and avoiding excess. Shake the contents of the well corked bottle vigorously for a minute or 2 and add 2 grams of powdered tragacanth. Shake again for another minute, give the small globules of tragacanth mucilage, time to settle, decant 40 c.c. (equal to 2 grams of fluid extract) of the clear Fluid into an Erlenmeyer flask of known weight, distill the ether, add distilled ether to common stock, dry the alkaloids at about 50 degrees C. in a current of air, to constant weight. Multiply by 50, to obtain the percentage and the assay is finished.

183. If a volatile alkaloid be present in the drug, it will generally be noticed by its odor, at whatever point of the operation it is liberated from its combination, by the alkali. Should its presence be thus detected or suspected, it may be conveniently isolated by adding excess of lime or baryta, and distilling the liquid. The alkaloid can be fixed in the distillate by adding a slight excess of hydrochloric acid, and after concentrating the liquid to a small bulk, may be liberated by adding a large excess of caustic alkali and extracting by agitation with ether.

184. All methods in which an aliquot part of an immiscible solvent is taken to represent the corresponding aliquot part of the drug or extract, must be taken as only approximate. The practical man, even though a chemist, is willing to sacrifice exactness when good approximate results can be reached without expenditure of time required for exact determinations. Majority of chemists prefer plan of dissolving extract in dilute alcohol and if a reasonably clear solution results, treat as in (150); otherwise, adding saw-dust after the method of Thompson (159). When the extract contains chlorophyll, the method of (173) is preferable, although extraction with acid water and filtration will often give a solution containing the whole of the alkaloid, which can be rendered alkaline and shaking out with ether or other approximate solvents.

ACONITE.

185. Description of drug:- The tuber of *Aconitum Napellus* is almost napiform, abruptly tapering about the thick-

ness of a finger at the top, which is tuberculated; externally dark brown, wrinkled longitudinally at the lower portion, stem scars visible, rootlets usually detached; fracture short, horny or starchy, exhibiting sometimes a spongy or resinous, white, grayish or brownish tissue; taste at first, sweetish, then acrid and tingling. This peculiar tingling sensation on the tongue is one of the most prominent characteristics upon which the toxicologist depends for the recognition of this drug and its preparation. At the upper portion of this drug root, there often projects a lateral branch connecting a second tuber which is an offspring of the other. A cross section of the root shows a thick bark and a pith in the form of a star, the two being separated by a nucleus sheath; the cambium, following the outline of the pith, is also three to seven rayed and at the terminal basal extremities of each ray are found small groups of vascular bundles; these, however, are inclined to follow the whole cambium line.

186. Active Constituents :- There is as yet much to learn about the alkaloids of aconite. They are exceedingly unstable bodies, liable therefore to undergo changes in the process of extraction, even when these are conducted with extraordinary care. The principal constituent is aconitine $C_{33}H_{45}NO_{12}$, forming about $1/3$ the total alkaloid of the root. This is white, amorphous and lumpy, but with difficulty may be obtained in rhombic tabular crystals; almost insoluble in cold water, but soluble in ether, alcohol and dilute acids. The most recent researches of Dunstan, Unney, and others indicate the presence of aconine and napuline as the remaining alkaloids of aconite. However, our knowledge of them is not satisfactory.

187. Practical Manufacture of Crystallized Aconitine:- Of the various processes that have been proposed perhaps the best is the following : (40) Exhaust the powdered drug with mylic alcohol (fusel oil) by maceration and percolation, extract the alkaloid by shaking repeatedly with highly diluted sulphuric acid; remove traces of amylic alcohol from the aqueous solution by shaking with ether, and warm to expell dissolved ether; precipitate the alkaloid with sodium carbonate, collect the precipitate and dry on blotting paper without heat, boil the crude alkaloid with pure (alcohol free) dry ether and set aside to crystallize. The crystals thus obtained must be washed with a little cold ether to remove amorphous alkaloid.

188. The aconitine thus prepared represents as nearly as possible the alkaloid upon which the activity of aconite depends, but it is a curious fact and apparently well established that if this alkaloid is converted into a nitrate and from this into a crystallized be prepared, this last will be physiologically six times as active as before conversion into the nitrate.

189. Characteristic reaction of Aconite. Dunstan and Carr (41) have recently called attention to a reaction by which aconitine may be distinguished from most other alkaloids Potassium permanganate produces in its solutions a crystalline precipitate which appears even at dilutions of 1:40000.

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The other alkaloids of aconite also produce precipitates but only in much stronger solutions 1:100. so that it is possible to determine approximately in a mixture of alkaloids, the proportion of aconitine by diluting with water and finding the limit of precipitation. The only alkaloids beside those of aconite which produce precipitates with potassium permanganate, are cocaine, hydrastine and papaverine, the first alone giving a crystalline precipitate and all requiring solutions as strong as 1:100.

190. Assay of Aconite Root may be easily made by method of Lyons (71) or by that of Keller, as follows:- (42)

Formula "A."

Aconite Root (No. 80 powder)-----	12.0	gms.
Ether -----	90.00	"
Chloroform -----	30.00	"
Ammonia-----	10.0	"
Water -----	20.0	"
Pour off -----	100.0	"

Formula "B."

Aconite Root (80 powder) -----	25	gms.
Ether -----	100	"
Chloroform -----	25	"
Ammonia -----	10	"
Water -----	30	"
Pour off -----	100	"

Extract with hydrochloric acid, eventually with chloroform-ether or, better with pure ether. According to Hager, the tubers contain .6-1.25 percent aconitine. Five samples examined gave .37; 1.14; 1.05; 1.23; .97% alkaloid. The alkaloid is recovered as a colorless residue but after several treatments with ether, it becomes a foamy, partly crystalline mass, in which form it may be recovered directly if ether is used as the solvent. It is easily and completely soluble in alcohol,, the solution becoming turbid on the addition of water and is easily titrated with N/10 or N/20 acid solutions. 1 c.c. N/10 hydrochloric acid equals .0647 gm. alkaloid in titration. Although the alkaloid obtained is a mixture, it is no doubt principally aconitine.

191. The pure crystalline aconitine may be separated from the above as follows:- After the alkaloids have stood for 24-48 hours, they are washed with repeated small quantities of cold ether, by which the amorphous bases are dissolved, leaving the aconitine as a pure white crystalline powder. If the solution of the amorphous bases is evaporated, a further amount of crystalline aconitine may be recovered. From a mass of .282 gm. crude alkaloid, .239 gm. crystalline aconitine and .043 amorphous alkaloid were obtained.

192. The method suggested by Wright and Luff, and described in detail by A. H. Allen, (43) is more exact, but, like the previous method, is open to the objections as regards approximate results in purity of alkaloid. The alkaloidal residue is dissolved in alcohol, sodium hydrate added, and the solution boiled until the alkaloid is completely saponified. From the residue after evaporation, the benzoic acid formed in the process is extracted with ether after acidifying with hydrochloric acid, and determined by titration

with baryta water N/50, using phenolphthalein as indicator. Each molecule of benzoic acid represents one molecule of aconitine; therefore each c.cm. of baryta water corresponds with 12.94 milligrams of aconitine. More recently (1896), Dunstan and Tickle propose to determine aconitine by the acetic acid produced in its partial hydrolysis, but there seems to be no advantage in this method over the previous method.

193. Mayer's reagent in assays of aconite:- Titration with Mayer's reagent is not recommended in the case of an alkaloid so easily extracted and determined alkalimetry, as aconite. If, for any reason, the operator choose to employ this method, he may proceed as described in (105), making up the solution for titration so that each c.cm. shall represent 0.62 gram of aconite root. Under these conditions, each c.cm. of Mayer's reagent used will indicate nearly 15 milligrammes of alkaloid. According to Snow, the titration equivalent of Mayer's reagent for solutions of aconitine, is:-

Dilution	1c.c. precipitates aconitine
1:500-----	0.0129
1:450-----	0.0132
1:400-----	0.0136
1:350-----	0.0138
1:300-----	0.0140
1:250-----	0.0141

194. Physiological Test of Dr. Squibb:- There is an easier way of arriving at the value of any preparation of aconite. It consists in testing by physiological experiment, the actual effect it produces, under prescribed conditions, on the nerves of the tongue and lips. The test is applied in the following manner:- Make up an aqueous solution representing in 200 parts, the alkaloidal contents of 1 part of the drug. Thus, a fluid extract would be diluted 200 times with water, containing a little hydrochloric acid; the alkaloidal residue from 2 1/2 grams of drug would be dissolved in a little alcohol, a few drops of dilute hydrochloric acid (to decided acid reaction) added, and the solution made up with water to a volume of 500 c.c.

195. The solution should be allowed to stand half an hour before proceeding to the actual test. Put into a 25 c.c. measuring flask, 8.3 c.c. of the above solution add water to the mark and mix by shaking. Rinse the mouth well with water, take into it one fluid dram of this solution and hold it in the anterior part of the buccal cavity one minute, by the watch. Eject the solution and rinse the mouth once more. In a few minutes is the root be of standard strength, the tingling sensation characteristic of aconite, will be perceived in the tongue and this will continue 30 to 45 minutes.

196. If the effect is greater or less than that expected, a trial must be made for the second time, after an interval of several hours, and the relative strength of the preparation can be thus judged after practice, with a considerable degree of precision. Different persons, of course, differ in susceptibility so that each must work out his own

personal equation as regards this test. To make the results quantitative, it would be necessary to have in the first place some pure crystallized aconitine, of which a solution containing one part in 60000 should be made as a basis of comparison. While this test is seldom used quantitatively, it is quite frequently used, after having standardized a preparation of aconite, to substantiate the standardization.

197. Aconite leaves contain a much smaller proportion of alkaloid than the root and the constituent alkaloids are claimed by some to be different. Keller's method of assay of the leaves is as follows:- (44)

Formula--

Aconite leaves	80 powder-----	25 gm.
Ether-----	-----	100 "
Chloroform-----	-----	25 "
Ammonia-----	-----	10 "
Water-----	-----	50 "
Pour off-----		100 "

Extract with hydrochloric acid and finally with chloroform-ether. Decant 105 grams of the deep green solution; allow it to settle for a few moments and then transfer 100 gms. of it to a separatory funnel. The alkaloid is recovered as light yellow coating. From commercial powdered aconite leaves of good appearance, Keller found 18-20% alkaloid. The alkaloid from the leaves appears to be different from that of the tuber, requiring less normal acid neutralization. The equivalent for the alkaloid from the tubers is 645-647 and that from the leaves 440-450. The titration is best performed with N/20 acid upon a concentrated solution of alkaloids.

198. Galenical preparations of aconite:- Preparations made without heat like fluid extracts and tinctures, may be valued, with results as good as those obtained in the case of the drug, by general processes already given in detail; particularly (150) et seq. or (155). Oleate of aconitine extracted from it by repeated washings with water containing hydrochloric or sulphuric acids. Solid extracts, however, must either be judged by the physiological test or dissolved in dilute alcohol and treated as fluid extracts. The subject of heat is a very important problem in aconite assays as the alkaloids are so easily decomposed. It is for this reason that the perforator method cannot be used as the alkaloids are too long in contact with alkali before being extracted and hence suffer decomposition.

199. Percent of alkaloid contained in Aconite. Aconite root contains from 0.6 to 1.25 per cent of alkaloid. Keller reports out of five samples, only one containing less than 0.9 and the average about 1.15 per cent. Prof. Lyons out of 17 samples, found them running from .56 to 1.20 per cent, average about 0.39 percent. In aconite leaves, the alkaloid is about 0.2 percent.

200. Commercial aconitine may be judged by the physiological test. A solution 1:50000 ought to produce a strong impression of tingling on the tongue. The test should be commenced with a solution 1:75000, and if in a solution 1:25000 we fail to obtain a tingling comparable with that produced by a good sample of the root 1:600, we should condemn the article. Of course hydrolysis of the alkaloid and determination of the benzoic acid produced will give more exact, although still possibly fallacious results.

ALOES.

201. There are three principal varieties of aloes, known as Socotrine, barbadoes and Cape Aloes resp. While these varieties differ somewhat in external appearance, they are all alike in containing the crystalline principle aloin, upon the content of which the drug is judged as regard medicinal effect.

202. Determination of Aloin:- Schafer(45) has used the following process with satisfactory results:- Dissolve 50 grams of the aloes in 300 c.c. of hot water to which has been added a few drops of hydrochloric acid. Allow the solution to stand until resinous matter has separated, decant, and mix with 50 c.c. of a 20% solution of ammonia. Now, add a solution of 15 grams of calcium chloride in 30 c.c. water and stir vigorously. A compound of aloin and calcium separates and, after 15 minutes, may be collected on a filter and drained. The precipitate is then mixed in a mortar with a slight excess of hydrochloric acid, boiling water added just sufficient to dissolve the aloin, the solution filtered, the filter washed with a little boiling water and the filtrate and concentrated washings exposed to a low temperature to crystallize. The crystals should be washed with a saturated aqueous solution of aloin which has been prepared in the same manner from the same variety of aloes, dried at 100° C. and weighed.

203. Aloes in mixtures may be roughly estimated by the following method of H. Hager(46):- Exhaust the powder substance with a mixture of absolute alcohol 1 vol., chloroform 2 vol., benzol 3 vols., and dry the residue. Digest this with 80 percent alcohol at a temperature near 50°C. frequently shaking, evaporate the solution in a tared vessel and weigh the residue. Treat this with twelve times its weight of 2 percent solution of ammonia, which will dissolve any aloes present, add to the filtered solution lead acetate in slight excess with ammonia enough to restore a slight ammoniacal smell. Collect the precipitate, wash with a little distilled water, collect, dry and weigh. The weight multiplied by 0.4256, will be approximate that of the aloes originally present, although other substances may also be present. By mixing the lead

1:00, we should consider the effects. Of course the
effects of the alcohol and determination of the
main and produced will also have effect, although it is
possible to follow the results.

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compound with an equal weight of ammonium sulphate, repeatedly moistening with water and drying and, finally extracting the mixture with 80% alcohol, the aloes is recovered with a loss of about 12 percent and will be recognized by its physical characteristics.

204. Detection of Aloes in Pharmaceutical Preparations:- In addition to tests given in the dispensaries, of which that of Cripps and Dymond is the best, the following, by Pierre Apery (47) is worthy of notice. Extract the substance with 80 percent alcohol, filter, evaporate to dryness, extract the residue with water, precipitate the aqueous solution with lead acetate, filter, concentrate, remove excess of lead by sodium carbonate, filter once more and neutralize the filtrate with acetic or nitric acid. Upon adding a few drops of solution of ferric chloride, a distinct red brown color is produced even in dilutions of one part of aloes in 2000 or 3000 of water.

205. Belladonna and allied Drugs:-- Belladonna, root and leaf Stramonium seed and leaf, and Hyoscyamus may be considered under one head since they contain identical or nearly related alkaloids easily destroyed or altered. Methods are to be chosen which avoid the application of heat or the action more than momentary, of such agents as the caustic alkalies. Henbane contains so little alkaloid that the assay is rather difficult. It is necessary to use a large quantity of the drug and we can hardly hope to recover from fluid extracts or tinctures, all the alkaloids, by any one of our best methods. That which will yield the largest proportion of alkaloid is the method of Thompson (159).

206. Belladonna leaves are of two sizes, the larger about 1 1/2 d.m. long and the smaller about 1/2 that size. They are brownish green upon the upper surface and gray-green below, broadly ovate-long, narrowed into a petiole; apex, acute or acuminate; margin entire, the petiole and nerves of the leaf particularly are downy hairy and glandulous. Both surface of the leaf possess trichomes; numerous cells are apparent, filled with crystal like contents, giving the leaf the particular and peculiar spotted appearance it possesses. The leaf is membranaceous, odor narcotic and taste bitter and disagreeable.

207. As found in the market, belladonna leaves, especially the finer grades, when crumpled or broken up, look very much like the mints, but are easily distinguished from them by the narcotic odor and the disagreeable bitter taste. They somewhat resemble the narcotic herbs, stramonium and hyoscyamus but from these may be easily distinguished.

208. Stramonium leaves are dark green and not quite so smooth as belladonna, the hairs shorter, with a many celled apex, and in the mesophyll are numerous

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cells containing large single crystals of calcium oxalate. The perforations and cork formations in the leaves are numerous. The base of the leaf is unequal and does not taper into a petiole. The fruit is a capsule and very often a few reuniform seeds will be found present.

209. *Hyoscyamus* leaves are furnished with long hairs which tend to become tangled and matted, so giving the leaf a hairy appearance. There is an absence of petiole and a presence of stem stalks. The fruit is a pyxis in an urn shaped calyx. The seeds are much smaller than those of stramonium.

210. *Belladonna Root*:- The root of belladonna is a fleshy, spindle-shaped primary root. When fresh, it is about 5 dm. long and about 5cm. in deameter. It then possesses a number of stout branches,, the remnants of which are sometimes seen attached to pieces of the commercial root. The bark contains the largest amount of alkaloid,, therefore,, roots are selected by careful buyers,, which possess the larger portion of bark compared with the woody tissue. Young roots of but two or three years are preferred. Chemical anolysis shows that the amount of alkaloid in roots collected about the time of flowering is twice as much as in spring, so roots should be collected about the flowering or fruiting season,, carefully dried and preserved.

211. The commercial root, to hasten the drying, is invariably split into smaller pieces. It occurs in rough irregular pieces from 1 or 2 in. in lenght to 6, 8 or even 12 and 15 inches, varying in diameter according as the root is split. Externally, it is logitudinally, wrinkled, of a pale brown or grayish color, internally brownish or whitish,, ofor heavy and licorice like, taste peculiar, characteristic, sweet at first and afterwards acrid or bitter. The fracture may be mealy, horn like or weedy and from these characters arise the three commercial varieties known by the above names.

212. For the assay of the respective drugs follow either Dr. Lyons method (71) or method of Kellar(48) uses for the assay of belladonna root, 12 grams of drug, and ether 90 grams., chloroform 30 grm., water of armonia 10 grm., water 15 c.C. to pour off 100 grm., of the ethereal fluid. For the assay of belladonna or stramonium leaves the quantities are:- powdered drug 25 grams, ether 100 grams, chloroform 25 grams, ammonia 10 grams, water 40 c.c., to pour off 100 grams. For hyoscyamus, a still larger quantity of the drug would have to be used. in the short process #2 as applied to hyoscyamus, use 20 grams of drug.

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10. *Phytolacca*. The leaves are large, ovate, and have a wavy margin. The fruit is a globose, fleshy berry, which is green when young and becomes red when ripe. The plant is a perennial herb, and is common in wet places.

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213. The following is recommended(48) for the assay of the three drugs 20 grams of the powdered drug (40grams hyoscyamus leaves) are digested with 150 c.c. of a weak Prollins mixture (with stramonium leaves only 100c.c. are required while with henbane, 200 c.c. are required for 12 hours, shaking frequently. Then allow to deposit and filter off through cotton 75 c.c. (with stramonium 50 c.c. and henbane 100c.c.) of the clear ethereal liquid corresponding to 10 and 20 grams of the drug. This is then placed in a shallow glass vessel; add 8 c.c. water, 2 or 3 c.c. dilute sulphuric acid (2.5%), and set aside in a moderately warm place, permitting the alcohol and ether to evaporate. The chryso-phyll, wax and fat etc., are hereupon deposited in small adhering particles or in the form of a thin coating. The solution is filtered into the perforator, washing the vessel and filter with a little water, and then add ether. This acid solution is washed with ether for about one hour; then after changing and replacing fresh ether, 4 or 5 drops of ammonia are added to perforator and again extract for some 3 hours. Evaporate solution to dryness, avoiding unnecessary heat as much as possible. Dissolve the alkaloids in 10c.c. N/20 sulphuric acid and titrate the excess of acid with N.100 caustic soda, using cochneal as indicator. 1 c.c. N/100 sulphuric acid = .00289 gm. mydriatic alkaloids.

214. It is best in all cases to determine the alkaloid by alkalimetry rather than by weighing, since, with the most careful manipulations, impurities will be carried over into the final product. However, in a well conducted assay, gravimetric results should not be very far from the truth, and in the hands of an unskilled operator, the liability to serious error may be greater in the use of the burette than of the balance. The beginner should use both and it is not a bad plan to make that a rule in any case.

215. Dr. Schwickerath(49) gives the following details of his method as applied to these drugs. (51--
Twenty grams of powdered drug(40 gms. hyoscyamus) are digested with 150 c.c. of a weak Prollins mixture (with stramonium seed only 100c.c. are required, with henbane, 200 c.c. must be used) for 12 hours, shaking frequently (best, continually by a mechanical shaker). Then remove of the clear fluid, 75 c.c. (with stramonium seed 50 c.c., with henbane 100 c.c.) corresponding with 10 grams (henbane 20 gms. of the drug. The assay is then continued as given in (51) et. seq.

216. Belladonna Root. Method of Dunstan and Ransom '50):--Exhaust 20 grams of the dry and finely powdered drug by hot percolation, preferably in the extraction apparatus (8) with a mixture of equal volumes chloroform and absolute alcohol; if an extraction apparatus is used about 60 c.c. of the mixture will be required. Agitate the percolate with two successive portions (25 c.c.) of distilled water, which are separated in the usual way carrying with them the alkaloid. Mix the aqueous solutions and shake with more chloroform to remove adherent coloring matter. Separate the chloroform add to the aqueous solution ammonia, and wash out the alkaloid by shaking twice with chloroform (25 c.c.). Wash the chloroform with a little ammonia water, transfer to a tared capsule and evaporate to constant weight, which usually requires a little less than an hour. The results reported by the authors are low as compared with those obtained by other processes. It seems advisable to add a little hydrochloric or sulphuric acid to the water before attempting to wash out the alkaloid with water from the alcohol-chloroform, although the authors state that this is unnecessary.

217. Belladonna Leaves (51) (same authors):--Exhaust 20 grams of the dried and finely powdered leaves in an extraction apparatus with absolute alcohol of which about 100 c.c. will be required. Add to the percolate an equal volume of water with a little hydrochloric acid added. From the slightly warmed liquid remove chlorophyll, fatty matter, wax, etc. by repeated washings with chloroform which must be continued as long as anything is removed by that solvent. The solution is then to be made alkaline with ammonia, and the alkaloid extracted precisely as in the assay of belladonna root, above.

218. Titration with Mayer's Reagent is not to be advised with these drugs. The precipitate does not separate promptly and the end reaction is not sharp. If Mayer's reagent is used at all, it should be for a gravimetric determination. When so used, the result is quite as good as that obtained by separating and weighing the alkaloid. The method is as follows:-- Place in a tared beaker the acid solution containing the alkaloid from 5 grams of the drug (ten of hyoscyamus) and add a moderate excess of Mayer's reagent. At the end of 12 to 24 hours, when the precipitate has completely subsided and adhered for the most part to the bottom and sides of the beaker, decant the fluid through a

[illegible]

small filter, wash the precipitate in the beaker several times with distilled water (1 or 2 c.c.) which is to be afterwards passed through the same filter., finally dissolve the precipitate remaining on the filter in strong alcohol, run the solution into the beaker, evaporate at 100° C. and weigh. Multiply the weight of the precipitate by 0.454 for the weight of alkaloid it contains. (119)

219. Determination of Atropine by the Periodide Method:- Instead of titrating the alkaloidal residue with standard acid, or, after titrating it, we may determine the atropine by the method recently put forth by Presscott and Gordin (114). Dissolve the alkaloidal residue in a little hydrochloric acid, and make up with water to a weight 250 times that of the residue taken. Put in a flask 10 c.c. of decinormal iodine solution (U. S. P.) add 2.5 grams of the alkaloidal solution and proceed according to (122). If the quantity of material is large enough, use 25 c.c. of the iodine solution, with a proportionate part of the alkaloidal solution. It is necessary to be certain, of the strength existing between iodine and thiosulphate solutions, and, should be of course, of decinormal strength, which means that they have been recently prepared and standardized. The method is therefore not to be recommended except where assays are frequently made.

220. Assay of Galenical Preparations of belladonna, henbane and stramonium. Fluid extracts may be assayed with advantage by (150) et. seq.; using ether to extract the alkaloid, or the method of (156), (157) may be employed, making the final extraction of alkaloid, however, with ether rather than with chloroform. Some prefer the method of (159) for fluid extracts of henbane and stramonium and know that good results are obtained with it. Tinctures may be assayed best, by first concentrating on a water bath and then treating as fluid extracts. Extracts may be assayed by methods of (171-173). Use for an assay, 5 to 10 c.c. of the fluid extract, except of henbane 15 c.c. are required; one gram of an alcoholic extracts of belladonna, 2 grams of an ordinary solid or powdered extract, except of henbane if which 4 grams should be taken. In most cases the extract can be best treated by (173) or with the intervention of saw-dust after dissolving in dilute alcohol.

221. British Pharmacopoeia method of assay of fluid extract belladonna. Shake 10 c.c. of the fluid extract with 10 c.c. chloroform, 50 c.c. of water and a decided excess of ammonia. Separate the chloroformic

of the population of 2,400 for the village of Alford
and, together with the village of Alford, the village
of Alford and the village of Alford, the village of Alford
is in Alford's parish. The village of Alford is in Alford's parish.

[illegible][illegible]

1. The first of these is the fact that the majority of the population of the United States is now living in urban areas. This is a result of the process of urbanization, which has been going on since the beginning of the 20th century. The process of urbanization is the movement of people from rural areas to urban areas. This is done for a variety of reasons, including the search for better living conditions, the desire for education, and the need for employment. The process of urbanization has led to the growth of large cities and the decline of small towns. This has had a significant impact on the way we live and work. The majority of the population now lives in cities, which are often crowded and expensive. This has led to the development of new urban planning techniques, such as the creation of suburbs and the development of public transportation systems. The process of urbanization has also led to the growth of the service sector, which is now the largest part of the economy. This has led to the development of new industries, such as the computer industry and the entertainment industry. The process of urbanization has also led to the development of new social and cultural norms. For example, the majority of people now live in nuclear families, which is a result of the process of urbanization. The process of urbanization has also led to the development of new political and economic systems. For example, the majority of people now live in democracies, which is a result of the process of urbanization. The process of urbanization has also led to the development of new environmental problems, such as air pollution and global warming. These problems are a result of the process of urbanization, which has led to the growth of large cities and the decline of small towns. The process of urbanization has also led to the development of new social and cultural norms. For example, the majority of people now live in nuclear families, which is a result of the process of urbanization. The process of urbanization has also led to the development of new political and economic systems. For example, the majority of people now live in democracies, which is a result of the process of urbanization. The process of urbanization has also led to the development of new environmental problems, such as air pollution and global warming. These problems are a result of the process of urbanization, which has led to the growth of large cities and the decline of small towns.

solution and twice repeat the agitation and separation with chloroform; shake the mixed chloroformic solution with 5 c.c. dilute sulphuric acid, B.P., mixed with twice its volume of warm water, separate and repeat the operation. Wash the mixed acid liquids with 3 c.c. of chloroform which is rejected, add ammonia in excess and agitate the solution with three successive portions (10 c.c.) of chloroform. Wash the mixed chloroformic solutions 5 c. c. of water containing one drop of solution of ammonia, evaporate on the water bath, dry at 100° C. and weigh. Then dissolve the residue in 10 c.c. of decinormal hydrochloric acid, neutralize with centinormal sodium hydroxide, using cochineal as indicator, deduct the measure of soda solution used from 100 c.c. and multiply the remainder by 0.00287, to obtain the weight of the alkaloid present in 10 c.c. of the fluid extract.

222° It is generally admitted that the most troublesome feature of method of assay as given above for the determination of the alkaloidal strength of fluid extract of Belladonna, is the emulsification which takes place on shaking the alkaline liquid with chloroform; an emulsion which unduly prolongs the time necessary for the separation of the solvent, which extends more or less throughout the whole of the subsequent stages of the process.

223. The cause of this behavior is not hard to find. Belladonna, amongst other constituents contains fatty and resinous bodies and these becoming partially saponified by the alkali, furnish the conditions necessary for the formation of a difficulty separable emulsion.

Naturally the remedy which suggests itself is the removal of the fat and resin. This is easily and quickly accomplished by a preliminary extraction of the acidified liquid with chloroform, a procedure recommended by Dragendorff in his general scheme for the extraction of alkaloids by immiscible solvents; and subsequently by Farr and Wright, and other authorities. A fair amount of acid is necessary and the contents of the separator should be heated over a water bath, until as hot as hand can stand, when complete separation takes place almost immediately. The advantage of this preliminary treatment of the acidified liquid with chloroform are; that emulsification is entirely removed or prevented; there is rarely a film of fat to interfere with the final solution of the alkaloid and the alkaloidal residue is frequently so pure that it is obtained in white silky crystals. The following quantities have been found to work well in conjunction with those given in the B. P. process:-

Fluid extract Belladonna-----	-10 c. c.
Water-----	40 c. c.
Dil. Sulphuric Acid-----	-10 c. c.
Chloroform-----	-20 c. c.

Agitate thoroughly, warm and separate. Wash a second time with 10 c. c. chloroform and again separate. transfer the mixed chloroform solution to another separator and wash with 1 c. c. Dilute Sulphuric acid and 4 c. c. water. Warm, separate and return washings to first separator. Reject the washed chloroform. To the aqueous liquid add,

Chloroform-----	10 c. c.
-----------------	----------

Ammonia-----a decided excess, and continue the process as detailed in the British Pharmacopoeia (221), assisting the separation of the chloroformic layer at every stage, by the application of heat.

224. The quantity of acid present in the aqueous layer and the absence of an excessive proportion of dissolved substance in the chloroform, are two important factors in promoting the prompt separation of the latter during the preliminary treatment. Less than 10 c.c. acid is apparently insufficient, the separation being sluggish and the chloroform remaining cloudy; while nothing is gained by using a larger quantity than 15 or 20 c. c. The chloroform solution of the resinous or fatty bodies also must not be too concentrated, or emulsification is unavoidable even in acid solution. 10 to 20 c.c. chloroform will generally be found sufficient, but more should be added if necessary. Thorough agitation of the contents of the separator for at least half a minute is important and is much more effective in removing alkaloid than the gentle rotation sometimes advocated. It is necessary to wash the chloroform with a little dilute acetic acid, both to remove any mechanically adhering aqueous liquid and also on account of the tendency which fatty bodies have of carrying small quantities of alkaloid into solution with them.

225. When working the strict process of the B. P., the alkaloidal residue (on account of accompanying traces of fatty impurities) is sometimes found to be slow in solution in N/10 acid. It is advantageous in such a case to take up the residue with a few drops of chloroform before

10. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

11. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

12. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

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15. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

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17. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

18. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

19. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

20. The following is a list of the names of the persons who have been appointed to the various committees of the Board of Directors of the United States National Bank, for the year ending December 31, 1900.

adding the acid, the solution being gently warmed before titration until all odor of chloroform has disappeared.

226. The results of several experiments made with a view of comparing the official method of assay with the modified process as indicated above, show that by the latter, a higher per cent of alkaloid is extracted, the difference varying from .02--.04%. The British Pharm. method as it stands is also open to the possibility of error to those hitherto pointed out, viz:- that a small amount of alkaloid may be lost through failure to obtain an absolutely sharp separation of the immiscible solvents. With some, complete separation may take several days and as with such samples, there is always a temptation to hurry the operation; a fourth treatment with chloroform will almost invariably remove a further small amount of alkaloid. Hence, it is apparent that the removal of those substances which interfere with extraction by the solvent and favor emulsification, will generally be attended by a slightly higher percent, especially as under these circumstances the percent of alcohol is hardly likely to affect the result.

227. Dr. Schwickerath advises for the extract of belladonna (root or leaf); Treat two grams of the extract with 3 successive portions (3c.c.) of dilute sulphuric acid, 2 1/2% working the extract well with a very small platinum spatula to insure solution of all the active principle. Filter the acid solution into a perforator (9), wash the filter with a little water, treat the acid solution one hour with ether, then add ammonia and extract with fresh ether three hours (52). The latter solution will contain the alkaloid.

228. Dunstan and Ransom advise to dissolve the extract (of belladonna) in warm water acidified with hydrochloric acid filter through absorbent cotton into a separator, wash the cotton with a little water, make alkaloid with ammonia, shake with two portions of chloroform (5 and 3 c.c.), which is to be drawn off into a second separator. Extract the alkaloid with two successive portions (5 and 3 c.c.) of acid water, and treat the aqueous solution once more with water ammonia and chloroform (5 and 3 c.c.), obtaining, thus, finally a solution from which the alkaloid is procured by evaporation in sufficient purity to weigh.

229. New method of Assay of Fluid Extracts Belladonna, Henbane and Stramonium (52):- Two grams of absorbent cotton are firmly packed in the bottom of a 4 oz. bottle. Then, into the centre of the cotton, by means of a pipette are placed 10 c.c. of the fluid extract to be examined. The fluid is allowed to remain until it is thoroughly taken up by the cotton, and then there are added 100 c.c. Prollins mixture modified (ether 250 c.c., chloroform 90 c.c., alcohol 25 c.c., and ammonia 10 c.c.) and the whole allowed to remain for about 1/2 hour. After thoroughly shaking the mixture, 55 c.c. are poured into a beaker containing 5 c.c. distilled water which has been rendered thoroughly acid by a solution of 1-5 of sulphuric acid. Carefully mix the acid and the etheral solution and allow the latter to evaporate spontaneously or by means of a gentle heat. Digest on the water bath for

a few moments to remove the last traces of chloroform and alcohol. Then, to the contents add 20 c.c. strong ether and carefully rotate with the water and then pour the whole into a separatory funnel, washing the beaker with sufficient water and ether to remove all adhering particles. Then, in the separatory funnel wash the acid water with 2 more quantities of ether (20 and 10 c.c.) and separate. Add sufficient ammonia water to render the aqueous liquid alkaline and shake out with 3 portions chloroform, 15, 10 and 10 c.c. resp. Evaporate the chloroform solutions on a water bath, dry to constant weight at 100 degrees C. and weigh.

280. Assay of Belladonna Plasters (53) Frank X. Moerk publishes a process now used for the assay of Belladonna plasters, as follows:- The belladonna plaster of the U. S. P. differs from most others in that it contains soap-plaster. It is prepared by incorporating 20 grams of the extract of belladonna with 40 grams each of resin and soap plaster. Ten grams of the plaster are placed in a beaker and covered with a mixture of 1 c.c. sulphuric acid (92.5% by wt.), and 15 c.c. water. The plaster is disintegrated by stirring as heating causes the lead sulphate and fatty substances to separate out in a pulverent form that is difficult to manipulate. The acid solution is filtered into a separator, and the residue in the beaker treated with successive portions of acidulated water (2c.c. sulphuric acid in 50 c.c. water), 2 portions of 10 c.c. each being followed by 3 portions of 5 c.c. each. To the mixed filtrates in the separator are added 25 c.c. ether-chloroform and 10 c.c. water of ammonia and the process from here is conducted the same as for fluid extracts. The assay is effectually blocked by the formation of a perpetual emulsion. The author finds that by the addition of a small quantity of stearic acid, say 10 or 15 mg. in several small fragments, is effectual in separating the emulsified alkaloidal solvent, and that by adding it before agitating the alkaline solution with the solvent, serious emulsification may be prevented. Experiments made to determine whether stearic acid interferes with the accuracy of the assay, show no difference. The plasters prepared from an extract from English leaves gave 0.371% to .570% alkaloid. The German weed and cultivated leaves gave figures ranging from .3003-.3445%.

(2 c.c. sulphuric acid in 50 c.c. water), 2 portions of 10 c.c. each being followed by 3 portions of 5 c.c. each. To the mixed filtrates in the separator are 25 c.c. ether-chloroform and 10 c.c. water of ammonia and the process from here is conducted the same as for fluid extracts. The assay is effectually blocked by the formation of a perpetual emulsion. The author finds that by the addition of a small quantity of stearic acid, say 10 or 15 mg. in several small fragments, is effectual in separating the emulsified alkaloidal solvent, and that by adding it before agitating the alkaline solution with the solvent, serious emulsification may be prevented. Experiments made to determine whether stearic acid interferes with the accuracy of the assay, shows no difference. The plasters prepared from an extract from English leaves gave 0.371% to .50% alkaloid. The German weed and cultivated leaves gave figures ranging from .3003-.3445%.

231. Percent of alkaloid contained in Belladonna, etc. Belladonna root yields from .03 to .08 percent of alkaloid, average about 0.55 percent; Belladonna leaves .02 to .05, average .035 percent; Stramonium seed, .02 to .045, average .033 percent; Stramonium leaves .02 to .045, average, .033 percent; Hyoscyamus .05 to .2 percent. The above figures are based on determination of the alkaloid by acid titration. Results obtained by gravimetric determinations have generally been 20 to 30 percent higher. Some recent assays of belladonna leaf by W. A. Puckner (54) show a range from 0.01 to 0.52 percent., indicating the worthlessness of some of the drug in the market and the need for an official standard.

CANTHARIDES.

232. Constituents: The chief constituents of cantharides are: (a) cantharidin, the active principle, a fatty crystallizable body, forming shining, colorless plates, soluble in alcohol, ether, acetic ether, glacial acetic acid, chloroform and oils; volatilizable by heat at 100°C. without decomposition, the vapor condensing in acidular crystals; (b) a volatile oil, giving the odor of cantharides and said to have vesicatory properties; and (c) a green oil, the coloring principle, closely allied to chlorophyll. When the drug is treated with chloroform, the cantharidin is removed, accompanied with fatty matter. If the chloroform be allowed to evaporate, the cantharidin crystallizes out and can then be freed from fat by washing with carbon bisulphide.

233. Assay Process of Proctor and Mordreux, based upon the facts above stated, had been improved by Nagelvoort, as follows:- Moisten 10 grams of the drug in moderately fine powder with a 1 percent solution of caustic soda to render the mixture strongly alkaline and digest 6 hours in

... and (130°F.) place until the ... is ...; add hydrochloric acid to a decided acid reaction and again dry at a low temperature (130°F.) to pulverize; transfer to a modified Soxhlet extractor and exhaust by hot alcohol by repercolation, about 50 c.c. being required. After 3 or 4 hours of percolation, evaporate to recover the chloroform by distillation from the flask; add carbon disulphide, transfer the contents to a filter and continue to wash with carbon bisulphide as long as it takes up soluble matter. Allow the filtrate to dry spontaneously; treat with hot chloroform, collect the filtrate and pass through a small quantity of purified charcoal, thoroughly washing with chloroform and then evaporate the solution in a tared capsule; dry the crystalline residue in a desiccator or over sulphuric acid to constant weight and weigh as cantharidin.

254.----Determination of Total Cantharadin:- Twenty grams of the flies in No. 40 powder are mixed in a small mortar with 25 c.c. of a mixture of

Glacial Acetic Acid-----1 volume
Rectified spirit-----2 volumes
Chloroform-----3 volumes

The moistened mass is covered over for about an hour and then either allowed to dry spontaneously or at a slightly raised temperature. This is easily accomplished without loss of cantharidin. The dried mass is then packed in a Soxhlet extractor and exhausted with chloroform, the latter being used to rinse out the mortar used. About one hour usually will suffice for complete extraction if the substance be well packed, but complete exhaustion should always be ascertained by removing the flask with the chloroform solution and continuing the extraction with a little fresh chloroform. The chloroformic solution thus obtained is placed in a separator containing a little water and the acetic acid which passes into the water but not quite neutralized with solution of potassa and the whole well shaken. The chloroformic layer is then run off into a glass dish and evaporated, cautiously toward the end. The residue consists of fat in which can be the crystals of cantharadin. The fat is removed by washing with petroleum spirit (the washing being set aside) leaving in the dish cantharadin mixed with a green substance of a resinous nature. The residue is allowed to dry and is then washed with small quantities of absolute alcohol until all the green matter is removed and perfectly white cantharadin remains. The alcoholic washings are then carefully evaporated.

235.----The cantharadin, dissolved or mechanically removed while washing out with petroleum spirit, is now recovered; 20 c.c. of 10 percent solution of caustic potash are

added to the petroleum spirit solution and the mixture warmed until completely saponified; during this process most of the petroleum spirit is dissipated. The soap solution thus formed is diluted with warm water and transferred to a separator, sufficient petroleum spirit being added to dissolve the fat acids when liberated; it is now acidified with hydrochloric acid, when the fat acids rapidly rise and dissolve in the petroleum spirit. The aqueous layer is quickly run off from beneath the petroleum spirit solution, into another separator, the petroleum spirit solution washed with water and the washings added to the first. The cantharadin is then removed by shaking with successive quantities of chloroform as long as cantharadin is removed; this, of course, must be ascertained. In the chloroformic solution thus obtained, the residue from the alcoholic washings of the crystallized cantharadin are dissolved.

236.----The chloroform now contains in solution chiefly cantharadin and the green resinous matter previously mentioned. It is placed in a separator and shaken with lime water, containing excess of calcium hydroxide suspended in it and solution of common salt, the latter causing the chloroformic layer to separate more quickly. In this way, cantharadin passes into aqueous solution probably as cantharidate of calcium, while the chloroformic layer containing green resin and coloring matter is rejected. The aqueous solution is filtered, acidified with hydrochloric acid and shaken out with chloroform as before. This chloroformic solution is added to the cantharadin previously separated, evaporated cautiously, dried in a desiccator and weighed. In this way a crystalline residue of cantharadin only very slightly colored is obtained.

237.---Proportion of Cantharadin in the drug:- assays by Martin(56) show a percentage of cantharadin ranging from 0.25 to 1.06 percent. E.A. Thompson(57) reported on seven samples containing from a trace to 1.00 percent; Average all but the worst sample 0.97. per cent.

238.###Cinchona Bark###----The genus *Cinchona* is composed of over three dozen species, less than a third of this number furnished the commercial barks. It is well known that the original source of this drug is South America, the area of the growth of the various species being confined exclusively to the Andes, chiefly on the eastern side of the Cordilleras--occasionally on the western face, which is covered with forests. The cinchonas seldom form an entire forest, but rather groups interspersed among tree-ferns, gigantic climbers, bamboos, etc., sometimes growing separately in exposed situations, but under peculiar climatic conditions, such as a great humidity of atmosphere and a mean temperature of about 62 °. Shade seems to favor the development of alkaloids.

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It is quite certain that the fossil of *Strophomena* is a new species of *Strophomena* and is not a new genus. The fossil is a small, rounded, oval-shaped object, about 1.5 mm in length and 1.0 mm in width. It is a light brown color and has a smooth surface. The fossil is a small, rounded, oval-shaped object, about 1.5 mm in length and 1.0 mm in width. It is a light brown color and has a smooth surface. The fossil is a small, rounded, oval-shaped object, about 1.5 mm in length and 1.0 mm in width. It is a light brown color and has a smooth surface.

Dymock calls attention to the fact that the north or shaded side of a tree has a richer bark than that on the south side, a fact which explains the fact of the "mossing" system. Cultivated trees in recent years have been the chief source of the commercial barks. To some extent the cultivation has been carried on in South America, but great success has attended the preserving efforts of the Dutch Government and the Government of British India. Extensive plantations of cinchona are now flourishing to the extent of over five million trees of the more important species. The tree is also cultivated in Ceylon, Java, Jamaica (Blue Mountains), and other countries.

239.----There are two barks officinal in United States Pharmacopeia, as follows;

(a) Cinchona--In quills or in curved pieces, varying in length, and usually 2 or 3 mm. ($1/12$ to $1/8$ in.) and sometimes 5 m.m. ($1/5$ in), thick; the outer surface covered with a gray or brownish-gray cork, usually slightly wrinkled, marked with transverse, and also with intersecting longitudinal fissures and sometimes with scattered warts and slight longitudinal ridges; inner surface light cinnamon-brown, very finely striate; fracture short and granular in the outer layer, and finely fibrous in the inner layer; powder light brown or yellowish brown; odor slight, somewhat aromatic; taste bitter and somewhat astringent.

58 (b) Cinchona Rubra:- In quills incurved pieces varying in length and from $1/12$ to $1/5$ in. thick; the outer surface covered with a grayish-brown cork, more or less rough from warts and longitudinal, warty ridges and from few, mostly short, transverse fissures; inner surface more or less deep reddish-brown and distinctly striate; fracture short, fibrous in the inner layer; powder reddish brown; odor slight; taste bitter and astringent.

240.----Cinchona bark is usually exported in packages which are subjected to hydraulic pressure and arrive in the market with the bark in a more or less crushed or broken condition. Mossed bark has a dark surface, is usually free from lichens and occurs in thick, half or single quills. Renewed bark is light in color, easily fractured on account of the absence of much fiber, and is known by the peculiar smoothness of its external surface. Microscopically, it may be said of Cinchona bark that, as compared with other barks, the fibers of the 'liber are shorter and more loosely arranged, being for the most part, separated into simple fibers imbedded in the bast parenchyma or united into very short bundles. Grahe's test for the distinction of cinchona bark is as follows;- On heating about 0.1 gr. of powdered

of the more important species. The first is also well-
represented in the record of over five million years
British India. Numerous specimens of different
forms of the Indian Government and the Government of
the United Kingdom have attended the Government of
the United Kingdom. The first is also well-
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British India. Numerous specimens of different
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the United Kingdom have attended the Government of
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(c) *Clonostomum* sp. - in small numbers; 1 specimen found in 1944 and 1 in 1945; the other 2 in 1946. The specimens were small, with a yellowish-brown body, and a yellowish-brown head. The specimens were found in the same place as the other specimens.

500.---Orange Lake is usually regarded in water-
ways which are subject to hydraulic pressure and action
in the water with the lake in a more or less rounded or
rounded condition. However, there is a fact which is
usually in a few lakes and rivers in which, with a
single gullies. However, there is light in color, and
considered as a result of the absence of much light, and
is known by the general appearance of the water and
form. Microscopically, it may be said of Colorado and
Ohio, as compared with other bodies, the lakes of the
latter are smaller and more loosely arranged, but the
two most striking, somewhat like the lakes of the
in the last paragraph or called into very sharp con-
dition. There is a fact for the distinction of various
is as follows:- On passing about 5.5 mi. of water.

bark in a dry test tube, tarry distillate of a red color is obtained.

241.----Constituents:- Upon quinine the bark almost exclusively depends for its value. This alkaloid is colorless, amorphous, or in acicular crystals; inodorous very bitter; soluble in 1670 parts of water, 6 parts alc alcohol, 23 parts ether. Aqueous solutions of the salts have a blue fluorescence, and when treated with chlorine water and ammonia, a beautiful green color is produced-"Thalleoquin test". The other prominent principles, also official in the U. S. P., are cinchonidine, cinchonine and quinidine. Among the unofficial alkaloids and principles found in the bark, are the following:- Isomeric with quinine and quinidine is quinicine; with cinchonine and cinchonidine, are cinchonidine, homocinchonine, homocinchonidine, homocinchonidine and apoquinanine; a brown amorphous alkaloid is obtained from the mother liquor, known as chinidine, a mixture of various not well defined alkaloidal substances; Kinic acid and Kinovic acid; kinovin; bitter cinchonic acid and a small quantity of a volatile oil.

242.----The method of Prollins more or less modified is now almost universally adopted for the determination of total alkaloids in cinchona bark. For rapid work, where great exactness is not demanded, 4 grams of the finely powdered drug is digested with 100 c.c. of the modified Prollins mixture (13) following the routine of (72-74). If the drug is rich in alkaloid, 25 c.c. of the ethereal fluid, representing one gram of the drug, suffices for the assay and a duplicate can be carried out with a second portion by the abbreviated process of (154).

243.----Method of assay of German Pharmacopoeia. This is essentially the process of W. Haubensack (58) which was modified in 1892 by C. Kursteiner (59). The German Pharmacopoeia directs:- Shake vigorously and repeatedly 20 grams of finely powdered bark with 10 c.c. of solution of ammonia, 20 c.c. alcohol and 170 c.c. there and after 24 hours pour off 100 c.c. of the clear solution (which seems to be taken to represent 10 grams of drug). Add to this, 3 c.c. normal hydrochloric acid and 27 c.c. water, distil off the ether and alcohol and, if necessary, add enough normal hydrochloric acid to make distinctly acid. Filter the solution, add to it 3.5 c.c. normal caustic potassa or sufficient to show excess by reddening phenolphthalein. The precipitate is collected on a tared filter, washed repeatedly with small amounts of water until the washings no longer redden phenolphthalein, drained, moisture removed by pressing between blotting paper, dried over sulphuric acid and then on the water bath and weighed.

1971-1972 - 1973-1974 - 1975-1976 - 1977-1978 - 1979-1980 - 1981-1982 - 1983-1984 - 1985-1986 - 1987-1988 - 1989-1990 - 1991-1992 - 1993-1994 - 1995-1996 - 1997-1998 - 1999-2000 - 2001-2002 - 2003-2004 - 2005-2006 - 2007-2008 - 2009-2010 - 2011-2012 - 2013-2014 - 2015-2016 - 2017-2018 - 2019-2020 - 2021-2022 - 2023-2024 - 2025-2026 - 2027-2028 - 2029-2030 - 2031-2032 - 2033-2034 - 2035-2036 - 2037-2038 - 2039-2040 - 2041-2042 - 2043-2044 - 2045-2046 - 2047-2048 - 2049-2050 - 2051-2052 - 2053-2054 - 2055-2056 - 2057-2058 - 2059-2060 - 2061-2062 - 2063-2064 - 2065-2066 - 2067-2068 - 2069-2070 - 2071-2072 - 2073-2074 - 2075-2076 - 2077-2078 - 2079-2080 - 2081-2082 - 2083-2084 - 2085-2086 - 2087-2088 - 2089-2090 - 2091-2092 - 2093-2094 - 2095-2096 - 2097-2098 - 2099-2100 - 2101-2102 - 2103-2104 - 2105-2106 - 2107-2108 - 2109-2110 - 2111-2112 - 2113-2114 - 2115-2116 - 2117-2118 - 2119-2120 - 2121-2122 - 2123-2124 - 2125-2126 - 2127-2128 - 2129-2130 - 2131-2132 - 2133-2134 - 2135-2136 - 2137-2138 - 2139-2140 - 2141-2142 - 2143-2144 - 2145-2146 - 2147-2148 - 2149-2150 - 2151-2152 - 2153-2154 - 2155-2156 - 2157-2158 - 2159-2160 - 2161-2162 - 2163-2164 - 2165-2166 - 2167-2168 - 2169-2170 - 2171-2172 - 2173-2174 - 2175-2176 - 2177-2178 - 2179-2180 - 2181-2182 - 2183-2184 - 2185-2186 - 2187-2188 - 2189-2190 - 2191-2192 - 2193-2194 - 2195-2196 - 2197-2198 - 2199-2200 - 2201-2202 - 2203-2204 - 2205-2206 - 2207-2208 - 2209-2210 - 2211-2212 - 2213-2214 - 2215-2216 - 2217-2218 - 2219-2220 - 2221-2222 - 2223-2224 - 2225-2226 - 2227-2228 - 2229-2230 - 2231-2232 - 2233-2234 - 2235-2236 - 2237-2238 - 2239-2240 - 2241-2242 - 2243-2244 - 2245-2246 - 2247-2248 - 2249-2250 - 2251-2252 - 2253-2254 - 2255-2256 - 2257-2258 - 2259-2260 - 2261-2262 - 2263-2264 - 2265-2266 - 2267-2268 - 2269-2270 - 2271-2272 - 2273-2274 - 2275-2276 - 2277-2278 - 2279-2280 - 2281-2282 - 2283-2284 - 2285-2286 - 2287-2288 - 2289-2290 - 2291-2292 - 2293-2294 - 2295-2296 - 2297-2298 - 2299-2300 - 2301-2302 - 2303-2304 - 2305-2306 - 2307-2308 - 2309-2310 - 2311-2312 - 2313-2314 - 2315-2316 - 2317-2318 - 2319-2320 - 2321-2322 - 2323-2324 - 2325-2326 - 2327-2328 - 2329-2330 - 2331-2332 - 2333-2334 - 2335-2336 - 2337-2338 - 2339-2340 - 2341-2342 - 2343-2344 - 2345-2346 - 2347-2348 - 2349-2350 - 2351-2352 - 2353-2354 - 2355-2356 - 2357-2358 - 2359-2360 - 2361-2362 - 2363-2364 - 2365-2366 - 2367-2368 - 2369-2370 - 2371-2372 - 2373-2374 - 2375-2376 - 2377-2378 - 2379-2380 - 2381-2382 - 2383-2384 - 2385-2386 - 2387-2388 - 2389-2390 - 2391-2392 - 2393-2394 - 2395-2396 - 2397-2398 - 2399-2400 - 2401-2402 - 2403-2404 - 2405-2406 - 2407-2408 - 2409-2410 - 2411-2412 - 2413-2414 - 2415-2416 - 2417-2418 - 2419-2420 - 2421-2422 - 2423-2424 - 2425-2426 - 2427-2428 - 2429-2430 - 2431-2432 - 2433-2434 - 2435-2436 - 2437-2438 - 2439-2440 - 2441-2442 - 2443-2444 - 2445-2446 - 2447-2448 - 2449-2450 - 2451-2452 - 2453-2454 - 2455-2456 - 2457-2458 - 2459-2460 - 2461-2462 - 2463-2464 - 2465-2466 - 2467-2468 - 2469-2470 - 2471-2472 - 2473-2474 - 2475-2476 - 2477-2478 - 2479-2480 - 2481-2482 - 2483-2484 - 2485-2486 - 2487-2488 - 2489-2490 - 2491-2492 - 2493-2494 - 2495-2496 - 2497-2498 - 2499-2500 - 2501-2502 - 2503-2504 - 2505-2506 - 2507-2508 - 2509-2510 - 2511-2512 - 2513-2514 - 2515-2516 - 2517-2518 - 2519-2520 - 2521-2522 - 2523-2524 - 2525-2526 - 2527-2528 - 2529-2530 - 2531-2532 - 2533-2534 - 2535-2536 - 2537-2538 - 2539-2540 - 2541-2542 - 2543-2544 - 2545-2546 - 2547-2548 - 2549-2550 - 2551-2552 - 2553-2554 - 2555-2556 - 2557-2558 - 2559-2560 - 2561-2562 - 2563-2564 - 2565-2566 - 2567-2568 - 2569-2570 - 2571-2572 - 2573-2574 - 2575-2576 - 2577-2578 - 2579-2580 - 2581-2582 - 2583-2584 - 2585-2586 - 2587-2588 - 2589-2590 - 2591-2592 - 2593-2594 - 2595-2596 - 2597-2598 - 2599-2600 - 2601-2602 - 2603-2604 - 2605-2606 - 2607-2608 - 2609-2610 - 2611-2612 - 2613-2614 - 2615-2616 - 2617-2618 - 2619-2620 - 2621-2622 - 2623-2624 - 2625-2626 - 2627-2628 - 2629-2630 - 2631-2632 - 2633-2634 - 2635-2636 - 2637-2638 - 2639-2640 - 2641-2642 - 2643-2644 - 2645-2646 - 2647-2648 - 2649-2650 - 2651-2652 - 2653-2654 - 2655-2656 - 2657-2658 - 2659-2660 - 2661-2662 - 2663-2664 - 2665-2666 - 2667-2668 - 2669-2670 - 2671-2672 - 2673-2674 - 2675-2676 - 2677-2678 - 2679-2680 - 2681-2682 - 2683-2684 - 2685-2686 - 2687-2688 - 2689-2690 - 2691-2692 - 2693-2694 - 2695-2696 - 2697-2698 - 2699-2700 - 2701-2702 - 2703-2704 - 2705-2706 - 2707-2708 - 2709-2710 - 2711-2712 - 2713-2714 - 27

[illegible]

"Toll-free 800-855-8555". The sales literature explains:

Two officials in the U.S. are also mentioned, one of whom was mentioned in the previous paragraph.

and principal focus is the following:-

Einzelne, besonders wertvolle, wissenschaftliche und populäre

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11-11-61

quantity of a volatile oil.

is an almost universally accepted fact for the determination of actual effects in classroom settings. For such work,

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7-10-68. It has been in use in Alaska, U.S.A. of
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out with a second portion by the abbreviated process of

212. ---holding in memory of German slaveholders.

which was collected in 1885 by G. K. Krasovskii (189). The

...of the

10-10-68

1. The following information is being furnished to you for your information only. It is not to be used for any other purpose.

1. *Hydrochloric acid*. Dilute the solution with 10 c.c.

normal mental balance is utilized to show extent of

on a large scale, would require the use of a large number of people, and the cost of such a project would be very high. It is therefore not feasible to build a large-scale system of this type.

[illegible]

WATERBURY, CONN. (AP) — A woman who said she was the mother of a young man who had been shot and killed in a drive-by shooting in Waterbury, Conn., on Monday, said she was not sure if she was the mother of the victim.

244. The method departs in the last stage from that of Haubensak, dissolves out the alkaloid, after adding caustic soda, with chloroform, evaporates the solution, dries and weighs. Kursteiner substitutes for the chloroform a mixture of chloroform and ether as less apt to emulsionize. It would seem advisable instead of weighing the precipitate on a tared filter, to dissolve it in alcohol, evaporate the solution, dry and weigh, or else dissolve in alcohol and determine alkaloid by alkalimetry. Haematoxylin, Brazil wood or cochineal may be used as indicator.

245. Short method of H. Hager (60) :- Mix 10 grams of the finely powdered bark with 100 c.c. of water and 10 c.c. of a solution of caustic potash, sp. gr. 1.35; heat and keep at the boiling point 15 minutes, add 15 grams of dilute sulphuric acid, sp. gr. 1.115 and boil 20 minutes, cool, transfer to a measuring cylinder and dilute to a measure of 110 c.c. (allowing this 10 c.c. for the bulk of the woody fiber, etc.), pass through a dry filter and to 60 c.c. of the filtrate, taken to represent 6 grams of the drug, add 50 c.c. of a cold saturated solution of picric acid. After half an hour, collect the precipitated picrates on a pair of mutually counterpoised filters, wash with a little cold water, dry and weigh. The product contains 42.5 percent. of its weight of alkaloids, which may be separated and weighed as such, by suspending the precipitate in cold water, adding excess of caustic soda and washing out with chloroform.

[illegible][illegible]

246. Method of the British Pharmacopoeia:- Mix 15 grams of cinchona bark in No. 60 powder, with 4.5 grams of calcium hydrate, moisten with 16.5 c.c. of water, mix intimately in a capsule, let stand an hour or two, when the mixture should be moist, dark brown powder with no lumps or visible white particles. Transfer to a small flask, add 100 c.c. benzolated amyl alcohol (amyl alcohol, 1 part, benzol sp. gr. 0.850, 3 parts). Connect the flask with an inverted condenser, boil half an hour, decant and drain off the liquid on to a filter, leaving the powder in the flask; repeat the boiling with two fresh portions of the same solvent, transfer the residue to the filter and exhaust by percolation with the benzolated amyl alcohol. Introduce the filtrate while still warm, into a separator, add 1.3 c.c. dilute hydrochloric acid and 8 c.c. water. Shake well together, separate the acid solution, repeat the washing with successive small portions of acidulated water until all the alkaloid is removed.

247. Neutralize accurately the mixed acid solutions with ammonia, while warm, and concentrate to a volume of 12 c.c., add one gram of sodium and potassium tartrate in powder, stir well with a glass rod and set by in a cool place. After an hour, collect the quinine and cinchonidine tartrates on a pair of mutually counterpoised filters, wash with several small portions of water, drain, press, dry and weigh. The weight multiplied by 0.8 will be approximately that of the quinine and cinchonidine present. The remainder of the alkaloids is contained in the filtrate and washings, to which solution of ammonia is to be added in slight excess. Collect the precipitate on a pair of mutually counterpoised filters, press dry and weigh. The weight added to that of the quinine and cinchonidine already obtained, is that of the total alkaloids in 15 grams of the drug. Of course, the precipitation with sodium and potassium tartrate may be omitted if we desire only total alkaloids.

248. Method of U. S. Pharmacopoeia:- To 20 grams of cinchona in a very fine powder and contained in a bottle fitted with accurately ground stopper, add 200 c.c. of a previously prepared mixture of 19 volumes of alcohol, 6 volumes of chloroform and 1 volume of ammonia, stopper the bottle and shake thoroughly and frequently during 4 hours. Then pour off through a funnel containing a pellet of absorbent cotton, 100 c.c. of the solution (representing 10 grams of the bark), and evaporate to dryness. Dissolve the residue in 10 c.c. water and 4 c.c. normal sulphuric acid with the aid of a gentle heat, cool, filter into a separatory funnel and wash breaker and filter until the filtrate is no longer acid, using the smallest practicable amount of water. Add c.c. of normal potassium hydrate to render decidedly alkaline and extract alkaloid by shaking the mixture first with 20 c.c. and then repeatedly with 10 c.c. chloroform, until a drop of the last chloroform extraction leaves no residue when evaporated on a watch glass. Evaporate in a tared beaker, dry at 100 C. and weigh.

249. The practical difficulty in the above process is in the tendency of the alkaline solution to emulsify when shaken with chloroform. This is much less likely to occur if a mixture of 1 volume chloroform and 4 volumes ether be used for the extraction and when a quantity of the solution re-

representing not more than 0.5 gram of the drug is employed, this solvent not working in a wholly satisfactory manner. If one wishes to work with a large amount, it is better to precipitate the alkaloid from the acid aqueous solution with caustic soda or potassa as in (170). See also (171).

250. Assay by Kerosene:- E. Lordin (61) uses kerosene as a solvent for the liberated cinchona alkaloids in a process of assay of Java Red bark, as follows: 300 grams of finely powdered bark are mixed with 75 grams lime suspended in water and 75 grams of a solution of soda 40° Baume. The use of two alkalies is essential for the complete extraction of the alkaloids. Two litres of petroleum are then added and the mixture heated at 100° C. for 20 minutes with considerable agitation. The petroleum is decanted off and the residue treated in a similar way with a second 2 litres. The four litres of oil are then agitated for 10 minutes with 75 c.c. of 10% sulphuric acid and 150 c.c. water: The acid liquid decanted off and the treatment repeated with same quantity and a third time with 1/2 the quantity. The first and 2nd acid solutions are then heated to boiling and neutralized with ammonia in order to precipitate resins, and the 3rd acid solution which is used to wash the filter in the first operation is treated in a similar manner. When the neutralized liquids cool, they deposit in the form of sulphates about 90% of the alkaloids present in the bark. The mother liquors are precipitated by soda and the precipitate is treated with just a sufficient quantity of dilute sulphuric acid to convert it into sulphate. The sulphates are weighed together and the alkaloids separated if desired.

251. The lime process:- The U. S. Pharmacopoeia of 1880, adopted for the assay of cinchona bark, the lime process which was generally practiced at that date. It has been shown that a notable loss of alkaloid results from a prolonged action of lime. For this reason, among others, the method has fallen into disuse, but it had at least a historic importance. The process was as follows:- Five grams of freshly slaked lime are mixed with 50 c.c. water, 20 grams of the finely powdered bark thoroughly incorporated with the mixture and the whole then dried at a temperature not exceeding 80° C. The powder was then exhausted (best by hot repercolation) with strong alcohol and dilute sulphuric acid added to a distinctly acid reaction as shown by litmus paper. The solution was filtered to separate calcium sulphate, the alcohol recovered by distillation from the filtrate and washings, the residue treated with acidulated water to procure a solution from which, after filtration, the alkaloids were either precipitated by soda solution or washed out with chloroform after addition of alkali.

252. Preforator Method (62) by Lidden Holsebosch:- Place 3 grams of finely powdered cinchona bark and a mixture of 1.5 c.c. ammonia, 3 c.c. of strong alcohol and 25.5 c.c. ether in a tightly closed bottle fitted with a glass stopper. Macerate for 24 hours with frequent agitation. From the upper part of the clear fluid draw off 10 c.c. with a pipette and place in a small beaker, add 1 c.c. or, if necessary, 2 c.c. of dilute hydrochloric acid and 9 c.c. water and evaporate off the ether and alcohol by warming on the water bath, making sure that the residual fluid has an acid reaction. If such is not the case, add a few drops more of hydrochloric

acid. On cooling, filter through a mat of cotton into the perforator, rinse beaker and funnel with a very small quantity of water and add to other fluid. Connect and wash the acid solution with ether for an hour or so as to remove all ether-soluble substances. Now, attach new receiving flask, render acid solution slightly alkaline and wash with ether for 2 hours or until exhausted. Separate, evaporate, dry and weigh.

Wt. x 100 equals percent.

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1875

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253. Assay for total alkaloids (63) :- 20 grams of very fine powder are placed in a flask holding 500 c.c. of 10% ammonia and 20 c.c. alcohol of 94% added, and a mixture well shaken. Then, 170 c.c. ether added and shake occasionally for 2 or 3 hours. Then decant 100 c.c. of the clear liquid into a separatory funnel containing 50 c.c. water and 2 c.c. dilute sulphuric acid (sp. gr. 1.117), or sufficient quantity to give the aqueous solution an acid reaction after agitation with the ethereal solvent. Separate the yellowish acid solution from the ethereal layer, warm to expel the dissolved ether and return to a clean separatory funnel; add 300 c.c. chloroform and then enough ammonia to precipitate the alkaloids and agitate at once for several minutes; the chloroform solution is received in a small tared flask and the agitation repeated with portions of 20 c.c. each, until the alkaline solution after acidifying, fails to give a precipitate with iodine solution; distill off the chloroform or allow it to evaporate, dry contents at 100°C. and weigh. In case the chloroform forms an emulsion when shaken with the alkaline solution, it should be poured upon a filter well wetted with chloroform, stirred with a glass rod and washed with a little more chloroform. The success of the method depends upon the fineness of the powder used.

254. Schwickerath Method (64) :- 3 grams of the drug, finely powdered and dried are macerated with 150 c.c. weak Prollins mixture for about 20 hours, shaking frequently (it is best to use an agitating apparatus). Then filter off 50 c.c. corresponding to 1 gram drug. Place in a shallow dish, add 10 c.c. dilute hydrochloric acid (1 to 10), and evaporate the alcohol and ether at moderate heat. The acid solution thus obtained is now filtered into a perforator and method conducted as per (51).

255. Assay by acid was also formerly much used. The method of Dr. De Vrij gives fairly good results and depends chiefly upon the facts that the alkaloids are dissolved out by means of a mixture consisting of 88 parts ether, 4 parts ammonia and 8 parts alcohol. After maceration and separation, the solution is evaporated to dryness, leaving the crude alkaloids, which are purified by solution in acidulated water, filtration and precipitation by means of an alkali and re-dissolved in chloroform which upon evaporation, leaves pure alkaloids. This process has been improved and made a very easy method of assay as follows:- 400 grams of the bark in fine powder are boiled for 10 minutes with 5 ounces of water and 45 minims strong hydrochloric acid. When cool, the liquid portion is filtered through absorbent cotton placed in the neck of the funnel, into which the powder having been transferred, is rather tightly pressed and 2 ounces of water poured on and allowed to percolate. This is added to the filtrate and the powdered cinchona again boiled with 5 ounces water and 30 minims acid. This is then filtered same as before, using same funnel and cotton. The bark is then thoroughly exhausted by percolation with acidulated water, the acid being used in proportion of 5 minims to fluid ounce and requires in all about 5 ounces. The filtrates are now

[illegible]

mixed and re-filtered through absorbent cotton. The filtrate is then thoroughly agitated with 6 drachms chloroform and after clean separation, drawn off. The washing is then continued a second time with like amount of chloroform.

256. From the acid solution above, the alkaloids may be separated (a) by precipitating with caustic soda in excess, (add to weight obtained, as a correction for solubility of alkaloid, 0.000585 gm. for each c.c. of filtrate and washings) or (b) by adding excess of caustic soda and shaking out with chloroform. Evaporating, drying and weighing. The author lays particular stress on the avoidance of heat in the extraction of bark with dilute acid, and declares that sulphuric acid will not completely exhaust the drug while hydrochloric acid certainly will.

257. Modified Assay Process:- Ekross (66) proposes the following process, which is a modification of that of C. C. Keller. 12 grams of the finely powdered bark are macerated with occasional agitation, in a mixture of 120 gm ether and 10 c.c. of a 10 percent. solution of sodium hydrate, during 3 hours and 10 c.c. water are then added to the mixture; 100 gm of the clear ethereal solution are then weighed direct into a separatory funnel, shaken with 30 c.c. N/10 sulphuric acid, the ether washed twice successively with two portions of 20 c.c. water and the united acid aqueous liquor is titrated with N/10 potassium hydrate to determine excess of acid, haematoxylin being used as indicator. 1 c.c. N/10 sulphuric acid corresponds to 0.034 gm. alkaloid.

258. Assay with the aid of Chloral Hydrate (67) :- The extraordinary solvent action of a concentrated solution of chloral hydrate (8 to 5 parts of water) upon the dry cell contents, well known to microscopists, has been successfully applied by Dr. W. Lenz, to the extraction of alkaloids in assay processes, but more particularly to the assay of cinchona bark. By its use, the troublesome pulverization to extremely fine powder as well as the application of strong reagents, is avoided; the process as given by the author is briefly, as follows:- 10 grams of the powdered bark are moistened in a flask of about 300 c.c. capacity, with a solution of 20 grams of chloral hydrate in 12.5 grams of water, and allowed to stand over night. The somewhat tough mass formed is heated for 1/2 hour on a water bath with 150 c.c. dilute alcohol and 2 gm. of hydrochloric acid, filtered through glass wool and the residue washed with the aid of a suction pump to complete exhaustion with warm dilute alcohol, containing a few drops of hydrochloric acid. The alcoholic solution is concentrated to consistence of syrup and this is then carefully mixed with water acidulated with a few drops of hydrochloric acid, so long as the separation of resin takes place, observing that this separation of resin shall be flocculent and not in a coherent mass. The filtered aqueous solution is then made alkaline with soda solution and the alkaloids shaken out with three portions of 100 c.c., 50 and 50 c.c. of chloroform. This chloroform solution of the alkaloid is then, in turn, shaken out with three

... and the following results were obtained: ...
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... in the case of ...

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portions of 100, 50 and 50 c.c. water containing 2 percent. hydrochloric acid and finally with small amount of pure water. The acid aqueous solution is then again made alkaline with soda solution and shaken with 100 c.c. ether, the ether solution removed as soon as it separates and this shaking out repeated in the same manner, using fresh portions of 50 c.c. ether, until nothing more is exhausted by that solvent. This part of the process must be carried out with expertness and expedition so that the alkaloids which are with difficulty soluble in ether may not separate from the solution into which they have temporarily entered. Evaporation to dryness and constant weight at 100°C. finishes the process. The alkaloidal residues obtained in this manner, are colorless and apparently purer than those obtained in most assays.

63/2
259. Acetic Assay process of Dr. E. R. Squibb (68):- Ten grammes of the powdered cinchona in a capacious capsule is moistened with 10 c.c. of 10% acetic acid, the lumps all well broken up, the moist powder packed firmly in some form of percolator and percolated to complete exhaustion with 10% acetic acid. The degree of exhaustion is judged by the degree of bitterness of the final percolate which is not quite bitter free when the lower part of the powder is quite bitter free though not tasteless.

[illegible]

260. The entire percolate is evaporated in a flat-bottom capsule to the condition of a soft solid, when cold, capable of being stirred while hot. This extract usually weighs 35 to 38 percent of the cinchona and it retains a small amount of acetic acid. While heated on the water bath, 30 c.c. of a previously made mixture of 5 volumes of 10% water of ammonia, and 15 volumes of 91 percent alcohol is added, the mixture stirred to a uniform condition and poured into a separator of 160 to 180 c.c. capacity. The capsule is rinsed into the separator with a mixture of 10 c.c. of the ammonia mixture and 10 c.c. of alcohol and the whole is well shaken together. If much ammonia has been lost in dissolving the extract; if much acetic acid should have been retained in the extract, or if the cinchona should be very rich in alkaloids, the 40 c.c. of the ammonia mixture may be insufficient to set the alkaloids free. This point is always to be assured by the smell of ammonia at the mouth of the separator or by holding a strip of wet and neutral litmus paper in the air space of the separator. If the alkaline reaction be not full and prompt, 5 c.c. more of the ammonia mixture is added and the shaking and testing repeated.

261. Then 40 c.c. chloroform is poured into the separator, the whole is vigorously shaken for 5 min. and then allowed to separate and requires ten to fifteen minutes and then this chloroform solution is drawn off into a tared flask of about 100 c.c. capacity and is then put on the water bath to boil off the chloroform. Then 5 c.c. of 91 percent alcohol is added to the residue in the separator, is shaken in and then a second 40 c.c. chloroform added, and the whole again shaken for five minutes, allowed to separate and the chloroform drawn off into the tared flask with the first portion and the whole of the chloroform boiled off in the bath. If the alcohol be omitted from the residue before the second washing, an emulsion is almost certain. The apparent excess of the chloroform is necessary not so much for the washing out of the alkaloids as to avoid emulsion. The residue is run from the separator into the beaker, is well stirred, five or six drops are transferred by the stirrer to the end of the strip of bibulous paper and dried on the bath. This, when taken into the mouth and well chewed, should be bitterless.

262. The chloroform solution, when the chloroform, ammonia and alcohol are boiled off, leaves a very dark residue in the flask, usually weighing about one gramme. This is dissolved in 20 c.c. of chloroform by shaking and 10 c.c. of water added and shaken. Then 20 c.c. of decinormal sulphuric acid is run into the flask from a burette, shaken for 5 minutes and the whole transferred to the separator and well shaken. When the liquids separate, the lower chloroform layer is drawn off into a small beaker with the first watery portion. The chloroform solution is now tested by drying upon bibulous paper, as before described, and if found bitter free, it is thrown away, but, if still bitter to the taste, it is again washed.

263. To the watery acid solution in the larger beaker, 30 c.c. of decinormal potassium hydrate is added with stirring the whole transferred to a separator, 25 c.c. ether added and the mixture well shaken. When the liquids separate, 5 c.c. of decinormal alkali is added to the separator, producing a

12
heavy precipitate that is re-dissolved when shaken. This addition of decinormal alkali is repeated until one addition-fails to produce a cloudiness. Then the mixture is shaken for five minutes, allowed to separate and the lower watery liquid is drawn off into the larger beaker. The ethereal solution cannot be drawn off clean through the stop-cork, but can be poured off through the mouth of the separator, to the last drop, into the tared beaker, leaving the little emulsion and water drops behind. To these residues in the separator, 20 c.c. ether is added, again shaken for 5 minutes, allowed to separate, drawn off and poured off as before and this washing is repeated a third time.

264. The watery portion is now tested and should be found bitter free, or to be againether-washed. The ether solutions in the tared beaker are boiled off in the bath and leave a varnish like residue of an amber color, consisting of total alkaloids and a little insoluble waxy matter. This is weighed in order to get the approximate percentage of alkaloids, and for each one percent of these crude alkaloids, 5 c.c. decinormal acid is run into the beaker from a burette and 10 c.c. water added. But these alkaloids are difficult and slow to dissolve in the acid, so that time is saved by first dissolving them in 3 or 4 c.c. ether, by rotary agitation, before the acid is run in. When the acid is run in, the waxy and fatty matters are precipitated and a stirrer and warming are then used to free this precipitated matter from alkaloids and to drive off the ether. The Alkaloids are thus converted into acid salts and dissolved and the insoluble matter is deposited on the sides and bottom of the beaker. If the nearly clear solution be now evaporated and the weight taken from the weight of crude alkaloids, the pure alkaloids are known. The alkaloids may then be precipitated and dissolved by immiscible solvents or tetrated.

265. Assay of the alkaloids of Cinchona Bark:- As a general rule, it is sufficient generally to determine the amount of quinine in a given sample of total alkaloids and the most simple way is first to convert the mixed alkaloids into sulphates. Dilute the solution moderately, heat to about 85 degrees C., neutralize carefully and cool, when the quinine sulphate nearly all crystallizes out, accompanied by a small quantity of the other alkaloids. Another plan is to precipitate together quinine and cinchonidine as tartrates, as in the method of the British Pharmacopoeia (247). In the case of red barks, rich in cinchonine, this is not very satisfactory. A third plan is to determine simply the total ether-soluble alkaloids (practically quinine and cinchonidine), or better the amount of alkaloid, which is held in solution one hour by a limited amount of ether, cinchonidine, which is taken up freely when first precipitated, being soon deposited in crystals.

266. The method of the U. S. Pharmacopoeia is an attempt to come still closer to the quantity of quinine. It is conducted as follows:-- The alkaloids from 5 grams cinchona bark, by whatever process it may have

204. The primary purpose of this paper is to present a method for the determination of the relative amounts of the various components of a mixture. The method is based on the principle that the relative amounts of the components can be determined by measuring the relative intensities of the peaks in the spectrum. The method is applicable to mixtures of compounds which are capable of being converted into a common form, such as the oxides of the elements. The method is described in detail in the following sections.

The first step in the method is to convert the mixture into a common form. This is done by heating the mixture in a stream of oxygen. The products of the combustion are then collected in a series of absorption tubes. The relative intensities of the peaks in the spectrum are then measured. The relative amounts of the components can then be determined by comparing the measured intensities with the intensities of the peaks in the spectrum of a known mixture of the components.

The method is applicable to mixtures of compounds which are capable of being converted into a common form, such as the oxides of the elements. The method is described in detail in the following sections.

205. A study of the literature of this subject has shown that the method described in this paper is a new and original method for the determination of the relative amounts of the various components of a mixture. The method is based on the principle that the relative amounts of the components can be determined by measuring the relative intensities of the peaks in the spectrum. The method is applicable to mixtures of compounds which are capable of being converted into a common form, such as the oxides of the elements. The method is described in detail in the following sections.

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206. The method of the U. S. Bureau of Standards is a method for the determination of the relative amounts of the various components of a mixture. The method is based on the principle that the relative amounts of the components can be determined by measuring the relative intensities of the peaks in the spectrum. The method is applicable to mixtures of compounds which are capable of being converted into a common form, such as the oxides of the elements. The method is described in detail in the following sections.

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The method is applicable to mixtures of compounds which are capable of being converted into a common form, such as the oxides of the elements. The method is described in detail in the following sections.

been extracted, is brought into solution in chloroform (or alcohol) and poured little by little, over about 5 grams of powdered glass contained in a porcelain capsule on the water bath, causing the powder to absorb nearly all of the alkaloid. The solvent is wholly driven off, the capsule allowed to cool and the powder moistened with ether transferred without loss by aid of successive small additions of ether to an ether moistened filter 7 cm. in diameter, in which it is treated with ether, drop by drop until exactly 10 c.c. of filtrate are obtained. The receiver is then changed and the treatment with ether continued until another 10 c.c. has been obtained.

267. Evaporate in separate tared capsules, the two portions of ether, dry at constant weight at 100 degrees C. and weigh. The residue from the first portion will contain nearly all the quinine together with a portion of the less soluble alkaloids. The second portion will contain about as much of the less soluble alkaloids as the first, with almost no quinine. We have then simply to deduct the weight of the latter from that of the first to obtain the amount of quinine in 5 grams of the bark. The method is faulty, in taking no account of amorphous ether-soluble alkaloids of which there may be a notable quantity present, reckoned by this method as quinine. The alkaloidal residue dried at 100 degrees C., will contain still one molecule of water; to convert into anhydrous alkaloid, multiply by 0.947.

268. Another mode of determining ether-soluble alkaloids is that of Dr. Otto Kaspar. Dissolve the alkaloids from 10 grams of the bark in a slight excess of hydrochloric acid, make up to a volume of 10 c.c., add caustic soda in excess (according to the author, 15 grams of a 10% solution) and shake immediately with 15 c.c. ether; separate the ether and shake again twice with fresh portions of 15 c.c. each, unite the ethereal solutions, let stand at least twelve hours for the crystallization of the less soluble quinidine and cinchonidine, evaporate, dry at 100 degrees C. and weigh. It seems that the quantity of ether as well as that of the soda solution, is needlessly larger than is necessary. With a moderate excess of soda solution and three portions of ether, 15, 10, and 10 c.c., the

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results would be as well; also, it seems as though better results would be obtained in the use of petroleum-ether in place of ether, but experimentation would be necessary to determine the quantity of this solvent required. Perhaps a still better plan would be to extract the bark direct with petroleum-ether and ammonia, let stand 24 hours for the crystallization of the less soluble alkaloids, and recover the alkaloid in pure form by shaking out with acidulated water, rendering alkaline and shaking out with ether.

269. Method of DeVrij, by precipitation with Chinoidine iodosulphate. (69):-- Dissolve the mixed alkaloids in 40 times their weight of 92% alcohol, containing 0.76 percent of sulphuric acid (or dissolve in normal sulphuric acid, using 6.2 c.c. for each gram of alkaloid. Evaporate to one-half and add 46 c.c. strong alcohol for each gram of alkaloid). If the bark under examination contains a large porportion of cinchonidine, digest the crude alkaloid in powder with 10 times its weight of ether; after standing half an hour or more, decant the ether and wash the residue with a small additional portion of the solvent. Evaporate the dryness, the etherealsolution, which will contain all the quinine and employ this instead of the total alkaloids for the test.

270. To the solution in sulphuric acid and alcohol, add solution of chinoidine iodosulphate (27) from a pipette, drop by drop, stirring constantly, as long as a dark brownish red precipitate of herepathite is produced. As soon as all the quinine is precipitated and a slight excess of reagent added, the solution acquires an intense yellow color. The beaker is now to be covered and heated to boiling on the water bath. Cool, note the volume of fluid, filter and wash the precipitate on the filter with a saturated solution of herepathite in alcohol of 92%. Dry the precipitate at 100 degrees C. and weigh. Add to the weight found, for each c.c. of fluid previous to filtration, 0.0011 gm., as a correction of solubility of the herepathite in alcohol. Multiply the corrected result by 0.55055 to obtain anhydrous quinine, or by 0.7409, to obtain crystallized sulphate of quinine.

271. Improved Ether method of A. Petit. (70):- Dissolve the alkaloids from 30 grams of cinchona bark in a slight excess of sulphuric acid, add 25 c.c. ether

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the investigation, which will contain all the following and which will be used as the basis for the report.

100. The results of the solubility tests are given in Table I. The solubility of the polymer in water is very low, and the solubility in organic solvents is also low. The polymer is soluble in benzene, toluene, and chloroform, and in some of the higher alcohols. The solubility of the polymer in water is very low, and the solubility in organic solvents is also low. The polymer is soluble in benzene, toluene, and chloroform, and in some of the higher alcohols.

is a slight excess of potassium; and, the 20.0 g. of
Disodium hexafluorantimonate from 50 grams of sodium hexa-
fluorantimonate was dissolved in 250 ml. (10.41 g.)

and 5 c.c. water of ammonia and shake. Decant the ether into a vial, shake the alkaline solution once more with 10 c.c. ether, which is to be added to the first ethereal portion. Let the ether stand 15 minutes. Decant the clear solution into a separator, add 10 c.c. of dilute sulphuric acid (1 to 20), shake and separate. Wash the ether a second time with 5 c.c. of the same acid, and then with water enough to make in all 25 c.c. of fluid. Heat this in a beaker to boiling add cautiously dilute solution of ammonia until the liquid is faintly alkaline, cool to crystallize quinine sulphate, which is collected on a tared filter, washed with a saturated aqueous solution of quinine sulphate, dried at 115 degrees C. to constant weight and weighed as anhydrous sulphate.

272. Oxalate Method of G. Shimoyama (71) :--

Dissolve the alkaloids (at least 0.5 gm.) in a beaker in 30 or 40 c.c. of water, by aid of the smallest possible amount of acetic acid. Filter into a tared beaker, wash the filter and neutralize exactly with dilute solution of soda, add for each gram of the alkaloids, 10 c.c. of a cold saturated solution of sodium oxalate. Concentrate on the water bath, to 8 or 10 grams, should a slimy mass separate during the concentration, it must be filtered off and well washed with boiling water. To the contents of the beaker, add 10 to 15 c.c. of water and stir until a clear solution results. Set aside three hours at a temperature of 18 degrees C., stirring frequently. Collect the precipitate on a double filter and wash thoroughly with a saturated solution of quinine oxalate. Dry at 110 degrees C., weigh and add for each c.c. of fluid previous to tetration, 0.00064 gm. to obtain the weight of the quinine as oxalate. Multiply this by 0.878 for anhydrous quinine, or by 1.1815 for crystallized quinine sulphate.

273. Full Assay of Cinchona Alkaloids. John Muter (72) directs to dissolve the alkaloids, which have been weighed after drying at 116 degrees C., in absolute alcohol and divide into two equal portions A. and B. To portion A., add from a burette, volumetric sulphuric acid (11.6 grams of acid sp. gr. 1.843, to one litre of water; each c.c. equals 0.1 gram crystallized quinine sulphate) until just faintly acid to delictae litmus paper and note the quantity of acid used as a guide in the further operations. Evaporate the alcohol and dissolve residue in water at 85 degrees C., using 5 c.c.

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2751 70th Street, St. Louis, Missouri 63119. This house is a 1 1/2 story, brick, single family home, with a full basement. It is located in a quiet neighborhood, close to schools and shopping. The house has a large front yard, a two-car garage, and a finished basement with a family room, kitchen, and bathroom. The asking price is \$125,000. Call Bob Smith at 314-734-1234 for more information.

water for each c.c. of volumetric acid used. If necessary, add a little of the volumetric acid to effect complete solution. Keeping the temperature at about 85 degrees C., add cautiously, drop by drop, decinormal solution of caustic soda until all but neutral.

274. Cool, the solution rapidly to 15 degrees C.; keep at that temperature for an hour, filter through a pair of counterpoised filters, and wash the crystals with a little cold water (1.5 c.c. for each c.c. of the volumetric acid used in the preliminary titration). Drain the crystals, press, dry at 100 degrees C., raising the temperature gradually to 116 degrees C. and weigh as anhydrous quinine sulphate. (In the weighing, bear in mind that this is exceedingly hygroscopic; it should be weighed in a weighing bottle, securely stoppered). Measure the filtrate and washings, and for each c.c. of the fluid, add to the weight actually obtained, 0.000817 gm., as a correction for the solubility of quinine sulphate in water. Multiply by 0.8686 for quinine alkaloid.

275. To portion B. add hydrochloric acid (dilute), until it has a faint acid reaction, evaporate, and dissolve the residue in a minimum quantity of water at 38 degrees C. Neutralize accurately with decinormal soda solution, add a saturated solution of sodium and potassium tartrate in excess, cool and keep at temperature of 15 degrees C., for one hour, frequently stirring. Collect on a pair of mutually counterpoised filters, wash with 100 c.c. of water at 15 degrees C., dry at 104.4 degrees C., and weigh. Add for each c.c. of filtrate and washings, 0.00083 gm. to obtain weight of tartrates of quinine and cinchonidine. Deduct the weight of quinine tartrate, found by multiplying the weight of anhydrous quinine sulphate by 0.915. The remainder, multiplied by 0.804, will give cinchonidine alkaloid.

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276. Concentrate the filtrate and washings from the tartrate to its original volume, cool, render faintly acid with acetic acid, and add with constant stirring, an excess of a neutral saturated solution of potassium iodide. After an hour or so, collect, wash, dry and weight precisely as in the case of the tartrate. Add 0.00077 gm. for each C.C. of filtrate and washings and multiply by 0.7168 for quinine alkaloid.

277. From the filtrate and washings, precipitate the rest of the alkaloid with sodium hydrate, collect on a pair of mutually counterpoised filters, wash, dry at 104 degrees C. and weigh. Heat with 40 percent alcohol to dissolve out amorphous alkaloid, dry the residue at 105 degrees C. and weigh as cinchonine alkaloid. The difference between this weighing and the previous one gives the quantity of amorphous alkaloid, but must be corrected by deducting for each c. c. of filtrate from the precipitated tartrates 0.00066 gm., and for each c. c. of filtrate from quinidine hydriodide 0.00052 gm.

278. Assay the Galenical Preparations of Cinchona Bark:-- For fluid extracts:-- put into a 25 c.c. measuring flask 5 c.c. of the fluid extract and fill to the mark, with dilute alcohol. Use 5 c.c. of the mixture equivalent to 1 gram of the drug, for the assay. If the fluid is thought to be poor in alkaloid, use 10 c.c. instead of 5 c.c. to make the dilution. Assay according to detail in (150) to (152). Should there be any tendency to emulsionize, use Thompson's sawdust process (159).

279. Carl Schwickerath (73) directs to put into a 50 c.c. measuring flask 10 c.c. of dilute Hydrochloric acid (10 percent), add 5 c.c. of the fluid extract (with Cinchona Comp., 10 c.c.), shake, make up to 50 c.c., shake well, allow to settle and filter. Put into a perforator (9), 10 c.c. of the filtrate and extract one hour with petroleum-ether to remove fatty substances then add an excess of caustic soda and extract 3 to 4 hours with a mixture of chloroform and petroleum-ether. Pour off the supernatant liquid into the flask and evaporate the solution on a steam bath preferably with the aid of an air current. The alkaloids thus obtained are perfectly white. Dry for a short time at 100 degrees C. when they will become slightly yellow. Finally determine the amount of alkaloids by weighting. The weight obtained x100 (with cinchona comp. 50) -percent alkaloids.

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1961. The following information was obtained from the records of the Department of the Interior, Bureau of Land Management, regarding the land owned by the United States in the area of the proposed project. The land is located in the area of the proposed project and is owned by the United States. The land is located in the area of the proposed project and is owned by the United States. The land is located in the area of the proposed project and is owned by the United States.

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230. Solid Extracts are to be treated on the general principles stated in (171) et. seq.

231. Proportion of alkaloid present in Cinchona Bark. The U. S. P. requires that a bark shall contain 5 percent of total alkaloids and not less than 2 1/2 percent of quinine. The barks offered in the market vary from 4 to 7 percent, the average running from about 4.4 to 6 percent for yellow bark; and from 4.5 to 8 for red bark. The richest government bark brought to the market, until recently, has not exceeded 9 1/2 percent of sulphate of quinine; 7 to 8 percent is a good average in government plantations. Bark from the trees in the government gardens at Picoeng Goenoeg, Java have been recently analyzed and found to equal respectively 12.66 and 16.04 percent of quinine sulphate. Barks however, of this nature are not upon the market for sale. The standard of 5% for total alkaloids is a good average of commercial barks.

COCA LEAVES.

282. The leaves of *Erythroxylon Coca* are obovate or lanceolate, entire, from 20 to 70 m.m. ($\frac{4}{5}$ to $2\frac{4}{5}$ in.) long; midrib prominent, with two distinct curved lines at equal distances on each side running from base to apex; these lines are not ribs, however, but are folds caused by the manner in which the leaves were rolled in the bud; dark green on upper side, lighter beneath; odor tea-like; taste bitter and somewhat aromatic, temporarily numbing the lips and tongue when chewed. The leaves cultivated in Java and India are inferior to the South American variety.

283. The chief constituent of the leaves is the alkaloid cocaine. It is soluble in ether, petroleum-ether, and kerosene oil, by means of which solvents, it may be completely removed from alkaline solutions. The alkaloid is represented to be a methyl benzoyl compound of another organic base, ecgonine. This complex body cocaine is readily decomposed into its component parts, methyl alcohol, benzoic acid and ecgonine, by heating with hydrochloric acid. Hydrochloric acid, therefore, is unsuitable for the extraction of cocaine in the process of manufacture. Hence, being an unstable body, we must avoid heat or prolonged contact with strong alkalies and acids.

284. The assay may be made by the short assay process No. 3, (75), which yields a particularly pure alkaloid. The main object in coca assay is avoidance of heat, strong acids or strong alkalies for any length of time.

285. Schwickerath Process. (74):- Digest in an agitator for 12 hours, 12 grams coca-leaves, with 95 c.c. benzene, 1 c.c. 30% ammonia and 4 c.c. alcohol. Shake vigorously and then let settle; filter through cotton 50 c.c. (equivalent to 6 grams of the drug) add 2 c.c. dilute sulphuric acid (2.5%), and 8 c.c. water, evaporate alcohol and benzene, and filter the acid solution into the perforator. Wash first for one hour with ether and after adding 4 or 5 c.c. dilute ammonia, extract 3 or 4 hours with ether. Evaporate ether and determine alkaloid with N/100 sulphuric acid. 1 c.c. acid - .00303 grams alkaloid.

286. Assay by Percolation with Ammoniated ether:-
A. Gunn (75) prefers percolation to maceration and proceeds as follows:- Moisten 5 grams of the powdered leaves with a 2% solution of ammonia. After half an hour, place in a narrow tubular percolator (25x1.5 cm.) and percolate with ammoniated ether to obtain 100 c.c.

From the percolate, the alkaloid is washed out with 3 portions of 2% hydrochloric acid, in all about 50 c.c. from which in turn, it is finally extracted with ether after addition of ammonia.

287. Ketosene process of Dr. Squibb⁽⁷⁶⁾:- 100 grams of the powdered leaves are moistened with 100 c.c. of a 7% solution of crystallized sodium carbonate, packed at once in a percolator and percolated to about 700 c.c. with water white kerosene. The percolate is shaken out thrice successively with 30 c.c. of water containing 2% of hydrochloric acid. The acid solution is well washed with 30 c.c. of ether to remove fatty substances, the ethereal solution being rejected? Then 20 c.c. of ether are added with 10 c.c. of a solution of sodium carbonate containing 24" grams of the crystallized salt to the litre. (Dr. Squibb directs to use sodium carbonate sufficient to just neutralize the acid taken, and five per cent additional; there must be a distinct but not large excess), and the fluids well shaken together after the carbonic acid has escaped. The ether is separated and the treatment repeated twice with 20 c.c. of fresh ether. The ethereal solutions are transferred to a tared beaker, evaporated to constant weight, the weight of the residue in grams being the per cent of alkaloid.

288. The above procedure recommends itself by its directness and cheapness and, furthermore, it gives us a quantity of alkaloid sufficient to use for further determination of true cocaine. This may be carried out according to Grandval and Lajoux, by adding water equal to ten times the weight of alkaloids, and just enough hydrobromic acid to neutralize completely, heating the solution on the water bath and saturating rapidly with potassium bromide. On cooling, we obtain a crystalline mass of the double bromide of potassium and cocaine. Percolate the crystals in a funnel having the tube rather firmly plugged with absorbent cotton, with a saturated solution of potassium bromide, which will remove ecgonine. Finally, dissolve the crystals in hot water, cool and treat with ammonia and ether to remove the pure cocaine.

289. Koehler⁽⁷⁷⁾ mixes 50 grams of finely powdered leaves with 5 grams of dry crystallized carbonate of sodium and 15 grams of oxide of lead, macerates with 50 c.c. water and dries in vacuum at a temperature of the water bath. The mass is then twice macerated for 24 hours with 250 c.c. benzin each time, the alkaloid withdrawn from the benzin with hydrochloric acid which in turn is treated with sodium carbonate in excess and shaken out with ether. Van der Marck⁽⁷⁸⁾ mixes 50 grams of the powdered leaves with 20 grams of magnesia, dries at 60°C. and extracts with ether. The solvent is distilled over, the residue taken up with hydrochloric acid, 2%, the acid solution treated with ether to remove coloring matter,

[The text on this page is extremely faint and illegible. It appears to be a multi-paragraph document, possibly a letter or a report, written in a cursive or semi-cursive hand. The ink is very light, and the paper shows signs of age and wear.]

etc., made alkaline with ammonia water, and shaken out with three successive portions of ether (25 C.C.). Alexander Gunn⁽⁷⁹⁾ reviewing the different methods, decides that Lyons Ammoniated ether process is the best method; the only objection to the process being the time, it requiring 24 hours to complete, though there is no doubt that the extraction of alkaloids is complete. As a result of his work, he has modified the operation so that it may be completed in about two hours, as follows:- 5 grams of the powdered leaves are dampened with a solution of about 2% ammonia and allowed to stand for 1/2 hour. Then, placed in a narrow tubular percolator and percolated with ammoniated ether until 100 c.c. are collected. This is shaken out with 3 washings of 2 per cent hydrochloric acid, collecting about 50 c.c. in all of the washings. This acid solution is then washed once with ether, then made alkaline by ammonia and shaken out with 3 successive portions of ether. The ethereal solutions are carefully transferred to a tared dish, evaporated and weighed, after drying at 75°C.

290. Galencial Preparations:- For a fluid extract, follow the routine of (150) or (154), using for the first extraction ether in place of ether and chloroform; as an alternative, the saw-dust process (169). Tinctures and wine may be evaporated at very low temperature and treated by (159). Solid extracts are treated on general principles (171). When saw-dust is used, the solvent may be ether or petroleum-ether, as in the assay of leaves.

291. Proportion of Alkaloid in Coca leaves:- Coca leaves of good quality should yield of total alkaloid, as much as 0.6 per cent. Out of 15 samples examined, I have found the following percentages:- .63- .52- .65- .69- .58- .61- .57- .62- .68- .67- .43- .48- .5- .59- and .6, average .59. The standard strength now employed by leading manufacturers, is 5 per cent alkaloid, this representing an average sample of the drug.

COLCHICIUM.

292. Two parts of Colchicum autumnale are used, namely the corn and the seed. They are described as follows:-

(a) An ovoid corn about 25 to 40 mm. (1 to 1 3/5 in.) long, flattened and deeply grooved on one side; when dried and deprived of its outer membranous covering it is wrinkled and of a brownish gray color; internally whitish. It often comes into market in transverse starchy slices having a reniform outline, due to the lateral groove; inodorous; taste sweetish, bitter, and somewhat acrid. A very deep or large notch in the slices indicates that the

corn has been partially exhausted by the offset which springs from the base.

(b) The seeds are hard, brownish red; subglobular, 3 mm. (1/8 in.) diameter; somewhat pointed at the hilum and with a slight projection or carbuncle on one side; testa thin, somewhat scurfy, closely adhering to the white albumen which fills the entire seed and is known and characterized by its extreme hardness; embryo small, nearly opposite the hilum; inodorous; taste oily, bitter and somewhat acrid.

293. The active principle of colchicum seed or root (corn) is the alkaloid colchicine, which differs from most alkaloids in the following particulars:- 1st. It is removed from acid solutions by shaking with chloroform; 2nd. It is quite freely soluble in water; 3rd. It is precipitated from Mayer's Reagent, only from strongly acid solutions. The alkaloid is furthermore very easily decomposed, its aqueous solution rapidly losing strength even when quite neutral. Mineral acids, even quite dilute, decompose it on application of heat. These are facts to be borne in mind in devising a process of assay for the drug.

294. A very good process and one that has given very good results is the following method of Dr. Lyons:- Place 10 grams of the powdered drug in a flask or bottle, add 100 c.c. of Prollins mixture modified(12), cork securely and macerate with occasional shaking 12 hours, (or place in a mechanical shaker for 4 hours). Decant 50 c.c. of the clear liquid, evaporate in a beaker by a very gentle heat, nearly to dryness. Take up the residue with 10 c.c. ether, add 5 c.c. dilute hydrochloric or sulphuric acid (2.5%) and stir until the ether evaporates. Filter the acid solution into a separatory funnel, retaining the insoluble residue as much as possible, in the beaker to which it is indeed mostly adherent. Re-dissolve the residue in a little ether, add 2 c.c. of the dilute acid, stir as before, and filter the acid aqueous solution into the separator, wash the filter with a little of the acid, adding the washings to the contents of the separator.

295. Put into the separator, 15 c.c. chloroform, shake carefully but continuously---a rotary motion is best---during two minutes, let separate and draw off the chloroform into a tared beaker. Repeat the treatment with two portions of 10 c.c. each of fresh chloroform. Test a drop of the aqueous solution remaining after chloroform has evaporated, with Mayer's reagent; if this shows presence of alkaloid, repeat the treatment with chloroform, after having rendered the solution nearly neutral with ammonia. Three washings, however, will generally ex-

tract the alkaloid even in the presence of excess of acid. Finally, evaporate the chloroformic solution to dryness, re-dissolve in a little dilute alcohol and again dry to constant weight. The residue is nearly pure colchicine. It may have retained still some chloroform and therefore should be dissolved once more in dilute alcohol and dried.

296. Instead of extracting the alkaloid, we may determine it with reasonable precision, by titration with Mayer's reagent. The acid solution of (294) is made up to a volume of 10 c.c. for colchium root or 15 c.c. for colchium seed with dilute sulphuric acid 2.5% and Mayer's reagent is added from a burette as long as it produces any cloud in the filtered liquid (107). The quantity of alkaloid indicated by the titration may be found approximately by the following empirical rule:- Subtract from the quantity of Mayer's reagent, N 1-20 (14) consumed, for each c.c. of the fluid present at the end of the titration, 0.08 c.c. Each c.c. of the remainder will correspond with 14.7 milligrams of colchicine. Example- Taken 10 c.c. of acid solution; added 5.4 c.c. Mayer's reagent. $5.4 - 15.4 \times 0.08 = 5.4 - 1.23 = 4.17$; then $4.17 \times 14.7 = 61.3$ mg.

297. It is better to make the gravimetric determination as above (295), dissolve the alkaloid in about 300 times its weight of dilute sulphuric acid, 2.5 per cent and titrate as above. The result of the titration, when the above arbitrary rule is adopted, will be close if the alkaloidal solution has approximately an initial strength of 1.300; if weaker, the results are liable to be too high, if stronger, low. It is essential that the solution titrated contain not less than 2% of sulphuric acid; a little more will not materially affect the result.

298. K. Schwickerath (80) modifies slightly the process of Lyons, by using a modified Prollins mixture containing about 15 c.c. alcohol and 3 c.c. stronger water ammonia instead of 25 and 10 c.c. respectively. His process as given is as follows:- 20 grams of the drug rather finely powdered are consigned to agitation for 12 hours, with 120 c.c. of the modified Prollins mixture. Permits it to deposit and settle and then filters off 60 c.c. (equivalent to 10 grams drug), adds 8 c.c. water and adds acetic acid slowly until an acid reaction is obtained. The alcohol and ether are then evaporated at a moderate heat and the acid solution filtered through cotton into the perforator. Then, wash the solution with ether for one hour to remove impurities, then add carbonate of sodium to alkaline reaction and extract with a mixture of ether 3 volumes and chloroform one volume, taking care to insert just below the opening of the delivery tube, a ring of absorbent cotton. The alkaloid is to be dried with the

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precautions in (295) and weighed.

299. Proportion of Alkaloid in the drug:- Colchicum seed yields 0.5 to 1.0 per cent of colchicine, average about 0.7 per cent. Colchicum root is not quite so rich in alkaloid, but a drug of prime quality seldom falls below 0.5 or exceeds 0.75, average about 0.5 per cent. The regular standard now adopted for standardization of galenical preparations are 0.5 per cent for colchicum root and 0.5 per cent for the seed.

300. Assay of Galenical Preparations:- From a fluid extract (5c.c.) the alkaloid can be easily removed by adding an equal volume of water and shaking out with chloroform, using several portions of 15, 10, and 10 c.c. Determine the alkaloid exactly as in the Prollins mixture of (294). As an alternative dilute, 10 c.c. of the fluid extract with 85 c.c. water, add solution of lead subacetate in slight excess (i.e. until the fluid has a distinctly sweetish taste) make up to exactly 100 c.c. and filter. To the filtrate add sodium phosphate in powder, sufficient to throw down the excess of lead and filter once more. Put into a separator 50 c.c. of the filtrate and shake out with chloroform, three (or more) portions of 15, 10 and 10 c.c. being used. Dry and weigh. See (295). Solid extracts may be dissolved in dilute alcohol and treated as fluid extracts. Tinctures, wines, etc., may be concentrated at as low a temperature as possible (neutralized first, if necessary) mixed with saw-dust, dried and treated with the modified Prollins fluid precisely as in (294).

Conium.

301. The fruit of *Conium maculatum* is gathered when full grown but yet green, the yield of alkaloid being greatest at that time. It is small, roundish ovate, laterally compressed, and grayish green. The mericarps which are often separated, have five jagged ribs but no oil tubes; the flat side or commissure is deeply furrowed, giving to a transverse cut surface a reniform outline. Almost odorless and tasteless, but when triturated with a solution of caustic potash, conium emits the peculiar, mouse-like odor, characteristic of the alkaloid, coniine which is developed thereby.

302. The volatile alkaloid coniine is the active constituent of poison hemlock, occurring in all parts of the plant, but most abundantly in the immature fruit, which is the only part recognized by the U. S. Pharmacopoeia. Many specimens of conium leaves and not a few of conium fruit are almost inert from loss of the

volatile constituent. Some method then, of roughly estimating the value of the crude drug would be of great value. The strength of the odor developed by treating the drug with solution of potassa, becomes, to one acquainted with the use of the test, a ready means of judging the relative, if not the absolute value of given samples. The test serves at least to condemn a drug greatly deficient in alkaloid.

303. An assay of the drug is practicable by the following process; Put into a 4 ounce prescription vial, 12 grams of the finely powdered drug. Add 100 c.c. of the weaker Prollins mixture (12), shake well at frequent intervals for four hours, or continuously, during that time, by aid of a mechanical shaker. Let settle and pour off of the clear liquid exactly 50 c.c., add normal sulphuric acid, drop by drop, just sufficient to render distinctly acid. Dissipate ether by a gentle heat, add alcohol 15 c.c. and set aside in a cool place a few hours for separation of ammonia as sulphate. Filter, wash residue with a little alcohol, concentrate filtrate and washings (making sure that free acid is nearly neutralized previously) by a gentle heat, to 3 c.c., add 3 C. C. water and a few drops of dilute sulphuric acid. Wash twice with 10 c.c. ether to remove traces of fatty matters, rejecting the ether.

304. The assay may now be conducted by either the alkalimetric or the gravimetric method. In either case, add sodium carbonate in excess and shake out with three successive portions, 15 c.c., 10 c.c. and 10 c.c. of ether. (1) Treat with ethereal solution with exsiccated neutral calcium sulphate to remove minute droplets of alkaline, water, and titrate with standard acid, N 1-25 or N 1-100, using iodeosin as indicator (165). Calculate coniine from table of (94).

(2) Add to the ethereal solution, drop by drop, sufficient 5% hydrochloric acid to supersaturate, avoiding much excess; dissipate the ether by a gentle heat in a tared evaporating dish with flat bottom. Drive off the excess of acid by evaporating twice with a little alcohol (2-3 c.c.), dry a few minutes at a temperature not exceeding 60 degrees C., and weigh the residue of coniine hydrochlorate. After weighing, keep in a desiccator over sulphuric acid an hour and weigh again to make sure that the drying was complete. Multiply by 0.777 to obtain the weight of the alkaloid.

305. Alternative Method--Moisten 12 grams of the drug with an equal weight of a 5% solution of crystallized sodium carbonate, place at once in a suitable flask, add petroleum benzin 100 c.c., shake well and macerate with occasional agitation four hours (or else pack in a percolator and percolate to 100 c.c. with benzin). Pour off

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50 c.c. of the clear liquid. Extract the alkaloid by shaking out with three portions of acidulated water, 5, 3 and 3 c.c., wash the acid solution twice with 10 c.c. ether, to remove traces of fatty matters and then proceed as in (304).

306. In absence of iodeosin indicator, the alkali-metric process may be carried out, as follows:- Wash out the alkaloid from the acid solution in (304) with petroleum benzin, in place of ether, using three portions of 25 c.c. each. Wash each portion with 3 c.c. water and unite all finally, in a separator in which has been placed 10 c.c. of standard acid N 1-25, together with a little cochineal or Brazil-wood indicator. Shake together; if the reaction should not be acid, add standard acid sufficient to make it so persistently after shaking. Draw off the aqueous fluid, wash the benzin with two successive portions of 5 c.c. water, which is to be added to the alkaloidal solution. Finally titrate back to the point of exact neutrality with standard alkali N 1-25, and subtract the quantity used from that of the standard acid.

307. K. Schwickerath⁽⁸¹⁾ treats 10 grams of the drug with dilute Prollins mixture in the usual way, filters 50 c.c. of the fluid for the assay, adds 8 c.c. of water and 2 or 3 c.c. of dilute sulphuric acid (275 per cent) and evaporates. The acid fluid is filtered into the perforator (9) and then washed one hour with ether, the solution made alkaline with sodium carbonate and again washed with ether for three or four hours. Finally 10 c.c. of standard sulphuric acid N 1-20 is added, the ether dissipated by warming and the excess of acid titrated back with standard soda solution N 1-100. The extraction of the alkaloid would be much more speedily and perfectly accomplished by introducing into the flask, the standard acid; 20 or 30 minutes would then undoubtedly suffice⁽⁸²⁾ The process is faulty in that some ammonia must surely accompany the coniine.

308. R. A. Cripps⁽⁸³⁾ exhausts the conium fruit by percolating 5 grams of the powder with a mixture of 25 c.c. alcohol, 25 c.c. chloroform, and 10 c.c. chloroform saturated with hydrochloric acid gas and then extracting for 2 hours in a Soxhlet tube with the percolate. When cold, the solution is extracted in a separator with two successive portions of 25 c.c. of water. The aqueous solution is treated with several small portions of chloroform to remove coloring matter, etc., made alkaline with sodium carbonate and the alkaloid washed out with three successive portions of chloroform. The chloroform solution

is washed with a little alkaline water neutralized with a solution of hydrochloric acid in ether, evaporated at a temperature not above 90 degrees C and weighed. The weighing is checked by titration of the chlorine by N 1-100 silver nitrate.

309. There is no satisfactory method of titrating aqueous solutions containing salts of conine. The alkaloid affects the indicator phenolphthalein, so that the alkalimetric process (93) cannot be resorted to. Mayer's reagent precipitates the alkaloid only in rather strong solutions and the precipitate runs through an ordinary filter, so that useful results cannot be obtained. Titrations with sodium phosphotungstate or of sodium phosphomolybdate (Zinoffsky) have been employed with somewhat better satisfaction, and they furnish an available means of judging rapidly the relative alkaloidal strength of samples of the drug or of its galenical preparations.

310. Proportion of alkaloid in the drug. Conium fruit should contain not less than 0.5 per cent of alkaloid. Commercial samples vary from 0.23 per cent to as high as 0.9 per cent. There is such a variation in the alkaloidal content of this drug that an official assay of the alkaloidal per cent should be required. 0.5 per cent is an average sample and is now the standard among leading manufacturers.

311. Galenical preparations of conium. A fluid extract may be treated as follows:- To 5 c.c. of the fluid contained in a 2 ounce vial, add .2 or .3 gram potassium carbonate and about 50 c.c. petroleum benzin. Shake well, let separate and decant the benzin into a vial containing 5 c.c. of a 1% solution of hydrochloric acid. Shake, let separate return the benzin to the first vial, shake again separate and transfer the benzin once more to vial No. 2, shake let separate, decant with benzin into a 3rd vial containing 2 or 3 c.c. of acidulated water. Shake, let separate and reject the benzin. Extract the alkaloid from the acid solutions with ether according to (304). Otherwise the fluid extract may be mixed with saw-dust, after adding 0.1 gram tartaric acid, dried and the assay conducted according to (303) or (305). Solid extracts which generally are very deficient in alkaloid, are to be dissolved in dilute alcohol, and titrated as above. From 2 to 3 grams should be the quantity of sample operated upon.

DIGITALIS.

312. The leaves of digitalis purpurea are wrinkled,

velvety fragments the lower surface paler green than the upper, softly pubescent, especially along the midrib and veins; the midrib is prominent but not so much as in *hyoscyamus*; the venation forms prominent meshes on the upper surface of the leaf, the principal veins joining the midrib at a very acute angle.

313. Adulterations--Other dried leaves are often mixed with *digitalis*, the commonest of which are those of mullein, having a thick coat of branched hairs, and those of *Inula coryza* and *Inula helenium*, both having entire instead of crenate or serrate margins, and the latter having its veins branching off at about right angles to the midrib.

314. Constituents:- The exact composition of *digitalis* is as yet not definitely decided, but the latest analyses show it to be composed of at least five principles: digitalin (soluble in alcohol, insoluble in water), digitalein (soluble in alcohol and water), digitonin (readily soluble in water, insoluble in alcohol, the diuretic principle), digitin (inert) and digitoxin, the most active ingredient (insoluble in water, and sparingly soluble in alcohol, deposited as a sediment from the alcoholic preparations of the leaf). All but the last are glucosides.

315. The assay process of Keller is the only one now accepted as reliable. He believes that for practical purposes it will be sufficient to determine only the active constituent and base value of drug upon its content. His procedure is as follows:- Exhaust 20 grams of the powdered leaves with 70 per cent alcohol by percolation. Evaporate, dissolve the residue in water and add solution of lead subacetate in slight excess. Remove the excess of lead from the filtrate with sodium sulphate, filter, render alkaline with ammonia, and shake with several successive portions of chloroform. The chloroform solution upon evaporation leaves a residue of crude digitoxin, which should be weighed as such, then dissolved in 3 grams of chloroform, the solution mixed with 7 grams ether and poured into 50 grams petroleum ether. The digitoxin segregates in flakes which are caused to separate by vigorous shaking of the mixture and are then collected, dried and weighed as pure digitoxin.

316. Digitonin may be collected from the aqueous solution after shaking with chloroform, by expelling the ammonia, acidifying with hydrochloric acid, precipitating with tannin, dissolving the tannates in 50% alcohol, adding lead oxide, evaporating, extracting the residue with dilute alcohol, filtering and evaporating the filtrate to dryness. Digitonin, however, is of no medicinal use.

317. Digitalin (one of the active constituents of

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the drug) is obtained from the filtrate from the digitonin as follows:- Add more tannin solution and some sulphuric acid, dissolve the precipitate in 70 per cent alcohol, boil the solution with lead carbonate, decant, evaporate with addition of lead oxide, extract the residue with alcohol and evaporate the solution.

ELATERIUM.

318. Elaterium is a peculiar resinous substance obtained from the fruit of *Echallium elaterium* (squirting cucumber), a vine growing in the Mediterranean regions of Europe, Africa and Asia. The fruit when ripe, separates suddenly from the stalk, and the internal pressure forces the juice out of the aperture thus made, in a stream; in collecting therefore, the fruits are gathered green, sliced and the juice expressed by slight pressure; on standing it deposits a sediment, which, when dried, forms the Commercial Elaterium.

319. Elaterium is in flat pieces of varying sizes, light and friable, pale and green when fresh, but taking on a gray or light buff color as it becomes older; the surface is covered with small crystals of elaterin; odor somewhat tea-like; taste acrid and extremely bitter, due to the active ingredient elaterin which constitutes from 20-25 per cent of the drug; This principle is insoluble in water, readily soluble in chloroform and hot alcohol; it is a violent irritant poison.

320. Assay Process:- (1) Determine mineral matter by igniting in a porcelain or platinum crucible 0.25 grams until the ash is quite white. The ash ought not to weigh more than 0.02 grams.

321. Determination of Elaterin. Put into a small flask, 2 grams of the drug in fine powder with 15 c.c. of chloroform and macerate half an hour, at a temperature of about 55 degrees C. Transfer to a small filter, and when the chloroform has all passed, percolate on the filter with fresh chloroform to complete exhaustion. Evaporate the solution in a tared capsule, dry at 100°C. and weigh. Dissolve the residue in 15 c.c. ether added at once, transfer immediately to a small tared beaker, cover and set aside to crystallize. It will be found the ether always forms momentarily a perfect solution of the residue, from which crystals of elaterin have begun almost immediately to separate.

322. After a few hours, decant the ether into a second tared beaker, and allow the ether to evaporate until reduced to about 3 c.c. Decant the remaining ether into a 3rd beaker, leaving the crystals which have formed. Wash these with a little ether, by decantation. Allow the

ether in the 3rd beaker to evaporate entirely, add 3 c.c. of ether and observe whether any crystalline residue remains undissolved. If so, this must be carefully washed with a little ether. Finally, dry all the crystals obtained and weigh. The weight of the elaterin is usually about one half that of the original chloroformic extract. If it falls much short of this, loss of the elaterin in the crystallization may be expected. In any case it is safe to add an arbitrary correction of ten milligrams. Elaterium of good quality should yield 16 to 20 per cent of crystallized elaterin.

ERGOT.

323. The official ergot of Rye is from 10 to 30 m.m. ($2/5$ to $1\ 1/5$ in.) long and from 2 to 6 m.m. ($1/12$ to $1/4$ in.) in diameter. On other grasses, it is usually of less size. Triangular, slightly curved, tapering toward, but obtuse at, the ends; externally, purplish-black, internally, whitish with pink lines; fracture shoot (not very brittle). If a portion be macerated in water containing caustic potash or soda, then carefully crushed with a blade or spatula, the fragments of mycelium threads are plainly discernible under the microscope. Odor, (especially in powder or where treated with an alkali) heavy and unpleasant; taste oily and disagreeable. When more than one year old, it is unfit for use. "Old ergot, which breaks with a sharp snap, is almost devoid of pinkish tinge upon the fracture, is hard and brittle between the teeth and is comparatively odorless and tasteless; should be rejected" (U. S. P.).

324. The most recent study of ergot is that made by C. C. Keller⁽²⁴⁾ who arrives at the conclusion that ergot contains but one alkaloid, and that this is the active principle of the drug. This alkaloid, which Keller believes to be identical with Tanret's ergotinine, Kobert's cornutine and Dragendorff's picrosclerotine, has the following characters:- It is insoluble in petroleum-ether, which precipitates it from its ethereal solution; it is readily soluble in alcohol and in chloroform, but dissolves only with difficulty in ether after it has been crystallized. The alcoholic solution has a strong bluish-violet fluorescence, especially after acidulation. The neutral salts are readily soluble in water, the acid salts only sparingly so. From a somewhat acid solution, chloroform extracts the alkaloid; ether removes but little.

It is a very common mistake to suppose that the
theology of the Middle Ages is a mere repetition
of the theology of the Fathers. In fact, it is a
new and original system of thought, which
developed out of the philosophy of Aristotle.
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philosophy, which was based on the principles
of Aristotle. This philosophy was known as
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325. Assay process of Keller:- Pack in a small percolator, 25 grams of dry ergot in No. 60 powder, exhaust with petroleum ether until a few drops leave no residue when evaporated on a watch crystal. Dry the powder at a gentle heat, transfer it to a tared cylinder of 250 c.c. capacity, add 100 grams of ether and, after ten minutes, a mixture of 10 grams of magnesia and 20 c.c. water. Shake the mixture well and repeat the shaking frequently during half an hour. Then pour off 80 grams of the ethereal solution or as much as obtainable, four grams representing one gram of the ergot.

326. If the solution is not quite clear, let it stand for some time. Pour off any sediment and shake with three successive portions of water (25, 15 and 10 c.c.) acidulated with hydrochloric acid. (Wash with a fourth portion of acidulated water and test with Mayer's reagent to ascertain whether the alkaloid has all been removed). The mixed acid solutions are then made alkaline with ammonia and shaken out with three successive portions of 50, 25, and 25 c.c. of ether. Distill off the ether in a tared flask, treat the residue twice with a little fresh ether, finally dry to a constant weight and weigh.

326. Chloroform is a better solvent for the alkaloid than ether, but is liable to form obstinate emulsions; hence, ether is preferred and the quantities prescribed extract the whole of the alkaloid.

327. Proportion of alkaloid in ergot:- Different samples of ergot yielded in Keller's hands, from .095 to .245 per cent of alkaloid. From an old sample which had been kept in powdered condition, 0.165 per cent was obtained., showing that the drug may be kept for some time without becoming inert. Old samples may be distinguished from new, by the color of the ether extract which in the former is dark brown, in the latter, of a bright yellowish color.

328. Physiological test of Ergot:- Owing to the existing uncertainty concerning what is the real active principle of ergot. Robert and Grunfeld resorted to a physiological test of the activity of the drug, by feeding minute quantities of the sample to roosters. The effect of an active drug or preparation is promptly shown in the comb and wattles of the fowl, which assume a characteristic dark color from the peculiar action of the drug upon the capillary circulation. The two methods of assay, physiological vs. chemical have caused no small discussion but the chemical assay upon the quantity of contained alkaloid, holds preference.

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GELSEMIUM.

329. The rhizome and roots of *Gelsemium sempervirens* are the parts of the drug officinal. Generally in very light and fibrous cylindrical sections about 1 inch in length; externally of a brownish yellow color, slightly wrinkled; tough, breaking with a fibrous, splintery fracture; bark, thin, with silky bast-fibers, adhering to the light yellowish, porous, broad-rayed wood; pith small; odor slight; taste persistently bitter.

330. Yellow jessamine contains at least one alkaloid capable of yielding crystallizable salts. It is sparingly soluble in petroleum benzin, freely soluble in ether and still more so in chloroform. This is accompanied by an alkaloid which seems not to produce crystallizable salts and which, like amorphous quinine, seems always to be more or less colored. The drug contains a fluorescent principle analogous to aesculin, but regarded as peculiar to gelsemium and called gelseminic acid. This is removed from acid solutions by thorough washing with ether or chloroform, but a portion of it is almost sure to accompany the alkaloid when extracted in the usual way.

331. For the assay of the drug, Lyon's short Process No. 2 (71) to (74), the alternative of (72) being preferably followed. The alkaloid obtained is of a dark color and is of complex composition so that alkalimetric titration rather than direct weighing is to be relied upon. The titration equivalent may be taken as that of the pure crystallizable alkaloid, hence, 1 c.c. of N 1-25 acid ordinarily employed in alkalimetric titrations is assumed to neutralize 16.3 m.g. of alkaloid.

332. Titration with Mayer's reagent:- The acid solution of (72) may be titrated with Mayer's reagent with results almost as satisfactory as those by acid titration, since in either case, the equivalent factor is arbitrarily assumed, and we know nothing as yet of the relative medicinal activity of the several alkaloids presumably present. Perhaps a gravimetric determination by weighing the precipitate produced by Mayer's reagent in the acid solution will give as good a practical measure as any we can reach with our present knowledge, of the value of the sample.

333. Assay of Galenical Preparations:- The fluid extract may be easily assayed by the process of (150) and follows, the determination of alkaloid being finally made by alkalimetry as above. A purer alkaloid is obtained by the process of (149 b) and for a gravimetric determination this plan (or that of Farr and Wright, below) should be

and the United States, in the year 1861, was the first year
in which the number of immigrants from all countries was
greater than in any previous year. The number of immigrants
from all countries was 2,400,000 in 1861, and in 1862 it was
2,500,000. The number of immigrants from all countries was
2,600,000 in 1863, and in 1864 it was 2,700,000.

The number of immigrants from all countries was 2,800,000 in 1865,
and in 1866 it was 2,900,000. The number of immigrants from
all countries was 3,000,000 in 1867, and in 1868 it was 3,100,000.
The number of immigrants from all countries was 3,200,000 in 1869,
and in 1870 it was 3,300,000. The number of immigrants from
all countries was 3,400,000 in 1871, and in 1872 it was 3,500,000.
The number of immigrants from all countries was 3,600,000 in 1873,
and in 1874 it was 3,700,000. The number of immigrants from
all countries was 3,800,000 in 1875, and in 1876 it was 3,900,000.
The number of immigrants from all countries was 4,000,000 in 1877,
and in 1878 it was 4,100,000. The number of immigrants from
all countries was 4,200,000 in 1879, and in 1880 it was 4,300,000.

The number of immigrants from all countries was 4,400,000 in 1881,
and in 1882 it was 4,500,000. The number of immigrants from
all countries was 4,600,000 in 1883, and in 1884 it was 4,700,000.
The number of immigrants from all countries was 4,800,000 in 1885,
and in 1886 it was 4,900,000. The number of immigrants from
all countries was 5,000,000 in 1887, and in 1888 it was 5,100,000.
The number of immigrants from all countries was 5,200,000 in 1889,
and in 1890 it was 5,300,000. The number of immigrants from
all countries was 5,400,000 in 1891, and in 1892 it was 5,500,000.

The number of immigrants from all countries was 5,600,000 in 1893,
and in 1894 it was 5,700,000. The number of immigrants from
all countries was 5,800,000 in 1895, and in 1896 it was 5,900,000.
The number of immigrants from all countries was 6,000,000 in 1897,
and in 1898 it was 6,100,000. The number of immigrants from
all countries was 6,200,000 in 1899, and in 1900 it was 6,300,000.

adopted. Tinctures, solid extracts, etc., are to be treated on general principles See (169) to (172).

334. Process of Farr and Wright(85):- Fifty c.c. of a tincture or 10 to 20 c.c. of a fluid extract are evaporated on a water bath, to a small volume, adding water if necessary to remove all alcohol. To the solution when cool add 1 c.c. seminormal sulphuric acid, mix well and filter through absorbent cotton into a small separator. Rinse dish and filter with a little acidulated water, wash the acid fluid with three portions of 10, 5 and 5 c.c., of chloroform, which in turn, are washed with 5 c.c. water, added afterwards to the contents of the separator. Render the aqueous solution alkaline with ammonia and shake out with three portions (15, 10 and 10 c.c.) chloroform. The chloroform is then washed with four successive portions (5 c.c.) of water containing about 1.5 per cent of sulphuric acid. The acid solutions are united, an excess of Wagner's reagent (15) is added and the mixture set by until the precipitate has subsided leaving the fluid clear.

335. The fluid is decanted through a small filter, the filter washed with a little water and then 5 c.c. of a 5% solution of sulphurous acid is passed through it into the flask containing the alkaloidal precipitate. The flask is allowed to stand with occasional agitation until the alkaloid all periodides have been wholly decomposed, as shown by absence of dark colored particles. The solution is then filtered, flask and filter washed, first with 2 to 3 c.c. of sulphurous acid then with water until the washings are no longer precipitated by Mayer's reagent. Filtrate and washings are made alkaline with ammonia and shaken out with three successive portions of chloroform (10, 10, and 5 c.c.), the chloroform evaporated the residue dried at 100°C. and weighed.

Guarana and Kola Nut.

336. The active constituent of guarana, coffee and tea is caffeine (or theine) which is also the constituent of kola nut and of mate or Paraguay tea. The alkaloid is very feebly basic, so that it cannot be determined by alkalimetry, at least with any of the indicators ordinarily employed. It is not precipitated by Mayer's reagent, although a characteristic crystalline precipitate is produced by a solution of potassium iodide saturated with mercuric oxide. In an acid solution, it is precipitated by Wagner's reagent (15) and it is also precipitated by tannin.

337. Caffeine is soluble in 80 parts of cold water, in 9.5 parts of boiling water, also is freely soluble in cold aqueous solutions of certain salts, notably the salicylates and benzoates of the alkalies; it dissolves in 33 parts of alcohol in 555 parts of ether and in 7 parts

chloroform and it is also readily soluble in benzol and in carbon tetra-chloride. It is removed from watery solutions even in the presence of free acids, by shaking with chloroform, although not so readily as when the solution is neutral or alkaline. It crystallizes easily from its solutions in volatile solvents and may be easily sublimed without alteration.

338. Moses Gomberg⁽⁸⁶⁾ has shown that the alkaloid can be determined with a fair degree of precision by a volumetric process involving its conversion into a periodide. His procedure, applicable only in absence of other substances precipitated by iodine, is as follows:- To 25 c.c. of decinormal iodine solution (U. S. P.), add a solution of the caffeine acidulated with hydrochloric acid, the quantity of caffeine not to exceed 25 milligrams. See (122). Make up the volume with water to exactly 50 c.c. Shake the mixture well and let stand until the precipitate separates so as to leave the supernatant fluid clear. (This must be of a deep iodine red color, otherwise the experiment must be repeated, using a smaller quantity of the caffeine solution). Decant 25 c.c. of the clear fluid and titrate with decinormal solution of sodium thiosulphate; deduct twice the volume of the thiosulphate solution required, from 25, and multiply the remainder by 4.85 to find the weight in milligrams of the caffeine present in the portion of solution used.

339. In many of the older processes for extracting caffeine, lime was used. It has been shown that this involves loss of a portion of the alkaloid, hence it is not admissible in any process. Magnesia seems to be open to the same objection, and no direct loss is occasioned by the use of oxide of lead, oxide of iron, alumina or basic lead acetate, although some alkaloid may be withdrawn from a solution by occlusion in precipitates produced by these agents.

340. The method of J. U. Lloyd⁽¹⁵⁸⁾ is well adapted for extracting caffeine from aqueous extracts or other preparations not containing chlorophyll. The method as given for fluid extract of Guarana⁽⁸⁷⁾ is as follows:- Into an appropriate vessel (preferably a flat-bottomed graduate) pour 2.5 c.c. of fluid extract of Guarana, add 2.5 grams of a mixture of equal amounts of dry ferric hydrate and sodium bicarbonate, mix well, preferably with a mechanical stirrer, add 10 c.c. chloroform and stir well together. Should the magma remain flocculent and the chloroform not separated therefrom, add a sufficient amount (10 to 20 drops) of a mixture of equal parts glucose and water and incorporate thoroughly. Decant the chloroform into a tared beaker.

Repeat the treatment with two or three fresh portions (5c.c.) of fresh chloroform. (Should the magma collect on the sides of the graduate, above the stirrer, scrape it down occasionally). Finally, evaporate the chloroform, dry to constant weight and weigh.

341. Process of Petit and Terrat⁽⁸⁸⁾ (Proposed for the assay of tea, but stated by the authors to be equally applicable to guarana or kola). Treat ten grams of powdered tea with 30 c.c. boiling water, macerate 15 minutes then evaporate on the water bath until the liquid has disappeared, leaving the powder visibly and uniformly moist. Transfer to a small percolator and exhaust with chloroform (continue percolation until a few drops of the percolate evaporated and taken up with water, show no cloudiness on adding tannin). Distill off chloroform, treat residue with boiling water, filter, wash filter with hot water, evaporate filtrate to obtain caffeine in condition generally pure enough for weighing. The authors affirm that chloroform extracts from the thoroughly moistened powder, the whole of the caffeine, the use of lime, magnesia or ammonia being superfluous.

342. An obvious modification of the above would consist in macerating the moistened powder with 100 c.c. chloroform with frequent or constant shaking several hours, decanting to 50 c.c. of the chloroform, evaporating, taking up with boiling water as above and determining caffeine by the method of Gomberg. In applying the method to guarana or kola, maceration with warm water would, no doubt, be better than boiling in the first step of the process, owing to the presence of starch.

343. Guarana cannot be so conveniently exhausted with boiling water on account of the starch it contains. It is better to exhaust the powder, 10 grams by percolation with a mixture of 2 volumes of alcohol and one of water, obtaining about 100 c.c. percolate, evaporate the percolate to a volume of 50 c.c., pour into a 500 c.c. measuring flask containing 425 c.c. of water, add 8 c.c. of solution of lead subacetate or sufficient to impart to the mixture a sweetish taste, make up to 500 c.c. and proceed as in (318) remembering that of this solution 50 c.c. represents one gram of the drug.

344. Drs. Dohme and Engelhardt⁽⁸⁹⁾ direct to boil the powdered kola with a mixture of alcohol one volume, water 2 volumes, three hours, in a flask provided with a reflux condenser. Filter, evaporate nearly to dryness on a water bath, mix with calcined magnesia and sand, dry completely and extract by boiling with chloroform. Knox and Schlotterbeck⁽⁹⁰⁾ simply extract kola with chloroform for

ten hours in a Soxhlet apparatus. Carles (91) directs to use a very fine powder, mix 10 grams of this with 1 gram of slaked lime and 20 grams of 80 per cent alcohol, dry on a water bath to 14 grams, exhaust by boiling with four successive portions (35, 35, 30 and 25 c.c.) of a mixture of alcohol 20 grams, chloroform 100 grams. Evaporate and extract with slightly acidulated boiling water. The Kolanin (a glucoside also contained in kola) he determined by first exhausting with cold water to remove caffeine and then extracting with 70% alcohol. In the residue caffeine, formed from hydrolysis of the kolanin is determined by lime, chloroform and alcohol as above.

345. The proportion of caffeine in guarana is generally between 4 and 4.5 per cent, in tea varies from 1.5 to 4.25 per cent, average about 3 per cent with little variation, in kola not from .75 to 2 per cent average about 1 per cent. The standards adopted by manufacturers for their fluid extracts are 4% caffeine in guarana and 1 per cent caffeine in kola nut.

HYDRASTIS.

346. The rhizome and roots of *Hydrastis canadensis* are knotty and contorted; about 3/52 long and 1/52 thick; on the upper side are several scars which mark the positions and detachments of former herbaceous stems; these scars (cuplike projections) have given rise to the name "golden seal". Externally rough, of a dull yellowish brown color, amulate and beset with several slender rootlets; internally of a lemon yellow color; breaks with a short, resinous fraction; a cross section shows a thick bark, narrow wood wedges, from a large pitch. The rootlets show a woody center surrounded by a thick parenchymatous cortical tissue, which is bordered by an outer row of compressed cells.

347. Constituents--The alkaloids-hydrastine are the principle constituents. Berberine is very widely distributed in nature, being found in at least three different orders; it is present in berberis, coptis, colombo, menispermum, anthorrhiza, etc., hydrastine, when pure is in perfectly colorless, very brilliant, glassy crystals. As a rule however, they are white and opaque, owing to the presence of numerous fractures. The yellow color of the berberine adheres very tenaciously to the hydrastine, so the the absolutely colorless hydrastine is difficult to obtain. The resinoid, hydrastine should not be confounded with the active principle. This resinoid is made by precipitating a concentrated alcoholic ~~extract~~ tincture of hydrastis with acidulated water, and is probably in the main, an impure muriate of berberine. Hydrastine and berberine however, are the constituents upon which the value of the drug is examined.

hydrate and, being better acid
and berberine, of colombo and
menispermum, etc.

348. F. A. Thompson⁽⁴²⁾ assays hydrastis as follows:-
10 grams of the drug in moderately fine powder is exhausted with strong alcohol, by hot repercolation for 2 or 3 hours, percolate cooled and diluted to 100 c.c. with the same menstruum, 25 c.c. of this tincture are placed in a flask, 1.3 c.c. hydrochloric acid (W. S. P.), 0.2 c.c. sulphuric acid and 12.5 c.c. ether added, and mixture allowed to stand 24 hours in a cool place with frequent shaking. At the end of this time transfer the crystals to counterpoised filter papers, washing them with a mixture of equal volumes of concentrated ether and strong alcohol until filtrate gives no acid reaction. Dry crystals at 105°C., weigh and multiply by .9017 for amount of berberine and then multiply by 40 for percentage.

349. The filtrate from berberine is rendered nearly neutral, evaporated to a small volume, and mixed with 8 or 10 grams of saw-dust, (previously treated with acid, water and alcohol to remove extractive matter). The mixture is dried, placed in a suitable flask and 100 c.c. of modified Prollins mixture (ether 250 c.c., chloroform 100 c.c. alcohol 25 c.c. conct. ammonia 10 c.c. added. After maceration and frequent shaking for several hours, 50 c.c. of the ethereal fluid is evaporated to dryness, re-dissolved in acid water, extract with ether. Evaporate ethereal solution. Dissolve residue in 1 c.c. normal sulphuric acid (a small amount of ether facilitates the solution of the alkaloid add 20 to 20 to 30 c.c. water, 2 drops cochineal indicator and determine free acid by N/100 caustic soda solution. Each c.c. of N/100 caustic soda = .00383 gm. hydrastine, and this weight x 40 = percentage.

Assay of Hydrastis. (93)

350. 25 grams of powdered hydrastis are treated with a mixture of 125 c.c. ether, 10 c.c. water of ammonia and 30 c.c. water mixture thoroughly shaken and allowed to separate. 100 grams, representing 20 grams drug are poured off into a separator, treated with dilute sulphuric acid to extract the alkaloid, made alkaline with ammonia after separated from ethereal solution, and finally extract with ether. Evaporated dried and weighed, the yield of crude alkaloid is then dissolved by the aid of heat in 8 c.c. alcohol and 4 c.c. ether and then 20 c.c. water gradually added; after standing 24 hours almost the entire quantity of hydrastine will have washed out, so that the crystals can be removed to a filter, washed with about 6 c.c. cold water, transferred back to flask, dried and weighed.

351. E. G. Eberhardt⁽⁹⁴⁾ proposes the following:--
Into an arlenmeyer flask of at least 4 oz. capacity, is put 25 c.c. of the fluid extract to be assayed.

This is heated on the water bath to a point considerably short of boiling, 10 c.c. ether are now slowly and carefully added so as not to cause loss by violent ebullition and lastly 25 c.c. of a 2% solution of ammonia, or a mixture of 20 c.c. water and 5 c.c. water of ammonia. The contents of the flask are now rotated briskly for a few seconds and the whole then set aside for a few hours (12 or 15) frequently rotating during the first 2 or 3 hours. After 12 hours the liquid is poured into a funnel into the neck of which a small pellet of cotton has been loosely inserted and the whole dried and weighed. When the liquid has all passed through, the crystals remaining in the flask are carefully rinsed into the funnel, and washed with distilled water until the washings are free from color. The funnel and contents are now dried at a temperature not exceeding 100°C., cooled in a dessicator and weighed. Subtracting from this weight the weight of funnel and cotton, gives the amount of alkaloid obtained.

352. An alternative process of assay which however requires more attention consists in rendering 25 c.c. of the fluid extract. Alkaline with ammonia, and rotating in a separator with 3 portions of ether, extracting the alkaloid from the mixed ether washings by agitating with 3 portions of 10 c.c. each of 2% sulphuric acid and lastly with 5 c.c. distilled water; adding to the combined washing 10 c.c. alcohol, 3 c.c. ether and sufficient ammonia to render alkaline. After allowing it to stand 6 hours with frequent agitation, the crystals are collected, dried and weighed. A small amount of alkaloid is retained in the mother liquor for which a correction perhaps ought to be made.

353. Method of Keller. (95) is the best yet devised for the assay of hydrastis, where we merely desire to know content of hydrastine. It is given as follows:- Macerate 12 grams powdered hydrastis with 120 grams ether, 10 grams water of ammonia and 15 grams water; decant 100 grams to represent 10 grams drug; extract with hydrochloric acid and finally with ether. The alkaloid procured by this process is not strictly pure. It may be obtained in purer form by washing the acid solution well with petroleum benzin, rendering alkaline with ammonia, and washing out promptly with several portions of hot benzin. He then proposes to crystallize it by dissolving the alkaloidal residue (from 20 grams of the drug) in 8 c.c. alcohol, adding 4 c.c. water and letting stand 24 hours. The alkaloid can also be extracted by taking the acid solution (second stage of assay above) placing in a perforator, washing one hour with ether, render alkaline with ammonia and again extract 3 hours. Evaporate, dry and weigh.

354. Method of Lyons. (96)- A fluid of golden seal if made with dilute alcohol may be assayed for hydrastine by simply shaking out 2 c.c. of the fluid with 3 successive portions (15 c.c.) of ether following details of process (150) *ét. seq.*, but using no chloroform. Berberine may be determined approximately in the residue by diluting with water, filtering if necessary, acidulating with hydrochloric acid, and precipitating with Mayer's reagent in slight excess, collecting precipitate on a pair of mutually counterpoised filters drying and weighing. One-half the weight may be taken as approximately the weight of the berberine.

355. Assay of Hydrastine.--N. Rusting(97) recommends the following for determining hydrastine in fluid extract hydrastics:-- to 10 grams of the fluid extract 20 gms., water are added, the mixture is boiled with continuous agitation until all the alcohol is dissipated, cooled, brought to weight of 20 gms., shaken with a little infusorial earth and filtered. Then 10 grams of the filtrate (representing 5 grams of the fluid extract are shaken in a 100 gm. flask with 25 c.c. of ether and 3 c.c. ammonia. After a few minutes 25 c.c. of petroleum ether are added, the mixture is well shaken and 2 gms. of powdered tragacanth are added. The mixture is allowed to stand until the ethereal solution separates clear, and 40 c.c. of it are decanted into a small flask from which about 25 c.c. are evaporated or distilled off by immersion in warm water. The flask is then slightly stoppered and set aside in a cool place, so that the hydrastine may crystallize out completely. The supernatant liquid-- consisting mainly of petroleum ether and which is free from hydrastine-- is decanted, and the residual crystals are dried and weighed as hydrastine.

356. Assay by Periodide Method. (98) H. M. Gordin and A. B. Prescott have devised the following:-- The alkaloids of the powdered roots are first set free by the action of an ethero-ammonical mixture consisting of 5 c.c. stronger ammonia water, 5 c.c. alcohol, and 30 c.c. ether. After drying, the powder is extracted with absolute ether, and the ether extracted, after evaporation of the ether and solution of the residue in acidulated water, is used for the estimation of hydrastine by any suitable method. In this case as hydrastine hexiodide, (the factor being 0.60403). Through the powdered drug left in the extraction apparatus, air is passed until it is dry, and then the powder extracted with alcohol to exhaustion. The alcoholic extract, after dilution with water, evaporation of the alcohol acetic acid, is used for the estimation of berberine. The berberine acitone, the latter washed, decomposed by the aid of acid, and using silver nitrate and ammonium sulphocyanate for treating the excess used. By

multiplying the number of c.c. of 1/20 normal potassium iodide consumed by 0.167125, the percentage of anhydrous berberine in the root is obtained, as 1 c.c. of the potassium iodide solution is equal to 0.0167125 of berberine.

357. Proportion of Alkaloid --- Good samples of hydrastis contain from 1 to 3 percent hydrastine 2 to 2.5 being good average; of berberine from 1 to 3 percent. Standardized preparations are based on 2.5 percent hydrastine.

358. ---: Ipecac :---

The roots of *Cephaelis Ipecacuana* reach us in broken sections about 2 in. long and from the thickness of a straw to that of a quill. Externally dull grayish, reddish or dark brownish, depending upon the variety, prominently annulate with alternate thickenings and constrictions, the rings, numbering about 20 to the inch, usually not extending around the roots, however. Fracture short, granular, exhibiting a thin whitish or grayish woody column surrounded by a very thick bark (constituting at least 75% of the root). Odorless in entire state, but the powder (light-reddish gray to brownish gray in color) has a nauseous odor; taste nauseous, slightly bitter, and acrid. The wood is inert. *Carthagena Ipecac* is a variety from Columbia, which has crept into our market to take the place of a very scarce Rio variety. It is of a dull gray color thicker less frequently and sharply crooked, and lacks the constrictions characteristic of the Rio Ipecac, although it bears the annular thickenings.

359. Until recently Ipecac has been credited with but one alkaloid, called emetine, the researching of Paul and Brown have however shown that the emetine heretofore known consists of a mixture of two distinct alkaloids, differing in physiological and therapeutic action. To these alkaloids the names Emetine and Cephaeline have been given, the former being regarded as the expectorant, the latter as the emetic principle of the drug.

360. The following (100) is the method employed by Paul and Cowhley for the complete assay of Ipecac:-- Mix 50 grams of freshly slacked lime moistened with water, and extract by percolation with amyl alcohol. Extract the alkaloids by shaking out with dilute sulphuric acid, make alkaline with ammonia and shake out with ether. The ethereal solution is to be evaporated and the residue titrated with seminormal hydrochloric acid, of which one c.c. will neutralize 124 milligrams of emetine and 117 mg. of cephaeline.

361. The Hydrochloride solution is mixed with caustic soda in excess and shaken out with ether to remove emetine. Some cephaeline, however accompanies it, so that it is necessary to bring the emetine again into acid aqueous solution and repeat the treatment with soda and ether until the residual alkaline solution is no longer clouded by adding ammonium chloride. The purified emetine is finally determined by titration with standard acid. The cephaeline is obtained by adding to the residues containing it ammonium chloride and shaking out with ether and is also determined by alkalimetry.

362. The further studies of Paul and Cownley show there is a marked difference between Barzilian and Carthagena Ipecac in the relative proportion of the several alkaloids they contain. In the former the emetine constitutes about 70% of the whole, in the latter only 40%. We cannot therefore consider the two drugs as therapeutically identical.

363. For practical purposes in the present state of our knowledge, it is sufficient to determine the total content of alkaloid in a sample, the variety, Brazilian or Columbian, being always specified. The assay is easily made either by Keller's method (48), or by Lyons short process No. 2, the following (72) by that of Grandvel and Lajoux (45) or that of Cripps and Whitby.

364. In the short assay process No. 2, ether alone may be used instead of a mixture of ether and chloroform. In the following Keller's process use 1w grams ipecac, 90 grams ether, 30 grams chloroform and water of ammonia 10 grams, finally 10 grams water. Pour off 100 grams, extract with hydrochloric acid again with ammonia and a mixture of three parts, chloroform and 2 parts ether. Whichever process we may adopt, we may finally determine the alkaloid without purification either by titration with Mayer's reagent (367) or by alkalimetry, taking titration equivalent to conventional number of figure 254 from (94). Ra. Cripps and A. Whitby (101) use as the internal solvent either containing one percent of glacial acetic acid or a mixture of acetic ether, chloroform and acetic acid, and adopt the following procedure:-- shake down lightly, drench with menstrum, cork the upper end of the percolator and let macerate over night. Wash the acid solution once with ether, followed by two portions (6 c.c.) of chloroform. Evaporate in a current of air, dry in a desiccator for six hours over sulphuric acid and weigh. Finally determine alkaloid volumetrically with Mayer's reagent.

1. The Commission is of the opinion that the Commission should be authorized to conduct such investigations as may be necessary to determine the facts and circumstances surrounding the activities of the Commission and to report thereon to the Commission.

[illegible][illegible][illegible]

365. K. Kathmayer (102) directs to digest 15 grams of powdered epecac (air dried) with 148 c.c. of 90% alcohol and 2 c.c. of hydrochloric acid, sp. gr. 1.12, for four days at 40 degrees C. with frequent agitation; after cooling, measure out 100 c.c. of fluid, mix with 20 c.c. of a one percent solution of lead acetate in dilute alcohol, add 1.5 grams of slacked lime, evaporate to a pasty consistence; incorporate 5 grams of powdered glass, dry on water bath with constant stirring, extract the alkaloid by hot repercolation (10 hours) with chloroform. The crude alkaloid left on evaporation of the solvent is dried at 100 degrees C. and weighed, and then treated with 2 c.c. of normal hydrochloric acid, the insoluble residue matter washed on a filter, dried and weighed, and its weight deducted from that of the crude of the alkaloid.

366. & 367. Mayers reagent has been much used in determining "emetine", but without discrimination of the several alkaloids present. Practically no doubt, when the titration is made in a properly prepared solution, the results are as trustworthy as those obtained by other methods which determine only total alkaloid. The figure given in the table of (119) may be adopted as giving a sufficiently close approximation of the truth, if the fluid titration contain 2 to 5 parts alkaloid in 1000.

368. Method of Kunz. (105) - 8 grams of fluid extract are diluted with 8 grams water in an ordinary vial, 32 gms. chloroform and 48 gms. ether mixture frequently agitated during half an hour. After separation 50 grams of the chloroform -- ether solution representing five grams of the extract are poured on and filtered into a tared flask and the solvent distilled off. The varnish like residue is twice treated with 5 to 10 c.c. ether and evaporated by forcing a current of air into the flask by means of a rubber bulb, after the last trace of the ether have been removed and the residue dried on water bath, it is weighed, for the titration, the alkaloid is dissolved by aid of heat in 10 c.c. absolute alcohol, and sufficient water added to give it a permanent turbidity; after adding one or two drops haematoxylin solution 2/10 H.C.L. is added until the violet red color changes to a pure pale yellow. Emetine according to Kunz is diacid and has the molecular weight. 508. Hence 1 c.c. N/10 hydrochloric acid equals .1254 gm. emetine.

369. C. C. Killer (106) has improved the methods and offers the two following:--

(1). 12 grams of powdered ipecac deprived of fat and oil with ether transferred to a tared vial of 200 c.c. capacity, extracted with 90 gm. ether, and 30 gm. chloroform, and 10 c.c. water added and again agitated for two or three minutes. 100 gms. of the clear liquid are decanted, the solvent distilled off, the residue taken up twice with small quantities ether (to remove the last traces of chloroform), heated for 15 minutes on a water bath at 100 degrees weighed and afterwards titrated.

(2) 12 grams powdered ipecac are placed in a 200 c.c. vial, agitated frequently during 5 minutes with 90 gm. ether and 30 gm. chloroform; after adding 10 c.c. water ammonia and allowing it to stand one-half hour, 10 c.c. water are added and 100 gm. of the clear solution transferred to a separatory funnel where it is agitated with three successive portions of 25, 15 and 10 c.c. of 1% hydrochloric acid. The acid solution are next transferred to a separating funnel, made alkaline with ammonia and extracted with two portions of 50 gms. each, of a mixture of three parts chloroform and two parts ether. The alkaloidal solutions are filtered through an ether wetted filter into a tared flask, the solvent recovered (The last traces of the chloroform removed as before) the residue dried, weighed, and titrated as above.

370. The British Pharmacopoeia directs for the assay of fluid extract ipecac, the process outlined in (149 b) which perhaps is as good as any. The main point in this method is to have the solution quite dilute before adding lead subacetate.

371. Prescott and Gordin (107) extract the drug by any one of the general methods. In the iodometric estimation the total acidulated alkaloid solution is made up to a definite volume, an aliquot portion taken, and added to the measured excess of the iodine solution, as heretofore described. The iodine factor is taken as fairly near the means factor of the total alkaloids.

372. Galeucal preparations of ipecac may be easily assayed by the usual methods. See specially (150) to (153). In the case of a soluble fluid extract of ipecac, we may advantageously dilute 5 c.c. to 25 c.c. with water. Take 5 c.c. if the dilutions for the assay, add a little hydrochloric acid and wash twice with ether, 25 and 20 c.c. Then make alkaline with ammonia

and shake out twice with ether, 25 and 20 c.c.; once with a mixture of 15 c.c. ether to obtain an alkaloid pure enough to weigh. Of course it is a quicker way to make alkaline at once and shake out with ether and chloroform, and determine alkaloid by acid titration. If emulsious from resort to sawdust process.

373. The proportion of the total alkaloid in good ipecac is probably not less than two percent. Dr. Dohme has shown that the "worry" part of the root contains very little. Two percent alkaloid represents a very good root, and then the percent has been the one adopted among manufactures of the standardized goods.

---:: NUX VOMICA AND IGATIA BEAN :--

374. The seed of the *Strychnos nux vomica* occurs in orbicular discs from $3/4$ to 1 inch in diameter, and about $1/6$ inch thick; flat or slightly convex on one side and concave on the other, with a slightly raised margin on the concave side. On the one side is a ridge (raphe) extending from a raised point in the center (hilum) to a point on the edge where the radical is situated (chalaza). Both surfaces have a grayish or grayish green, shiny, silky appearance due to a large number of silky hairs closely pressed to the seed and forming a tuft around the edge. Testa thin, fragile, somewhat soft, enclosing two discs of horny, translucent or opaque, yellowish or whitish albumen around a large central cavity. The embryo is contained in the cavity, and consists of a short radicle and two flat, heart-shaped, veined cotyledons extending about one-fourth the distance across it. Inodorous; taste extremely bitter, powdered nux vomica is yellowish gray, and has a faint sweetish odor.

375. The total alkaloids amount to 2.6 to 5 percent. They consist principally of strychnine and brucine, the former being in excess. The action of the alkaloids is believed to be simular, but strychnine is much more powerful. A third alkaloid, igasurin, has been claimed, but in all probability it is simply a mixture of the other two. A glucoside loganin has been found in the seeds, but it exists in larger quantities in the pulp surrounding the seed in the fruit. Other constituents are a concreat fixed oil, gum wax, phosphates and a yellow coloring matter.

376. The seeds of the *Strychnos ignatia*, a tree growing in the Philippine Islands, where they are much

esteemed as a medicine, and whence they are introduced to the medical world by the Jesuits, who conferred upon them the name of the founder of their order. The fruit is pearshaped and contains from 10 to 15 of these hard heavy seeds lying one upon the other and imbedded in a dry medullary mass, but the seeds come into the market separate. Their shapes are various, owing to the manner in which they are situated in the fruit, but their general form is ovate, somewhat flattened, and more or less angular. They are about one inch long but considerably narrower, and have at one end a small depression indicating their point of attachment (hilum). Their testa is of a less silky nature than that of nuxvomica and of a grayish brown color. In commerce they are perfectly smooth, the testa and hairs being removed by the rubbing of the seeds against one another and therefore the outer surface consists of a dull brown or blackish horny albumen, translucent when fresh. The embryo is oblong, situated in the broad end of the seed, the cotyledons extending only about half the distance across the irregular cavity; Inodorous; taste exceedingly bitter.

377. The constituents are the same as in nuxvomica, but in the different proportions, the strychnine being present in larger quantity than in nuxvomica. Ignatia was once used for the preparations of this important alkaloid, strychnine, but rarely at the present day, as nuxvomica is important in such large quantities and hence is a much cheaper source.

378. W. A. Dinisten & F. M. Short have found the following process a satisfactory one for the assay of nuxvomica:-- (108) One part of nuxvomica is made into a paste with a solution of two parts crystallized sodium carbonate, the mixture dried and then again powdered equal to 5 grams nuxvomica is packed in a suitable extraction apparatus and exhausted by 40 c.c. chloroform containing 25% alcohol. This is usually accomplished in one to two hours. The solution thus obtained is well agitated with 25 c.c. of a 1% solution chloroform is much aided by gentle warming. After repeated agitation the chloroform is separated by means of separatory funnel, and again shaken with 15 c.c. dilute sulphuric acid. The mixture acid solution from which all the chloroform has been separated should be filtered if necessary, then made alkaline with ammonia

and shaken with 25 c.c. chloroform in a separatory funnel. The clear chloroform solution is evaporated on a water bath to constant weight, dried and weighed.

379. H. Beckurp gives the following:-- (109) Two grms. of the finely powdered extract are dissolved in a mixture of 5 c.c. water, 10 c.c. alcohol. The 5 c.c. ammonia added. The solution is then shaken with three successive portions of 20, 10 and 10 c.c. chloroform, and united chloroform solution evaporated. The residue is dissolved in 15 c.c. n/10 hydrochloric acid solution filters and filtered, well washed with distilled water. The untied filtrate and washing are then titrated with centinormal soda, cochineal being used as indicator. Subtract the number c.c. consumed of soda from 150 and multiply by 0.00364 to obtain the total alkaloids in 2 grams. The percent is then found by multiplying by 50.

380. Patch's Method (110). -- Ten grams of powdered drug are placed in a 200 c.c. erlemmeyer flask and dried for three hours at 100 degrees C. and then cooled in a dissicator. 100 c.c. Prollius liquid modified (ether 250 c.c. chloroform 100, alcohol 125 and ammonia 10 c.c.) added to the flask, securely corked and shaken vigorously from 12 to 24 hours, best in Mechanical shaker. 50 c.c. of the clear liquid are decanted from the flask into a separatory funnel shaken with 10 c.c. portions of 5 percent sulphuric acid, until all alkaloids are removed from the ethereal liquid (proved by withdrawing a few drops with a pipette, adding acidulated water, evaporating off the solvent, and testing with Mayer's reagent), the mixed acid washing are placed in a separator, made alkaline with ammonia, washed free from alkaloid with successive portions of chloroform solutions evaporated in a tared flask to constant weight. This gives total alkaloids and wet. x 20 gives percent.

381. Killer (111) proceeds as follows:-- Put into a small tubular percolator (13 cm. long, 2.5 cm. wide) 15 grams of the thoroughly dried drug in fine powder, exhaust by percolation with ether (remove fat, but this seems unnecessary) of which about 100 c.c. until be required. The ethereal solution will contain part of the alkaloid, which must be removed by shaking out first with 5 c.c. decinormal hydrochloric acid, then with three successive portions of acidulated water (6 c.c. each). The drug in the percolator is transferred by means of ether added to make in all 100 grams.

Fifty grams. of chloroform are then added, followed by 10 c.c. of 10 % solution ammonia, and the flask is well shaken frequently at intervals during half an hour. The acid solution containing the alkaloids removed from the ethereal percolate is then added, the mixture well shaken, and when the ethereal solution is well separated 100 grams. of it are transferred into an Erlenmeyer flask, the solvent distilled off, the residue treated repeatedly with a little pure alcohol to remove traces of chloroform, dried at 100 degrees C., and weighed.

382. The alkaloid in the residue may be determined approximately by alkalimetry. Killer directs to dissolve the residue in 5 c.c. chloroform with aid of a little heat, add 40 c.c. ether, 10 c.c. water iodeosin indicator (1% alcoholic solution) one drop, then decinormal hydrochloric acid 10 c.c. Titrate back with decinormal ammonia until a permanent red color appears in the aqueous solution. (Cork the flask, agitate after each addition of ammonia). Each c.c. of decinormal acid corresponds with 36.4 mg. alkaloid, assuming that nearly 50% of it is strychnine. The titration may also be conducted according to (90) and (91).

383. Schwickerath Method:-- (112). Macerate in an agitator 4 grams. of the dried and finely powdered drug, with 100 c.c. of the following mixture:-- (2 c.c. ammonia 30% ether). Filter off through cotton 50 c.c. (equal to 2 gm. drug), place filter in shallow dish; add 2 or 3 c.c. dilute sulphuric acid (2.5%), and 8 c.c. water; evaporate off the ether, alcohol and chloroform at a gentle heat, filter the acid solution in perforator and wash with petroleum ether for 1 hour. Then add 5 c.c. 5% ammonia arrange a ring of cotton in perforator and chloroform, the alkaloids their obtain are dissolved after evaporation of the petroleum ether and chloroform in 10 c.c. N.1-20 sulphuric acid, and titrated back with N. 1-100 caustic soda. 1 c.c. N.1-100 sulphuric acid being equal to .00364 gm. mixed alkaloids. The result times 50 equals percent, total alkaloids.

384. Assay of the drug may be made by Lyons Short Assay process No. 2, using 5 grams of the drug in fine powder, and increasing in proportion of chloroform (ether 3 volumes, chloroform 1 volume) followingly preferably the methods of (72). The methods of the following paragraph differs from this in some detail and is perhaps preferable.

1. The first step in the process of determining the concentration of a solution is to measure the volume of the solution. This is done by using a graduated cylinder or a volumetric flask. The volume is then measured in milliliters (mL) or liters (L).
 2. The second step is to measure the mass of the solute. This is done by using a balance. The mass is then measured in grams (g) or kilograms (kg).
 3. The third step is to calculate the concentration of the solution. This is done by dividing the mass of the solute by the volume of the solution. The concentration is then expressed in units of grams per milliliter (g/mL) or kilograms per liter (kg/L).
 4. The fourth step is to convert the concentration to the desired units. This is done by using the appropriate conversion factors. For example, to convert from g/mL to kg/L, you would multiply by 1000.
 5. The fifth step is to report the concentration. This is done by stating the concentration in the desired units, followed by the units of measurement. For example, "The concentration of the solution is 1.5 kg/L."

385. Alternative process:-- put into a four ounce perscriptive vial 5 grams of the drug in as fine a powder as can be made, add 100 c.c. of a mixture of ether 3 volumes and chloroform 1 volume (cool to the room temperature before measuring), add 1 c.c. of a 50% solution of ferric chloride; shake well and let macerate 1 hour. Then add 5 c.c. of a saturated solution of sodium chloride and 10 drops of 10% hydrochloric acid; shake occasionally during one hour; add 5 c.c. solution of 10% ammonia, Shake vigorously and macerate with frequent or continuous shaking four to six hours. Complete the assay by (72) to (74). The alkaloid obtained is nearly white and contains very little impurity, but may be titrated with standardize acid if derived, see (382).

386. C. E. Smith (113) exhausts the drug with acetic acid. The following is his outlined method:-- Place in a bottle 10 grams of the powdered drug with 100 c.c. of acetic acid, and shake frequently and continuously during 12 hours. Filter the solution and wash the residue with cold water until the washings are nearly tasteless. Evaporate to dryness in a shallow dish, while warm add 6 c.c. of a mixture of strong alcohol and solution of ammonia (10%) equal parts, rub to a uniform thick syrup with a rubber-tipped glass rod. Transfer to a separator, add 1 c.c. of ether and 45 c.c. of chloroform, wash the capsule with 6 c.c. of ammonia alcohol in three or four successive portions, shake 5 minutes, let stand for an hour or longer to separate. Filter the ethereal solution through a small dry filter, which is to be afterwards washed with a mixture of equal parts of chloroform and ether. Finally distill off the ether-chloroform, and determine alkaloids by alkalimetry.

387. By the following procedure, very fair results may be obtained in somewhat shorter time. Macerate 5 gms. of *nux vomica* in the finest practicable powder, for two hours with a mixture of 40% acetic acid 5 c.c. and 5 C.C. of a solution of sodium chloride. Add 90 c.c. of 50% alcohol, macerate with frequent or constant shaking for 10 hours. Take 50 c.c. of the clear liquid for the assay. Evaporate nearly to dryness on the water bath, transfer to a suitable vial by aid of a small amount of dilute alcohol containing 10% ammonia. Make sure that the ammonia is in excess and shake out with ether-chloroform (3-1) about 20 c.c., and then with 2 or 3 portions of 15 c.c. ether, to obtain an alkaloid pure enough to weigh. Better however titrate with standard acid.

388. Dragendorff's Method:-- (114) is efficient though it consumes a good deal of time -- exhaust 15 gms. of the finely powdered drug by boiling with three successive portions (150) c.c. of distilled water containing 10 drops sulphuric acid to each portion. After each boiling strain and press the residue. The mace should be nearly free from bitterness. Evaporate the mixed solutions to the consistency of honey, after nearly having neutralized with magnesia. To the syrup fluid add 2 1/2 times its volume of 90% alcohol, heat to boiling, filter while hot alcohol and wash the residue thoroughly with hot alcohol of 65% strength. Distill off the spirit, add some sulphuric acid, filter, wash repeatedly with benzol to remove fatty and waxy matter, finally add ammonia in excess and shake out with several successive portions of 25 c.c. chloroform, evaporate the chloroform to obtain an alkaloidal residue which may be weighed then titrated with acid.

[illegible]

389. Squibb's Method:-(II5) A fair sample of the drug is ground fine enough to pass through a # 9 sieve and 10 grams of the powder are exhausted by cold percolation with 10 percent acetic acid. The dry residue obtained by evaporation of the solution to dryness, is treated in a capsule with 10 c.c. of a mixture of two volumes of 91 percent alcohol, one volume of 10 percent ammonia and one volume of water. Move a stirrer over the smooth surface of the extract for 15 minutes:-then pour the contents of the capsule into a separator of 150 c.c. more of the ammonia mixture. Now add to the liquid in the separator 40 c.c. of a mixture of equal volumes and 99 percent chloroform and 96 percent ether. Shake vigorously for five minutes and then allow to separate. When the separation is complete measure the dark upper stratum, draw off the chloroform ether solution into a tared flask and immerse into a hot water bath, so that the chloroform and ether may be boiled off by the time another washing is ready. Meanwhile 40 c.c. more of the chloroform ether solution should have been added to the contents of the separator, and the shaking etc., repeated as before. A third washing may follow if required. If the dark upper layer is found to have increased in depth during the second treatment and separation, it is an indication that an emulsion has been formed to the extent shown: and after the chloroform ether has been drawn off, the dark liquid should be heated in a capsule until all the chloroform ether has been drawn off. Then return to the separator and wash as before. A very small quantity of the emulsion may be ignored. Finally add to the tared flask containing the total chloroform-ether extract, 10 c.c. N.I-10 sulphuric acid, rinse the sides of the flask with this and warm the flask by emersion in a water bath until all the soluble alkaloids are dissolved. Add 20 c.c. of hot water and 10 drops of logwood indicator and observe the color by transmitted light and match it by an similar quantity of liquid in another flask. Then drop in 1-10 N. caustic potash from another burette until the color changes to a slight pink tint. The tint should be very distinct when observed by reflected light. The number c.c. used subtracted from the number c.c. acid started with, gives the number c.c. acid saturated by the alkaloids: and the number times the mean of the molecular weights ($0.0334 \text{ plus } 0.0394$) plus 2) equals .0364, gives the weight of the mixed alkaloids obtained from 10 grams of nux vomica, the strychnine and brucine being assumed to be present in equal proportions. Then as 10 is to the product from 10, so is 100 to the percent?, of mixed alkaloids.

390. Prescott & Gordin. (II6) Method:- The acidulated water solution of the total alkaloids of the drugs obtained by any method of extraction, is made up to a definite volume, say 100 c.c. If four grams have been taken, the 25c.c. will represent one gram of the drug, and will be sufficient for the acid. This volume is run from a burette into a 100 c.c. flask in which have been placed 20c.c. of decinormal iodine solution, and 2 c.c. dilute hydrochloric acid when the amount of iodine have been consumed by the total alkaloids in that one gram of nux vomica is reached as before described. The multiply this amount by 47.8, which is equal to 100 times the mean factor of strychnine and brucine, and the percentage of total alkaloids is obtained.

DETERMINATION OF STRYCHNINE.

391. Assays of nux vomica in detail require the quantity of strychnine and brucine respectively in the total alkaloids. Any of the following are in general use.

392. Keller's Method (II7) For determination of strychnine is perhaps the simplest :- dissolve 1.10 gram of the purified alkaloidal residue in 10 c.c. dilute sulphuric acid, (10 %), add 1c.c. nitric acid (sp. gr. 1.42), mix well, and set aside for two hours. Then add 40 grams chloroform, 40 grams ether, and 10 c.c. of a 10 percent. of ammonia. Shake for several minutes, put into a flask 40 grams of the ethereal solution, and distl off the solvent, dry at 95 to 100 degrees C. and weigh. The distillation should be discontinued when the crystallization of the strychnine begins, and the remainder of the solvent driven off by air current. The purity of the strychnine must be established by dissolving a portion in concentrated sulphuric acid and adding a small crystal of potassium nitrate which should not produce any red color.

393. The assay process for nux vomica may obviously be simplified (strychnine alone determined) by dissolving the whole of the unweighed alkaloidal residue obtained by any of the above assay processes, and representing 2.5 grams of drugs, in dilute sulphuric acid, and treating as above. Observe, however, that the residue so treated should be pure enough to a tolerably clear solution in the dilute acid. If necessary the residue must be purified by dissolving in acid with the aid of heat, filtering and shaking out with ether and chloroform. It is better to extract all of the strychnine at last by the shaking out the successive portions of solvent than to follow Keller's method, which assumes that the whole of the alkaloid has been abstracted by a single washing, and which involve danger of loss of volatile solvent during the required filtration and weighing.

394. Nagelvoort, (II8) operating upon the crude alkaloid obtained by washing out with ether, and adopting a modification of Gerlock (II9) directs to dissolve the alkaloid from 5 grams nux vomica in 5 c.c. (more if necessary) of decinormal sulphuric acid, add decinormal soda to render nearly neutral, then an aqueous saturated solution of picric acid. Add ice water to make 100 c.c., set in a refrigerator until the precipitate has well settled (occasional shaking facilitates this), test supernatant liquid with more picric acid to make sure of excess, and add more if necessary. Decant the pure liquid as closely as possible and wash the precipitate four times by decantation with water. Dry in a heater at 104 degrees C. and weigh.

395. Treat the crystals with 25 c.c. of nitric acid of sp. gr. 1.056, keep at 60 degrees C. half an hour, stirring several times. Neutralize carefully with ammonia: the fluid will become darker when neutralization is complete. Acidulate again immediately with acetic acid. Let the strychnine picrate settle in a cool place, wash as before by decantation four times, dry to constant weight at 105 degrees C. and weigh. The weight multiplied by 0.5932 will be that of the strychnine present.

396. The Ferrocyanide Process of Dunstan and Short, as adopted by the British Pharmacopoeia is as follows:- (Having brought the alkaloids from 10 c.c. of the fluid extract of nux vomica into solution in 30 c.c. chloroform by the shaking out process), shake out the chloroform with 3 portions (10 c.c. each) of dilute sulphuric acid containing 3% sulphuric acid by weight, dilute the acid solution to 175 c.c., add 25 c.c. of a 5 percent solution of potassium ferrocyanide, shake well and frequently during half an hour in a stoppered flask. Transfer the precipitated which formed to a filter, rinse the flask with water containing one twenty fifth its volume of dilute acid and proceed as above.

397. H. M. Gordin & A. B. Prescott, in the course of their researches on the estimation of alkaloids as periodides, found that, along with modifications of Dunstan & Shorts method of assay, the periodide method afforded a very convenient way of estimating the amount of the two alkaloids separately in nux-vomica; The amount of total alkaloid having been ascertained in an acidulated solution obtained from nux-vomica, in a suitable way by the periodide method, the process is further conducted as follows:-- 50 c.c. of the acidulated solution, representing 2 grams of nux-vomica, is run from the burette into an Erlenmeyer flask of the capacity of about 300 c.c.; 10 c.c. of a 2% solution of sulphuric acid is added, followed by ferrocyanite, is run in. The flask is stoppered and the contents are shaken continuously for about half an hour. Now, filter, wash the precipitate repeatedly with water containing 1% of sulphuric acid, let a few drops of the filtrate diluted with a little water, have no bitter taste; The filter is then pierced and the precipitate rinsed with the wash bottle into a 100 c.c. flask. Then add 20 c.c. of a 5% solution of zinc sulphate and keep the flask on a boiling water bath for about 15 minutes. The zinc sulphate decomposes the strychnine ferrocyanide, strychnine sulphate enters into solution, and zinc ferrocyanide is precipitated, the brucine phosphate having been washed away by the previous treatment. The flask is then completely cooled and water enough added to make 100 c.c.:-- of this, 50 c.c., representing one gm. of the nux vomica but deprived of brucine, are then filtered off, run from a burette into a 100 c.c. flask containing 20 c.c. decinormal hydrochloric acid. The amount of iodine in excess is then ascertained by means of a standard solution of sodium thiosulphate and the amount consumed thus determined by subtracting from the original quantity employed and, by multiplying the amount of consumed iodine by the fraction ~~multiplied~~ 43.9, gives the percent. of strychnine. For the mixed alkaloids, the factor is 47.845; for brucine alone, it is 51.79.

398. Galenical preparations, Assay of:- Measure 5 c.c. of the fluid extract or 25 c.c. of the tincture into a capsule. Add one c.c. dilute sulphuric acid 10% and add 10 c.c. of water. Evaporate to expel alcohol, adding, if necessary, more water. Pour the watery solution, measuring about 10 c.c., into a 2 oz. vial having a good lip, rinse the dish with ether and a few drops of water and add the rinsings to the contents of the vial, wash the acid fluid with several successive portions of ether, using for the last washing, a mixture of chloroform 1 volume, and ether 3 volumes. Having decanted this, add ammonia to strong alkaline reaction and wash out the alkaloids with 4 successive portions (15, 10, 10, and 10 c.c.) of the same mixture of chloroform and ether. Bring the ethereal solution to a volume of 50 c.c., evaporate 25 c.c. to determine total alkaloid. In the remainder, after evaporation, determine strychnine as by (392) or (396).

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399. For solid extracts, the method of H. Beckurt's is commonly followed. (120) The extract (2 grams) is dissolved in a mixture of 5 c.c. water, 10 c.c. of alcohol and 5 c.c. of water of ammonia and shaken out with several successive portions of chloroform or a mixture of chloroform and ether. It is as well to dissolve the extract as above and make up a volume of 25 c.c. and, of this, take for the assay two portions, each of 5 c.c., in one of which, total alkaloids are determined, in the other, strychnine, by the method of Keller (392).

400. Nagelvoort (127) directs to weigh in a small flask a quantity of extracts approximating one gram. In case some of the extract adheres to the neck of the flask, no attention need be paid to this. Put into the flask, 5 c.c. of 10% sulphuric acid, cover the flask with a small beaker inverted and warm on the sand bath until the extract is all dissolved or reduced to a homogeneous semi-fluid. Wash the acid solution three times with alcohol free ether. Then render alkaline with ammonia and wash out the alkaloid. This method is preferable to the preceding. Here also, we may advantageously make up the acid solution to 20 c.c. and take aliquot parts for the assay, as suggested in the last paragraph.

401. Method of J. U. Lloyd:- Into a graduate, pour 5 c.c. fluid extract nux vomica and 10 c.c. of chloroform, then add 8 grams Lloyd's Mixture (equal amounts of dry ferric hydrate and sodium bicarbonate, mixed), stir together and add Glucose mixture (equal measures of glucose and water), from 2 to 4 c.c., enough to form a pulp. Stir briskly and decant the chloroform into a beaker-glass, then successively wash the magma with two portions of chloroform, each 10 c.c., decanting each into the beaker. Should the magma adhere to the sides of the graduate, above the stirrer, scrape it down occasionally by means of the spatula on side of stirrer. Evaporate the chloroform, pour upon the residue 6 c.c. dilute (1 to 49, by measure), sulphuric acid, warm gently and filter through a small paper into a four or eight ounce globular separatory funnel. Wash the residue in the beaker twice, with diluted acid, 4 c.c., each time stirring the undissolved back with acid, by means of glass rod, and filter through aforementioned filter into the first acid solution. Make the mixed acid solutions alkaline with ammonia and add 10 c.c. chloroform. Rotate (not shake) a moment, then abstract the underlying chloroform into a tared dish. Repeat the washing with two successive portions, each of 10 c.c. chloroform, abstracting them into the vessel with the first portion. Evaporate the chloroform, bringing the residue to the constant weight in dry oven; multiply its weight, expressed in grams, by 20. The result will be the alkaloidal percentage in the fluid extracts.

402. *Nux vomica* contains from 2 to 3.25 percent of alkaloids of which about 42 percent is strychnine. A fluid extract, however, cannot be easily made to contain more than 1.5 percent of total alkaloids, and this standard is the one now accepted by manufacturers houses. *Ignatia* contains about the same quantity of total alkaloid as *nux vomica*, but a larger proportion of strychnine.

403. OPIUM.----- Gum opium, the concrete milky exudation obtained by incising the green capsules of *Papaver Somniferum*, occurs in commerce in the regular subglobular lumps weighing from 4 oz. to 2 lbs. They are enveloped in remnants of poppy leaves and with chaffy fruits of a species of sumac adhering; when fresh, it is plastic, breaking or tearing apart, showing an irregular, chestnut-brown surface, shining when rubbed; odor peculiar, narcotic; taste bitter. When examined with a pocket lens, it is seen to be composed of yellowish, agglutinated tears. The value of ~~the~~ the gum is only determined by assay. It should contain, in the moist condition, not less than 9% of crystallized morphine. When well dried at a temperature of 105 degrees C., it should yield about 55 to 60 percent. extractive. Powdered opium (U. S. P) should contain not less than 13 to 15 percent. of morphine. When the powder is extracted with about 10% of ether, the ether solution rejected and sugar of milk added to the residue to restore it to its volume (original), it forms denarcotized opium (*Opium deodoratum* U. S. P.)

404. Adulteration-- To increase the weight, various articles are used, such as sand, clay scrapings of poppy capsules, and various mucilaginous albuminous and saccharine matters. Lead bullets are often used as well.

405. Opium is a mixture of sixteen or eighteen different alkaloids, with meconic acid, coloring matters and various inert substances. The principal constituents are the following alkaloids:-- Morphine, papaverine, meconidine pseudomorphine, codeine, laudanine and oxynarcotine; these are in combination with meconic and thebolactic acids.

406. Of the opium alkaloids, morphine is the most abundant and by far the most important, and an assay of the drug or of its galenical preparations calls usually for a determination of this alkaloid alone. Morphine exists in opium in the form of a salt readily soluble in water, which medium ~~is~~ then is better than alcohol, for exhausting this principle. The narcotine is mostly left behind in the aqueous extraction of the opium, although it is more certainly excluded by first treating the drug with ether. Otherwise, the separation is made either by precipitating the morphine with ammonia in the presence of ether, which ^{hold.} narcotine in solution, or else by the use of lime or baryta, which ^{hold.} ~~hold~~ in solution morphine but render ~~it~~ still less soluble narcotine.

407. Morphine (the alkaloid) is nearly insoluble in cold water. It requires for solution, 500 parts of boiling water, 100 parts of cold or 36 parts of boiling 90% alcohol, 60 parts of cooled or 13 parts of boiling absolute alcohol. When crystallized, it requires over 6000 parts of ether, nearly 9000 of benzol and 4400 of chloroform to dissolve it, but if the solvent is applied at the moment that the alkaloid is set free by an alkali, it requires ether about 1000 parts, benzol 2000 parts and chloroform 860 parts. Hence the alkaloid may be practically removed from an aqueous solution by shaking with ether immediately after it is added, but much of it will in a short time crystallize out of ethereal solution. In assay work, the only solvents suitable for a shaking out process are:-- acetic ether, amyllic alcohol or (less objectionable in odor and toxic effect on the operator) isobutylic alcohol. Mixtures of one or other of these with chloroform are sometimes employed; chloroform alone abstracts the alkaloid very imperfectly.

408. Separation of Opium Alkaloids:- The following scheme (122) for the separation of the principal alkaloids of opium, may contain suggestions useful to some. To an aqueous solution containing narcotine, papaverine, narceine thebaine, codeine and morphine, add a concentrated solution of sodium acetate and let stand 24 hours. Narcotine and papaverine are precipitated. Dissolve the washed precipitate in dilute hydrochloric acid, and dilute to 400 times its weight, add potassium ferrocyanide to precipitate (in 24 hours) papaverine. From the filtrate, narcotine is precipitated by neutralizing with ammonia. Concentrate the solution from which narcotine and papaverine have been removed and let stand 24 hours. Narceine will separate. Filter and add sodium salicylate. Acidulate the filtrate with hydrochloric acid and shake out repeatedly with chloroform to remove remaining salicylic acid, narceine and thebaine. Drive off dissolved chloroform by a gentle heat, and add potassium sulphocyanate to precipitate codeine. After 24 hours, filter and add to the filtrate ammonia to precipitate morphine.

409. Sampling opium for Assay:- Where assay had to be made of a case of opium, some systematic method must be adopted for sampling. Dr. Squibb directs:- From every fifth larger lump and every tenth smaller one, cut a cone shaped piece, the apex of the cone to be at the center of the lump. From each cone, take off a slice which shall represent in due proportion, the moist centre and the drier exterior portion. Collect these slices of approximately equal weight into a mass, working rapidly so as to avoid evaporation of moisture. Roll into a cylinder. Repeat the process six times to obtain a perfectly homogeneous mass, a weighed quantity of starch being used for rolling out if the opium is moist and sticky. Two portions, each

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Two portions, each representing 10 grams of the opium (allowance being made for the starch that has been added) are then weighed off. One of these is flattened into a thin disc and dried at 100 degrees C. to constant weight to determine moisture. The other is to be used for the assay

410. The Paris Society of Pharmacy agreed in 1882 upon the following method for the valuation of opium (123):-

15 grams of the opium to be tested, are intimately mixed with 9 grams calcium hydrate, 150 c.c. water gradually added with constant trituration and the mixture occasionally agitated for 1/2 hour. The mixture is then poured upon a filter and exactly 100 c.c. of the filtrate brought into a glass-stoppered bottle, 20 c.c. ether now added, and, after dissolving 6 grams of ammonium chloride in the liquid, it is allowed to repose for 2 hours. The ether is then decanted, replaced by a fresh portion and, after repeated agitation, again decanted. The precipitate of morphine is finally collected upon a smooth filter, washed with a few c.c. of cold distilled water, dried and weighed. The weight, minus the wt. of filter, gives alkaloid and this x 10 equals percent. morphine in the opium.

Squibb Assay Process

411. Squibbs Assay Process (124):- 10 grams of powdered opium are digested with 100 grams of cold distilled water for 12 hours, with frequent shaking, the liquid being acidulated by 1 or 2 drops of dilute sulphuric acid, if not already acid to litmus paper. The whole is poured on a tared filter, the residue on filter washed with water to 150 grams filtrate, which may be designated as Percolate No. 1. The residue on filter is carefully returned to the flask, 50 grams of water added, and in same manner as before 150 grams are obtained--"No. 2". The residue on filter is percolated to the extent of about 20 grams more, percolate #3, which is used for rinsing the vessels in subsequent operations. Percolate No. 2 is evaporated in a tared capsule to about 20 or 30 grams, then No. 1 added, and the evaporation continued until the whole is reduced to about 10 grams, not less and not much more. The dense solution is transferred to a flask, rinsing the capsule and making the weight of the whole not less than 16 or more than 22 grams. Then half its weight of alcohol, sp gr 0.817-0.820 is added to the solution, the mixture is shaken, 15 grams ether of sp. gr. 0.725 are added and the whole is then well shaken. Then 4 gms. solution of ammonia of sp. gr. 0.960 are added, the mixture shaken and allowed to stand over night; the ether layer is decanted as closely as possible, observing that no crystals of morphine shall be carried over with it, and 15 grams fresh ether are poured into the flask which is rotated so as to cause a thorough rinsing of the sides of the flask, and then decanted as before; a third portion of exactly 15 grams is used in the same way.

412. The crystallized morphine is collected on a double filter with the usual precautions and washed, observing that the filtrate and washings shall not exceed 40 c.c. ~~The~~ The morphine is then dried to constant weight at 100 degrees C. and then weighed, using the outer filter to counterpoise the inner.

413. About 0.1 gram of the morphine thus obtained is now agitated with 10 c.c. of lime water in a test tube. If the morphine dissolves to a solution which is nearly or quite transparent, and from which no weighable precipitate settles within one hour, then the contents of the filter are accepted as being practically pure morphine. Otherwise 0.5 gram of the powder is agitated with 50 c.c. lime water, solution filtered through a double tared filter, the filter washed with 3 to 5 c.c. of the rinsings of the vessel in which solution was effected, then washed with 5 c.c. more of water and dried to constant weight. The weight thus obtained, is calculated for the whole quantity of crude morphine obtained and is deducted from the latter as impurity.

414. The method of E. Dieterich (125) as adopted by the German Pharmacopoeia, is as follows:- Triturate 6 grams of finely powdered opium in a mortar carefully with 6 grams of water, dilute and wash the mass with water into a ~~suitable~~ suitable tared flask, and add enough water to make the mixture weigh 54 grams. Macerate with frequent stirring during 1 hour and then filter through a pliated filter of a diameter of 10 cm. Take 42 grams of the filtrate, mix with it, 2 c.c. of N/1 ammonia, without strong agitation, and pass it at once through a ready prepared pliated filter of 10 cm. diameter; 36 grams of the filtrate, representing 4 gms. of opium, are mixed in a tared Erlenmeyer flask, by circular rotation with 10 grams of ether: next, 4 c.c. more of normal ammonia are added, the swinging or rotating motion continued until the liquid has become clear and then the flask is corked and set aside. After standing 5 or, at most, 6 hours, the ether layer is first transferred as completely as possible, upon a plain filter of 8 cm. diameter; then 10 c.c. more of ether are added to the contents of the flask, the whole again rotated and the ether layer again passed through the filter. When this has all run through, the aqueous solution is poured in without having regard for the crystals which adhere to the walls of the flask. Finally, the latter as well as the filter are washed with 2 successive portions of 5 c.c. each of water saturated with ether. After the flask and filter have been allowed to drain well, both are dried at 100 degrees C, the minute quantity of matter retained by the filter transferred to the flask and the drying continued to constant weight.

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415. Cornwall's Modification of Dieterich's Method of Assay. (126):- Prof. Cornwall, at the request of Dr. Wm. K. Newton, the New Jersey Dairy Commissioner, has made a series of investigations for the purpose of determining the value of several of the assay processes proposed at that time. The principal object was to ascertain that method, which being at the ~~time~~ same time the most convenient and least liable to error on the part of the analyst, would give accurately the proportion of morphine, when the latter fell within a reasonable limit above or below the legal standard, rather than to seek a method which would give most accurately the percent. of morphine, whatever the amount. The various methods of Squibb, Dieterich, etc., were tried and the author concluded by recommending the following modification of Dieterich's method as giving the most satisfactory results:- Place 6 gms. of opium in a beaker, add 60 c.c. water, stir occasionally (breaking up all the lumps) over night for 12 hours. Filter into a graduated cylinder, wash the residue on the filter until the filtrate and washings amount to 75 c.c. and set this aside. Carefully return the residue to the flask, stir well with 20 c.c. water, let stand 10 minutes and filter through the same filter; repeat the operation twice more, each time with 12 c.c. water, finally pressing the residue with glass rod. Evaporate the last three washings in a dish 4 to 6 in. in diameter on water bath, below the boiling point heat. When down to 15 c.c., add the 1st. strong extract, rinsing the cylinder with a little water and evaporate the whole extract to exactly 50 c.c., including the water necessary to rinse the solution into the measuring flask. Add 2 c.c. normal ammonia and at once filter as directed in Dieterich's process. Of this filtrate, take a volume corresponding to 4 gms. of opium, add 3 to 14 c.c. of ether, mix by rotating the flask and then add 4 c.c. of normal ammonia as directed in Dieterich's process, and follow the assay directly, as outlined in this process.

416. Prof. A. Fluckiger estimates morphine as follows: 8 grms. powdered opium are placed in a pliated filter 12 cm. in diameter, the funnel being slightly tapered in order to bring the powder to the bottom and the whole dried at 100 degrees C. After half hour, a mixture of 100 c.c. chloroform and 100 c.c. ether is poured upon the powder, the funnel being covered and tapped a number of times; then, 10 c.c. chloroform additional are poured on. After the liquid has drained off, the filter is spread open and the powder dried at a slightly elevated temperature. The powder is then shaken with 80 c.c. water to which has been added 0.2 gm. ammonium oxalate to separate the calcium present and filtered after 2 hours. 42.5 gms. of the filtrate are treated in a small flask with 7.5 c.c. alcohol (sp. gr. .83) 15 c.c. ether and 1 c.c. ammonia (sp. gr. 0.96). After 6 hours of occasional shaking, the contents of the flask are poured upon 2 pliated filters, one inside of the other, and 10 cm. in diameter, the flask being rinsed with 10 c.c.

water or an aqueous solution of morphine (1-5000), and poured on the filters. These are dried at slightly elevated temperature and at last at 100 degrees C. The morphine is then transferred to the flask which has been dried at 100 degrees C. and the whole heated to constant weight. ~~The~~ The morphine obtained represents 1/2 the opium.

417. Method of J. Howard Wainwright (128) of the U. S. Laboratory, attached to Custom House. (This process differs only in some details from that of Dr. Squibb) Put into a 4 oz. wide-mouthed bottle, 10 grams of the opium with 100 c.c. of boiling water. Cork securely and allow to stand, with frequent ^{short} shakings, for 12 to 24 hours. Decant the clear liquid upon a filter of convenient size and collect the filtrate in a beaker. To the residue, add 30 to 50 c.c. more boiling water. Agitate again and transfer the mass to the filter with the aid of a little hot water. Drain well on the filter, wash with a very little hot water applied drop by drop, around the edges of the filter.

418. Return the residue to the bottle and shake up with 50 c.c. hot water. Pour again upon the filter and collect the filtrate in an evaporating dish. Percolate the residue with hot water until completely exhausted. Evaporate the filtrate and when reduced to small volume, add to it the first filtrate, a little at a time, until the whole is reduced to a volume of 20 c.c. Transfer with the aid of the least possible quantity of water to a tared Erlenmeyer flask and, when cool, add 10 c.c. strong alcohol (observe whether this produces any tendency to form a precipitate. If so, add 10 c.c. more of alcohol, let stand an hour, filter, reduce filtrate and washings once more to 20 c.c. and again add 10 c.c. alcohol). Add a volume of ether equal to that of the mixture, cork and shake well. Immediately add 4 c.c. (better 3 c.c.) of 10% ammonia, cork again and shake until crystals of morphine begin to separate. Set aside in a cool place or else shake continuously half an hour or more. (The best plan is to place in a mechanical shaker at least 6 hours).

419. When the morphine is completely precipitated, decant the ether upon a pair of mutually counterpoised filters. Add to the contents of the flask, 20 c.c. more of ether, shake once, let separate and decant this through the filter which is to be then washed with a little ether, applied drop by drop, to its edges. Remove the last traces of ether from the surface of the heavier liquid, by the aid of a strip of filter paper.

420. When the ether has drained through completely, pour on the filter the hydro-alcoholic solution, containing the crystals of morphine. Wash the crystals from the flask (and beaker) by aid of portions of the filtered liquid.

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When all the fluid has passed through the filter, rinse the flask (and beaker) with a little distilled water. (a saturated aqueous solution of morphine is better). Wash the ~~ex~~ crystals on the filter with this and then with pure distilled water until this comes through colorless. Drain the filter thoroughly, fold, press between dry filters, finally dry at 100 degrees C to constant weight and weigh. If any crystals have adhered to the flask, this must also be dried and weighed.

421. The morphine thus obtained is always impure. If dried at 100 C, it retains water of crystallization. To deprive it wholly of this, it should be dried at least an hour at 110 C. The better way I think, is to dry the residue at about 60 degrees C. and weigh the crude morphine, which is afterwards to be dissolved in volumetric hydrochloric or sulphuric acid and titrated back with volumetric soda solution, using cochineal as indicator. Each c.c. of decinormal acid indicates 30.23 mg. of monohydrated morphine which is commonly reported in assays as "morphine" or 28.44 mg. of anhydrous alkaloid.

422. Nagelvoort (129) modifies Fluckiger's process (416) in some particulars, as follows:- He dries the opium 3 hours, at 100 degrees C. noting loss of weight, then pulverizes in a dry mortar and weighs out 10 grams for the assay. He treats the opium the same with ether and chloroform but adds to the dried powder 100 c.c. of water and, after two hours maceration with frequent shaking, filters and introduces into a salt mouth bottle, 50 c.c. of the filtrate, supposed to represent 4 grams of the opium, adds strong alcohol, 20 c.c. ether and 1 c.c. 10% ammonia and proceeds otherwise as in Fluckiger's method.

423. Hager's lime process as modified by Beckurts (129) is as follows:- Macerate 8 grams of powdered opium for half an hour with 79 c.c. of water in a well stoppered flask, add 3 grams of freshly slaked lime and, after frequent shakings for one hour, filter off 51.5 c.c. representing 5 grams of opium. Pour upon this so as to form a layer 30 c.c. of a mixture of 1 volume alcohol, and 5 volumes ether, which mixture has been saturated with opium, add 6 c.c. of a saturated solution of ammonium chloride and shake vigorously. After 6 to 8 hours, pour off the ether-alcohol onto a filter moistened with ether, shake the mixture again with 10 c.c. ether-alcohol, transfer the ethereal solution to the filter, and after it has passed through, pour on the aqueous liquid together with the crystals of morphine; wash flask and crystals with a morphine-saturated solution of equal parts ether-alcohol and water, dissolve in boiling 90% alcohol, filter from the undissolved calcium meconate, to the filtrate; to the filtrate, add 25 c.c. of decinormal hydrochloric acid and titrate back with centinormal soda, using cochineal as indicator.

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424. Method of Farr and Wright: (130) -- Prepare an aqueous solution of opium of which 30 c.c. represent 8 grams of opium, mix this with 3 grams of freshly slaked lime, add water to make 85 c.c., set aside half an hour, stirring occasionally. Put into a 4 ounce bottle having a wide ~~xxx~~ mouth, fitted with an accurately ground stopper 50 c.c. of the filtered fluid, add 5 c.c. of 90% alcohol, 30 c.c. of ether and 2 grams ammonium chloride. Shake well at intervals during half an hour, set aside 12 hours for the morphine to separate, filter, wash with morphinated water and dry the crystals first by pressing between filter paper, then at 60 degrees C., finally for 2 hours at 110 degrees C. Weigh the crystals and titrate with decinormal sulphuric acid until the liquid, after boiling, slightly reddens sensitive blue litmus paper. Add to the weight of the morphine thus indicated, 0.05 gm. to represent the average loss of morphine in the assay.

425. Method of D. B. Dott. (131):-- Digest 10 grams of powdered opium with 25 c.c. of water, add a solution of 1.8 gm. of barium chloride in 12 c.c. water. Make up the mixture to 50 c.c., mix well and in a short time, filter. To 22 c.c. equivalent to 5 gms. opium, add dilute sulphuric acid just sufficient to precipitate the excess of barium (about 1 c.c.), warm the solution to cause the precipitate to subside, and filter. Wash the residue; to filtrate and washings, add dilute ammonia to nearly neutralize free acid and concentrate to 6 or 7 c.c. Add 1 c.c. alcohol, 1 c.c. ether and ammonia in slight excess, stirring well. There should be a distinct odor of ammonia. After 3 hours, collect the morphine on a pair of mutually counterpoised filters, wash with morphinated water, dry, wash with benzol, dry and weigh; finally, titrate with decinormal acid, as in (421).

426. Method of J. Perger (132):-- Boil 10 grams of the opium a short time with 150 c.c. water and 15 grams caustic baryta. Filter and boil the residue repeatedly with small quantities of water until filtrate fails to give a reaction with sulpho-molybdic acid. Excessive boiling is to be avoided and the filtrate should not measure more than 400 c.c. Pass through the solution a current of carbon dioxide to precipitate the barium. Evaporate readily on a water bath, to dryness. Moisten the residue with absolute alcohol, transfer to Erlenmeyer flask and exhaust by repeatedly boiling with absolute alcohol of which 200-300 c.c. will be required. Distill off the alcohol, add 15 c.c. water containing some ammonia, and allow to stand some time; stir well with a glass rod, collect the morphine on a tared filter, dry at 40 degrees C and treat repeatedly with chloroform. The product may be weighed as morphine (mono-hydrated) and titrated with standard acid.

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427. G. Loeff (133) has found that by the aid of sodium salicylate, the determination of morphine is materially improved; the salicylate binding or dissolving the resinous constituents of opium which usually contaminate the morphine; his process as given is as follows:-- 5 grams of powdered opium are carefully and without pressure, triturated with 5 gms. water, then diluted and washed into a flask with sufficient water to make a total weight of 44 grams. The flask is closed and shaken repeatedly for 15 minutes, 1 gm. sodium salicylate added and mixture again shaken several minutes and then filtered. To 25.8 gms. of this filtrate, representing 3 gm. of opium, 3 gm. ether and 1 gm ammonia are added, and the mixture vigorously shaken during 10 minutes. The morphine now separated, is collected on a small filter, the flask washed with 5 c.c. water, the washings being poured upon the filter and when this has completely drained, it is allowed to dry. After drying, ^{the} morphine on the filter is washed with benzol to remove any narcotine present, and then dried and weighed in the usual manner.

428. Method of Montemartini and Trasciatti (134):-- After testing many methods for the assay of opium, the authors approve those of Perger and Squibb, but offer the following, as equally good:- Macerate 10 grams of finely powdered opium in a mortar with 90 c.c. of a 20% solution of sodium chloride for one hour and filter. Treat the residue with 60 c.c. of the sodium chloride solution, filter and treat the residue further with sodium chloride, until a drop gives no reaction with Froehde's reagent (20) Evaporate the mixed filtrates to dryness on a water bath, extract the residue with boiling absolute alcohol (300-350 c.c.) until the fluid ceases to give a reaction with Froehde's reagent. Evaporate or distill, cover the residue with 15 c.c. of a very dilute solution of ammonia and let stand 24 hours. Collect the separated morphine on a tared filter, wash with water saturated with morphine until the washings are colorless and dry at 100 degrees C. Treat the dried morphine on the filter with chloroform until on evaporating a few drops, taking up the residue in hydrochloric acid and adding soda solution, no turbidity is obtained. The morphine is then dried at 100 degrees C. and weighed.

429. Assay by periodide Method of Prescott and Gordin. (135):-- One gram of the opium in very fine powder is put into a small mortar which can be well covered with admission of a small pestle. (a 4 oz. screw top ointment jar with rounded bottom answers very well, the cover being perforated to admit a pestle). A mixture is made of 5 c.c. stronger solution of ammonia, 5 c.c. alcohol, 10 c.c. chloroform and 20 c.c. ether. The opium is rubbed up with 2 or 3 c.c. of this mixture to make a uniform paste, the covered dish is put aside for three hours being gently moved from time to time: 15 grams of well dried and finely powdered sodium chloride is now added and carefully mixed with the mass.

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The dish is now left open in a warm place for 2 or 3 hours, when it is placed 12 hours in a desiccator containing sulphuric acid and a dish of paraffin, (a vacuum desiccator being preferable,) when the mixture should be perfectly dry and dusty. The powder is next carefully transferred to a small percolator (the barrel of a 1 oz. glass syringe), the dish being cleansed with two successive portions (very small amounts) of sodium chloride. The powder is percolated with pure benzene (benzol) until, upon evaporating two drops on a watch glass, dissolving in 4 drops acidulated water and adding a drop of Wagner's reagent (15), no precipitate is produced.

430. The benzol is rejected and the percolation is continued with acetone (boiling point 54° to 58° C.) to complete exhaustion; the percolate being received in a small capsule. (The percolation is carried on until 10 drops of the percolate evaporated on a watch glass and taken up with 4 drops, acidulated water give no turbidity with a drop of Wagner's reagent). Usually as much as 200 c.c. acetone will be required. The acetone is then evaporated off at a temperature not exceeding 45° degrees C. The dry residue, when cold, is treated with several successive portions of freshly prepared lime water, the quantity of solution being finally made up to a volume of ~~100 c.c.~~ 100 c.c. with lime water. The turbid fluid is shaken during 30 minutes and filtered. Of the filtrate, 50 c.c. is measured into a stoppered flask, dilute hydrochloric acid is added sufficient to render just perceptibly acid, and 25 c.c. of decinormal iodine solution is run in from a burette, the flask being gently shaken during the process. Water is now added to bring the volume up to exactly 100 c.c. and the mixture is then shaken vigorously and continuously until, on standing, the supernatant liquid is perfectly clear and transparent (about 20 minutes).

431. The color of the solution must be of a pronounced iodine red; if it is not, add 5 c.c. more of the decinormal iodine solution (or a sufficient quantity). Filter, titrate 50 c.c. of the filtrate (or one half its volume before filtration) with decinormal solution of sodium thio-sulphate, using starch as an indicator. The number of c.c. of the thio-sulphate solution is multiplied by 2 and the product subtracted from 25 (or the total number of c.c. of decinormal iodine solution used) and the remainder multiplied by 1.896 to obtain percent. of morphine in the opium assayed. The precautions to observe in the assay are (1) to make sure that the opium residue is thoroughly dry before percolation; (2) to use an acetone conforming strictly to the stated requirements as to boiling point; (3) to continue the shaking after addition of the iodine solution until the fluid is clear.

432. Morphine may be determined in the crude product obtained by other processes of assay (free from other alkaloids) by dissolving 150 milligrams in very dilute hydrochloric acid, rendering nearly but not quite neutral with solution of soda and making up the volume to 75 c.c. with water. To this, is added 25 c.c. decinormal iodine solution and the operation continued exactly as in (430) and (431). Each c.c. of decinormal iodine solution corresponds with 9.479 milligrams of alkaloid.

433. William R. Lamar, (136) who engaged in assaying a sample of powdered opium according to the U. S. P. method, noticed, after having concentrated the aqueous liquid and brought it to the weight of 20 gms. as officially directed, that the addition of the required 10 gm. of alcohol caused a pronounced flocculent precipitate. This precipitate, after the addition of 25 c.c. of ether, shaking etc., did not diminish and, as suspected, was by experiment, determined to contaminate the final precipitate of morphine, and to that extent vitiate the results of the assay. In searching for a method whereby this could be prevented, he found this in the use of increased amount of alcohol as the preliminary addition to the 20 gm. of aqueous extract. He adds 60 gm. of alcohol instead of 10 gm. under specific directions, filters off the precipitate produced, washes the filter with a mixture of alcohol and water in the same proportions until the washings pass bitterless and, having added 35 c.c. of water, evaporates off the alcohol and concentrates for 14 gm., as officially directed, for the original aqueous opium solution. This is transferred to an Erlenmeyer flask, brought with the washings to 20 gm., 10 c.c. alcohol is added and the process continued to completion according to the precise directions of the U. S. P., and as though this intermediate precipitation by alcohol had not been effected. This additional step is easily executed in one hour's time and insures the purity of the morphine finally obtained.

434. Tincture of Opium (160 c.c.) is to be evaporated to about 30 c.c. and poured in a thin stream with constant stirring into 115 c.c. of cold water, the dish well rinsed, first with portions of the mixture, then with water sufficient to make in all exactly 150 c.c. Let the mixture stand one hour, filter, evaporate 100 c.c. of the filtrate to 20 c.c., transfer to a tared Erlenmeyer flask and proceed with the assay, as per (367). As an alternative process, evaporate 80 c.c. of the tincture to 30 c.c. and proceed as in (424).

435. Lyman F. Kepler⁽¹³⁷⁾ proposes the following for assaying vinegar of Opium (137):-- 100 c.c. of the vinegar of opium are rendered alkaline with strong ammonia water (8 to 10 c.c.), intimately mixed. 2 c.c. ether added to prevent frothing, vigorously shaken for 10 minutes and then allowed to set over night. After the alkaloid is completely precipitated, pass through a filter previously wetted with water and wash the precipitate sparingly. While the precipitate is still decidedly moist, transfer it to a small capsule, by means of a wash bottle, using as little water as possible. To the contents of the capsule, add 10 c.c. of 5% sulphuric acid, or enough to render acid, warm on water bath, cool, allow to stand one hour or more, filter and ~~xxx~~ wash the filter and residue well with distilled water. The exact process of U. S. P. can be followed from here if desired or finish by any preferred method.

436. Solid Extract of Opium (10 gms.) is to be dissolved in 25 c.c. water, the solution poured into 115 c.c. cold water and the process carried on exactly as in the first process of (434). Otherwise, 5 gms. of the extract may be dissolved as far as possible in 25 c.c. water and the solution treated as in (424).

437. Detection of Morphine in mixtures, syrups, pills, etc. The detection of morphine is not always easy; its quantitative determination is rarely attempted save by expert pharmaceutical chemists and then by different methods from given here. From mixtures containing much morphine, it is possible to separate enough morphine for identification, (unless other alkaloids are also present) by simply adding ammonia and shaking out with amyl, or better, isobutyric alcohol. To obtain it in sufficient purity for tests, the solution should be shaken with water containing sulphuric acid and the acid solution should again be extracted with the same solvent, which, on evaporation, will leave a residue that can be tested qualitatively for morphine. Complex mixtures should be subjected to dialysis for 24 hours and the dialysate concentrated and tested as above. Good reactions should be obtained where morphine is present in anything like medicinal doses.

Physostigma.

438. The seed of *physostigma venenosum* is about the size of a pecan nut,; oblong, somewhat flattened and kidney shaped, invested with a light to deep chocolate brown testa. Along the entire convex edge, there extends a prominent black furrow, bordered on each edge by a reddish ridge and traversed the entire length, by a raphe as a little ridge in the center. This raphe is terminated at one end by a small funnel-shaped depression, the micropyle. Internally, the bean consists of a short, curved radicle and two concave-convex cotyledons, the concave surfaces enclosing a rather large cavity, thus enabling the bean to float on water. Nearly odorless; taste bean-like.

439. Calabar bean contains two alkaloids; physostigmine, also called eserine, and calabarine or eseridine. It is the former of these that we may regard as the active principle of the drug. It is readily removed from its aqueous solutions by adding ammonia and shaking out with ether, which leaves behind the second alkaloid.

440. Assay Process:- Put into a 4 oz. prescription vial, 15 grams of calabar bean in No. 60 powder, with 105 c.c. ether, shake and let stand for one hour. Add 7.5 c.c. of a saturated solution of common salt and 1 c.c. of 5% hydrochloric acid, shake well and macerate one hour with occasional agitation. Take for the assay, 70 c.c. of the ethereal fluid, corresponding to 10 gms. of drug and follow routine of (72) to (74) to obtain the alkaloid, using ether as the solvent. This must be used rather liberally. Chloroform will still remove a little alkaloid, which may be weighed separately, the drug valuation being based on the quantity of ether-soluble alkaloid present. The short assay process of Lyons No. 2 (71) may be used but does not ~~xxxxx xxxxxxx~~ give as high a percent. of alkaloid as the one described.

441. Alternative Process:- Digest 20 gms. of the finely powdered drug in a flask 12 hours with 50 c.c. alcohol and 1 c.c. of 40% acetic acid, add 50 c.c. alcohol and heat to boiling. Decant the alcohol, add 50 c.c. more alcohol, boil 20 minutes connecting the flask with a reflux condenser. Repeat the boiling with two additional portions of alcohol, unite the alcoholic solutions, distill off the alcohol and dissolve the residue in 10 c.c. water and 25 c.c. ether, adding also a few drops of dilute sulphuric acid. Transfer to a 2 oz. vial, shake the fluids together and let stand; when completely separated, decant the ether carefully into the waste ether bottle, wash the aqueous solution with 2 or 3 successive portions (10c.c.) of fresh ether and decant as before.

Add now, ~~the~~ 20 c.c. of fresh ether and solution of ammonia in slight excess, shake, decant the ether when completely separated, into a tared beaker or dish. Treat the alkaline fluid with 2 or 3 successive portions of 15 and 10 c.c. of fresh ether, until no more of the alkaloid is taken up. Evaporate the mixed ethereal solutions at a gentle heat in a place sheltered from strong light, dry at 100 degrees C. to constant weight, cool and weigh.

442. Solid extract calabar bean must be dissolved in water and ether as described above, one gram being sufficient for the assay. Fluid extracts or tinctures are to be evaporated and the residue treated in the same manner.

443. The yield of ether soluble alkaloid from calabar bean is generally between 0.15 and 0.25 percent, sometimes as low as 0.1 percent. The standard adopted for fluid extracts for standardization is 0.2 percent ether soluble alkaloid.

Pilocarpus.

444. The leaflets of *Pilocarpus jaborandi* are nearly sessile, pinnate with a terminal leaflet; the leaflets, which come into market separate, are ovate-~~long~~ oblong, entire, about 4 inches long and about 2 inches wide; short petiole, uneven at the base, slightly revolute at margin, near which the anastomosing veins form one or two distinct wavy lines; coriaceous; dull green, finely marked with small, transparent dots or oil-cells, plainly visible when held up to the light; when bruised, a peculiar, rather unpleasant odor is emitted; this odor is predominant in the fluid extract. Taste disagreeable, slightly pungent and bitter.

445. Constituents:- A volatile oil, and two alkaloids, (1) pilocarpine, deliquescent, crystalline, inodorous and slightly bitter, and (2) jaborine, chemically isomeric, with, but distinctly antagonistic to the first named in physiological action. Pilocarpine is the most active and yields jaborine and pilocarpidine when heated with hydrochloric acid; its salts are readily soluble in water; their action is similar to nicotine. Jaborine is yellow amorphous and resembles atropine in action; its presence in the commercial pilocarpine explains the different effects following the use of the latter when improperly made. It is ~~xxx~~ therefore very necessary in using pilocarpine or any of its preparations, to obtain them free from jaborine.

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446. Assay Process:-- The short assay process of Dr. Lyons, No. 2 (71) answers very well. It is better to use at least 12 grams of the finely powdered leaves for the assay.

447. Poehl (138) gives the following method of assay:-- Extract 10 grams of the leaves with 100 c.c. of water containing 1% hydrochloric acid. Precipitate the infusion with lead subacetate, remove excess of lead with sulphuric acid, filter, precipitate the filtrate with sodium phospho-molybdate. Collect the precipitate, wash with water containing hydrochloric acid, dry at 100 degrees C. and weigh. Multiply by 0.4566 to obtain the weight of the alkaloid.

Pulsatilla.

448. Constituents:-- A peculiar acrid crystallizable principle exists in the plant known as anemonin, an unstable principle not well understood. Some authorities state that it undergoes decomposition after its isolation, under conditions which are not precisely known, into anemonin, anemonic acid, etc.; others state that it is a volatile acrid principle, very susceptible to decomposition.

449. H. A. Bishop communicates the following assay process for pulsatilla, based on the assumption that the active principle of the drug is the neutral principle anemonin. This has, of late, been found and determined to be a crystallizable substance nearly insoluble in water and glycerine, while in hot alcohol, but only slightly so in cold alcohol, easily dissolved by ether and especially by chloroform.

450. The following is the proposed method of assay:-- Put into a suitable still, 500 grams of the fresh drug cut in small pieces, add enough water to cover, macerate at 60 degrees C., 24 hours, then raise the temperature to the boiling point and distill as long as the distillate gives an acid reaction. About 1000 c.c. of distillate will be obtained, which is to be put into a ~~standard~~ stoppered flask and set aside in a warm place for several days. The fluid is then to be shaken with several successive portions (50 c.c.) of ether, which will remove anemonin together with anemonic acid. The ether is to be evaporated or distilled off and the residue treated with several successive portions of hot alcohol. From the concentrated alcoholic solution, the anemonin crystallizes out on cooling, and at the end of 24 hours, may be collected on a filter, dried and weighed.

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Strophanthus.

451. The seed of *Strophanthus hispidus* is from 30 to 60 mm. ($1 \frac{1}{5}$ to $2 \frac{2}{5}$ in.) long, flattened; oblong-lanceolate, the base rounded but still retaining a pointed appearance, the apex narrowing into a long awn; surface grayish-green, covered with fine, silky, appressed hairs. On one side is a distinct ridge running ~~from~~ up into the awn, which is 3 to 4 inches in length, bare below but bearing on the upper half, a thick tuft of long straight, silky hairs; these awns, however, are generally removed before the seeds come into market. They are very bitter and almost odorless.

452. The active principle of *Strophanthus* is the glucoside strophanthin, which is freely soluble in water, less readily in alcohol and scarcely at all in chloroform or ether. It is precipitated from aqueous solutions, by tannin. Mineral acids and even the stronger organic acids decompose it, producing strophanthidin and glucose. Strophanthidin is nearly soluble in water, but dissolves in alcohol and chloroform. It seems to have toxic properties similar to strophanthin.

453. The direct determination of strophanthin is not an easy task. The following is Elborne's (139) method of isolating the glucoside:-- Digest one part of the finely powdered drug with four parts of water containing 10% of alcohol for 12 hours, add 52 parts by volume of absolute alcohol, shake and macerate 6 hours. Filter, wash residue with rectified spirit and distill off four-fifths of the volume of the solution. Add lead subacetate in excess, heat to the boiling point, filter, wash the residue with a little water and allow the filtrate and washings to cool. Treat the cold solution with hydrogen sulphide, to remove lead, filter and shake out with 3 volumes of amylic alcohol. On distilling off the amylic alcohol, strophanthin remains nearly pure. The process is open to objection for assay work, since hydrogen sulphide, according to Dr. Frazer, converts some of the strophanthin into strophanthidin; this fault can be remedied by using a neutral salt sodium sulphate or phosphate to remove excess of lead.

454. Pure Strophanthin may be obtained from an aqueous solution, according to Dr. Frazer, by adding a solution of tannin as long as it produces a precipitate, avoiding large excess, mixing the moist precipitate after filtering and slight washing with oxide of lead and extracting with rectified spirit and the solution poured into ether which precipitates the strophanthin. The precipitate is dissolved in weak alcohol and, through this solution, carbonic anhydride is passed to remove traces of lead. After filtration, the solution is evaporated and dried at low temperature or in vacuum over sulphuric acid.

The process is liable to be attended with loss, so that it is ~~next~~ not recommended in assay work.

455. John Barclay (140) proposes an indirect mode of determining strophanthin by converting it into strophanthidin. The drug having been exhausted with alcohol, most of the alcohol is to be recovered by distillation. Water is added and the remainder of the alcohol driven off by heat, the aqueous solution is shaken with chloroform to remove fatty substances, a little sulphuric acid is added and the mixture heated for one hour on the water bath. The turbid liquid is then shaken out with three successive portions of chloroform, which takes up the strophanthidin. The chloroform is distilled off and the residue dried at a temperature not exceeding 65.5 degrees C. The weight multiplied by the factor 2.74 may be taken as that of the strophanthin originally present.

456. Assay Process based on the foregoing:-- Mix 13.33 grams of finely powdered drug with 40 c.c. water containing 10% of alcohol. Macerate with occasional shaking, 12 hours, add 161 c.c. of absolute alcohol, shake and macerate 6 hours. Pour off 150 c.c. of the tincture and evaporate on the water bath until all alcohol is driven off. Having reduced the volume to 15 c.c., transfer to a separator with aid of a little water. Shake with 2 successive portions of chloroform (10 c.c.). Wash the chloroform with 5 c.c. water, which is to be added to the aqueous solution in the separator. Transfer this to a small flask, rinsing with a little water, add 1 c.c. of 10% sulphuric acid, connect flask with a reflux condenser and heat on a water bath for one hour. Transfer the turbid solution to a separator and extract with 3 successive portions of 10 c.c. chloroform, evaporate the chloroform, dry at 65 degrees C. and weigh. This weight multiplied by the factor 2.74, gives the amount of strophanthin in 10 grams of the drug.

457. Quick method of determination of Strophanthin in the tincture and extract by means of the Polariscope (141):-- Edward Dowzard recommends the following quick method for estimating the amount of strophanthin in the tincture or extract:-- 100 c.c. of the tincture are evaporated to about 20 c.c. on the water bath, 2 c.c. of solution of lead subacetate added, the heat continued a few minutes, the mixture filtered and the precipitate washed twice with small amounts of warm water. The filtrate and washings are then evaporated to about 10 c.c., then made up to exactly 20 c.c., a portion of this passed through a dry filter and its optical rotation taken in a 200 mm. tube, using an instrument of the Laurent half-shadow type. On dividing the rotation by five, that of the original tincture is obtained; one ~~xxxxxxx~~ minute being equivalent to .03 grams strophanthin per 100 c.c. of fluid examined. In the case of the extract, the procedure is essentially the same. The estimation must be made, however, before its reduction with milk sugar, as is required in making the B. P. extract, one gram of the extract being dissolved in

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5 c.c. water, and then treated with basic lead acetate as in the procedure for tincture.

Veratrum.

458. The rhizome and roots of *Veratrum viride* usually occur in commerce in small pieces or large slices. When entire, they are obconical, from 50 to 75 mm. (2 to 3 in) long, truncate at the base, tufted above with the inert stem-remnants and leaf stalks, and beset on all sides with light yellowish-brown rootlets about the thickness of a knitting-needle; externally blackish. A transverse section shows a dingy white surface dotted with darker colored dots and wavy lines within the nucleus sheath. Inodorous; very bitter, very acrid, causing a tingling sensation in the tongue.

459. Constituents:- *Veratrum viride* contains the alkaloids jervine (to which the depressant action on the circulation is partly due.), pseudojervine, rubijervine and cevadine. Veratrine was at first supposed to be the active principle of the drug but it has been found to either not exist in it or, at most, only in small quantities, the source of this alkaloid being *sabadilla* fruit. There are two varieties of *veratrum* but the same alkaloids are found in both, though in different proportions. In the ~~present~~ present state of our knowledge regarding the uncertainty of the various alkaloids, we cannot determine by assay the therapeutic value of the drug. We can simply determine the total content of alkaloid, and assume that this will indicate roughly, the quality of the drug.

460. The most characteristic alkaloid of *veratrum*, especially abundant in *veratrum album*, is jervine, which forms with the mineral acids, very sparingly soluble salts. This peculiarity of the alkaloid must be borne in mind in assaying the drug or we shall be in danger of losing some of the alkaloid. It is best to use acetic acid in place of hydrochloric, in abstracting the alkaloids from an ethereal solution.

461. An assay of *veratrum viride* to determine the total alkaloid present may be easily made by Lyons Short Assay process No. 2 (71) using as the primary solvent, a mixture of one volume chloroform and four volumes ether and remembering to substitute acetic for hydrochloric acid to extract the alkaloid from the ethereal solution (72). It is necessary to wash the ethereal solution repeatedly with the acidulated water, to remove the whole of the alkaloid. For the final extraction of the alkaloid, chloroform should be used. The drug should yield about 1 percent of alkaloids, but commercial samples vary greatly in strength.

462. Kremel (I42) exhausts the drug by hot repercolation with a mixture of chloroform and absolute alcohol, equal parts, agitates the solution with several successive portions of water acidulated with hydrochloric acid, filter the acid solution, renders alkaline with caustic potash, and shakes out with 3 successive portions of chloroform. He reports a yield of 1.3 to 1.5 percent. of white alkaloid from veratrum album, in the form of white scales and microscopic prisms.

463. Jervine, which is the most abundant alkaloid, although possibly not the most important, therapeutically, may be easily determined by taking advantage of the insolubility of its nitrate in a solution of potassium nitrate. The process (I43) is carried out in the following manner:—dissolve the crude alkaloid obtained from the drug or from one of its preparations in dilute acetic acid, filter the solution and add an equal volume of a saturated solution of potassium nitrate. Set aside for twelve hours, collect the jervine nitrate on a pair of mutually counterpoised filters, wash with solution of potassium nitrate and finally with a little water, drain, press between blotting paper, dry at 75 to 80 degrees C. and weigh. Assuming that the nitrate is an anhydrous salt of normal composition, we shall not be far out of the way if we reckon on 89 percent of the weight of the salt is alkaloid.

464. Assay of Galencial Preparations:—A fluid extract may be assayed by (I31) et. seq., but it will be found difficult to obtain the whole of the alkaloid. It is advisable after extracting several times with a mixture of chloroform and ether, to employ pure chloroform, adding at the same time a little alcohol to prevent the formation of an emulsion. If an emulsion should form, resort to the saw-dust process. (I59), which may indeed be adopted in the out-set, although not with our usual confidence that the whole of the alkaloid will be extracted. Tinctures must be evaporated to consistence of fluid extracts and then treated as above. Extracts are rarely used but would be dissolved in small amount of menstruum and treated as fluid extracts.

465. H.W. Snow (I44) after working for some length of time upon an assay process for veratrum proposes the following:— Mix 15 c.c. of the fluid extract with 60 c.c. of alcohol, containing about 6 c.c. of a saturated solution of lead acetate, shake and allow to stand a few minutes. Filter through a dry filter, take 50 c.c. of the filtrate, equivalent to 10 c.c. of fluid extract, remove excess of lead by hydrogen sulphide, evaporate to expell the alcohol, add water and a little acetic acid to make up the volume to 10 c.c., and titrate with Mayer's reagent (N-I-20), of

which each c.c. will indicate about 15 milligrams of alkaloid. Instead of estimating the alkaloid by titration we may extract it with chloroform after adding an alkaloid but, as long as our knowledge of what is the real active principle of the drug, is so imperfect, the above is the best method.

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--: Summary :--

The choice of methods for individual drugs and preparations will vary a great deal with the operators. What one chemist may deem a good method, another may think entirely worthless. I will give below the methods preferred by me in each drug in question:--

In the assay of aconite and its preparations, I have found prolonged contact with alkali decomposes the alkaloid and the results always run low. For that reason the perforator method in my opinion is utterly worthless. The sawdust method (159) yields the best results. The short assay process (71 and 72) also yields good results. No matter what the process of assay, after my finished product is completed, it should answer to Squibbs Physiological test (194, 195 and 196).

For Aloes I use method exactly as given in 202 with good results.

The drugs Belladonna, Stramonium and Hyoscyamus, I have classed all under one head, since they contain identical or nearly related alkaloids. The main thing to bear in mind is that we are dealing with alkaloids easily destroyed or altered. Methods used for standardization must avoid the application of heat, or long action of alkalies, strong acids, etc.

Henbane contains such a small amount of alkaloid, that double quantity is generally employed.

The method preferred above all others is Thompson's Sawdust Method (159) used on all three of the drugs. Such methods as Dr. Schwickerath's (215) etc. are utterly useless.

The Cantharidin from Cantharides is best separated by Nagelvoort's method. By continued use of it very close results may be obtained.

The assay of Ciuchona may be accomplished by any one of several. I prefer the methods of Prollius liquid by taking about four gms. of the drug, digesting with 100 c.c. of the modified Prollius fluid and then following the routine of (72 and 74). No few prefer the lime process (281), but the assay always is short, due to loss of alkaloid from the prolonged contact with the lime solution.

Cocoa leaves are best assayed by the short assay process (75). This method gives good results and a particularly pure alkaloid.

Squibbs Kerosene method yields nearly as good results, but is harder in manipulation.

The object of this report is to describe the results of the work done in the laboratory of the Department of Chemistry, University of Toronto, during the year 1934. The work was done under the supervision of the late Professor J. H. Hildebrand, and the results are presented in the form of a summary of the work done during the year.

In the study of the properties of the various types of polymers, it has been found that the properties of the polymers are determined by the nature of the monomer units and by the nature of the polymerization process. The results of the work done during the year are presented in the form of a summary of the work done during the year.

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The Assay process which I prefer for Colchicum Seed or Root is same as given in (294). It yields better results and purer alkaloid than any other method. The precipitation with Mayer's reagent is used by no small number but in my hands do not give as good results as with method above stated.

Conium containing a volatile alkaloid can be subjected to heat without loss of active principles. The Prollius mixture yields good results. But any method at its best is far from satisfactory as there is no satisfactory way of liberating aqueous solutions containing salts of coniine. The alkaloid seems to affect the indicator phenolphthalein, so that the alkalimetric process cannot be resorted to. Mayer's reagent precipitates the alkaloid only in quite strong solutions and the precipitate runs through an ordinary filter, so that good results cannot be obtained by this method. The method of (303) yields by far the best results.

The Assay of Digitalis Leaves has been a problem of a great amount of discussion. Some claiming no chemical means can determine therapeutic value of a sample of digitalis. Other claim the chemical assay the only correct way. I have always followed Keller's chemical assay as given in (315).

The assay of Elaterium is in its infancy. The method of (321) is a process I have of determining the content of elaterin and yields fairly good results being a drug of little medical use, the assay process is not as perfect as those of more extensive use.

Ergot comes again under the uncertain class of physiological vs chemical method of assay. While I believe in the physiological assay of ergot, my facilities compel me to use the chemical I always use (325).

The assay of Gelsemium is best conducted by the process of (71) to (73), the alternative of (72) being preferably followed. The alkaloid is always of a dark color and apparently of a complex composition. For that reason I always use the alkalimetric titration rather than direct weighing. The titration with Mayer's Reagent (332) also yields good results.

Guarana and other drugs containing caffeine are best assayed according to the method of Prof. J. W. Lloyd (168). The alkaloid is very feebly basic so that it cannot be determined by alkalimetry, at least with any of the indicators ordinarily employed.

For the assay of Hydrastis, I prefer the periodide method of Prescott and Gordin. The method works nice

[illegible]

and good results are obtained from it.

Ipecac is a drug difficult to assay due to the ease with which the alkaloid decomposes and is lost. I prefer the Prollius method and precipitation with Mayers Reagent (367). I have found the result obtained by this method more trustworthy than those obtained by any other method.

The assay of Nuxvomica is best worked by the Periodide method of Prescott and Gordon. Dragendorff's method (388) is efficient although it consumes a good deal of time. The short assay method of (71) also gives good results.

Opium presents several forms of assay methods. I always use the method of J. Howard Wainwright of the U. S. Laboratory of Custom House (417). It yields by far the best results. Prescott's method also yields good results.

Physostigma or Calabar Bean is best standardized by (440.) The alkaloids are here determined as total alkaloids and not separately.

For Pilocarpus I prefer the routine of (71). The process of (62) et seq., gives practically identical results.

The assay of Pulsatilla is new and very little is known about it. The assay of (450) is based upon the assumption that the active principle anemonin is a neutral substance. The exact estimation of strophanthin, the active principle of strophanthus, is no easy task. Elbornes method (453) gives the best results although duplicates never agree very closely.

Veratrum is another drug added to the list of those as yet imperfectly known. The assay process (71) gives best results but very little choice.

There is a large field open to the Pharmaceutical Chemist for work and research. Very few of our now largely used drugs have been accurately analyzed and their constituents determined. The work must come from our Universities, as the Pharmaceutical Chemists employed in manufacturing have little or no time for this class of work. We trust that more of our University students will publish their work along this line, so that we who are engaged in manufacturing may learn more of the theoretical side of these now uncertain and unstudied drugs.

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The study of American is best worked by the following method of Brownell and Brownell. Brownell's method (1931) is a revised although is somewhat a good deal of time. The most satisfactory of (1) also gives the following.

On the morning of the 1st of May, 1941, the writer was in the office of the U. S. District Court at New York City, when a man named "Joe" came in and asked to see the writer. He was told that the writer was not in the office at that time, but that he would be in the afternoon. The man then left the office and the writer did not see him again.

The following is a list of the names of the persons who have been
 identified as having been in contact with the subject of this report
 during the period of the investigation. The names are listed in
 alphabetical order.

The range of *Thalassia* is low and very local. It is known about 4000 ft. The range of *Thalassia* is low and very local. It is known about 4000 ft. The range of *Thalassia* is low and very local. It is known about 4000 ft.

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as long as the subject is maintaining any form of contact with the FBI, the FBI will continue to monitor the subject's activities. The FBI will also continue to monitor the subject's activities in the future. The FBI will also continue to monitor the subject's activities in the future. The FBI will also continue to monitor the subject's activities in the future.

The greater part of the research and library work was performed through the permission of Prof. J.W. Lloyd, as well as to Dr. Waldbott, the librarian, I am deeply indebted.

The researches have covered all copies of the following publications from first copy issued to Jan. 1st, 1901:--

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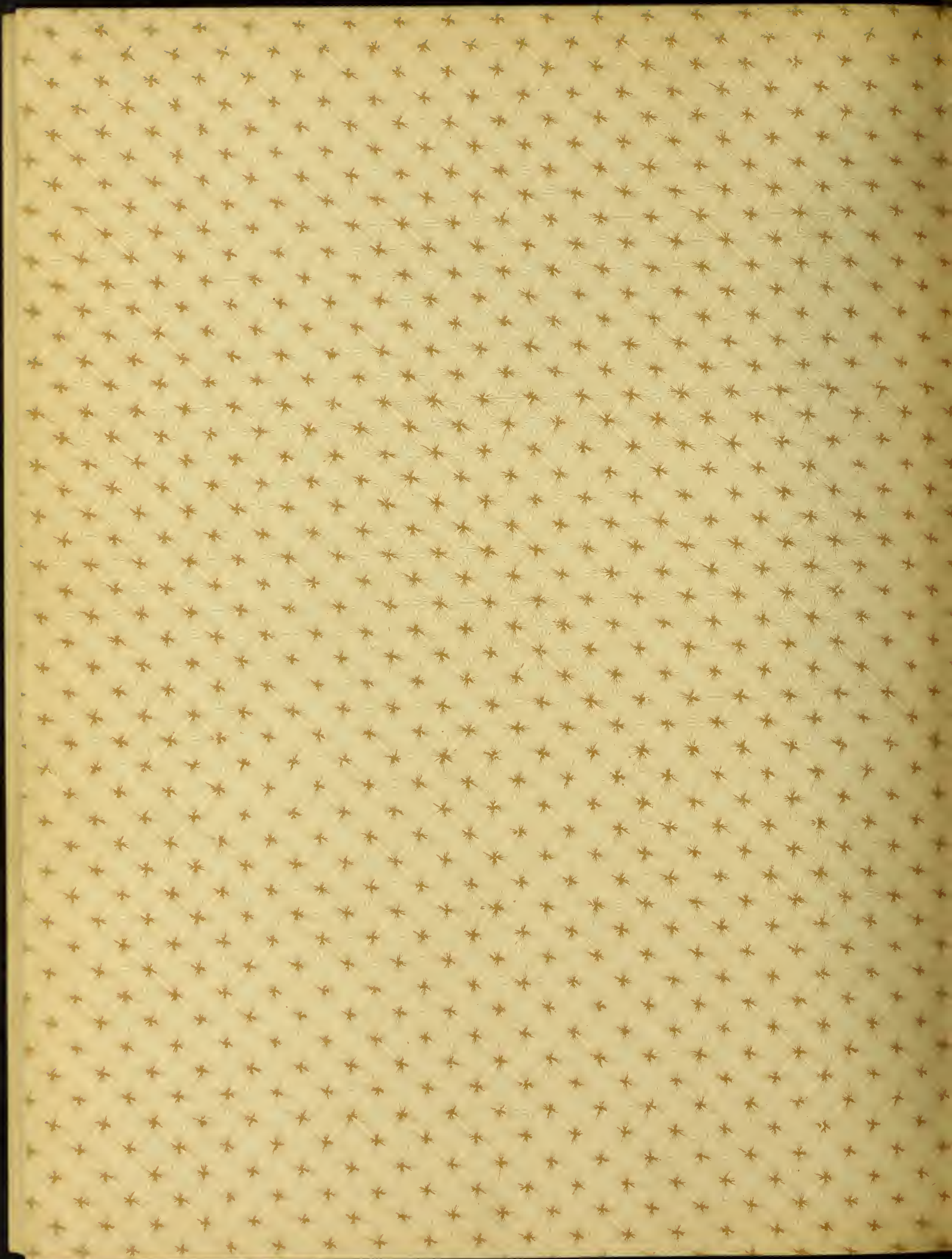
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HEAD OF DEPARTMENT OF

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