

THE REASONS FOR SOME OF THE CHANGES IN THE FORMULAS
OF GALENICALS MADE IN THE NINTH REVISION OF THE
UNITED STATES PHARMACOPŒIA.*

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Compliance with the legal standards, if there were no other reason, would necessitate a study of the changes made in the Ninth Revision of the Pharmacopœia. As my assignment in the symposium of this evening has been restricted primarily to Extracts, Fluidextracts and Tinctures, I will, necessarily, limit my remarks very largely to the changes made in the formulas for certain of these galenical preparations. To the pharmacists these are of the first importance and the users of the book should certainly understand why the changes have been made.

While the reasons for some of the changes may be apparent, the writer is aware, from the criticisms and queries propounded, that the reasons for many of these are not generally understood. Hence, it appears that this phase of the subject is worthy of special consideration and that an explanatory paper on pharmacopœial changes, even though it may sound elementary to some of my hearers, may not be an undesirable subject to present to this audience and, at the least, it may be of some assistance to students.

The changes in the titles of fluidextracts, extracts and tinctures have not been very numerous or important. The changing of the title *Fluidextractum Rhamni Purshianæ* to *Fluidextractum Cascaræ Sagradæ* was in recognition of the almost universal practice of physicians in using the latter title. The custom of physicians in prescription writing not infrequently determines changes in pharmacopœial titles.

The adoption of cardamom seed instead of cardamom fruit necessitated a reduction in the amount of cardamom directed in several of the formulas, such as Compound Extract of Colocynth, and in Tincture of Cardamom and Compound Tincture of Cardamom, as the inert capsule is eliminated.

Economic reasons at times have decided changes. An instance of this is seen in the official oleoresins, which, with the exception of Oleoresin of Cubebs, are again directed to be made with ether as a solvent instead of acetone. In the Eighth Revision, acetone was directed in place of ether, because at that time the former was cheaper. As it is now permissible to use denaturated alcohol in the manufacture of ether, that solvent is made so cheaply that it is again advantageous to use it in place of acetone.

One of the most noteworthy advances in the present revision has been the adoption of introductory chapters and the classifications and type processes given under Fluidextracts and Tinctures, thus saving a number of pages in the book and avoiding the unnecessary repetition of instructions. It is hoped that this attempt at condensing formulas will prove satisfactory and may be still further extended in future revisions.

The popularity and extensive use of powdered extracts required pharmacopœial recognition of a number of extracts in this form. Among these may be mentioned powdered extracts of Aconite, Belladonna Leaves, Colchicum Corn, Gelsemium, Hydrastis, Rhubarb, Stramonium and Viburnum Prunifolium. In addition, Purified Osgall is now official in the form of a powdered extract, and

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this class of powdered extracts will probably be added to in the future revisions.

The sub-committee recommended that a distinct class of Pulvextracta should be made so as to distinguish these from the pilular extracts. The conservatism of the General Committee of Revision, however, decided that the pilular or solid extracts and the powdered extracts should not be separated but all retained under the one class of Extracta and that in the monographs where both forms were recognized, the formula for the pilular extract should precede that for the powdered extract.

The preparation of powdered extracts presented some worrisome problems for the consideration of the sub-committee. In order to obtain a concentrated extract freed as far as possible from mucilaginous and gummy extractives, so as to permit of powdering and dilution in the form of a permanent powder, higher alcoholic menstrua had to be adopted than were required, as a rule, for the pilular extracts. Where the drug contained any appreciable amount of oil or fat it was found that this had to be removed before a satisfactory powdered extract could be produced. Hence, in the Powdered Extracts of Aconite Root, Colchicum Corm, Nux Vomica and Physostigma, purified petroleum benzine extractions had to be made to remove the fat, and in some cases, the recovery of the alkaloid from the benzine solutions became necessary. These added manipulations complicated somewhat the processes.

The standardizing of potent galenic preparations, wherever possible, is now an established principle in our Pharmacopœia, and the Ninth Revision has carried this out more fully than heretofore. In the Extracta, this presented to the committee the problem of selecting proper diluents by which concentrated extracts could be reduced to the standard adopted. Our experiments led to the adoption of powdered starch dried at 100° C. or, in some cases, a mixture of powdered and dried starch and magnesium oxide as the diluent for powdered extracts. In the introductory chapter on Extracts, however, permission has been given to the manufacturers to use other inert diluents, such as sugar, sugar of milk, powdered glycyrrhiza, magnesium carbonate or the finely powdered drug or marc from which the extract was made. A satisfactory diluent must be inert from a therapeutic standpoint, as well as chemically. It is difficult to select one substance that will prove pre-eminently satisfactory for all of the extracts. The committee had some difficulty in coming to a conclusion as to the proper diluent to recommend for reducing the standardized solid extracts. The final selection was glucose, as possessing the requisite qualification of being inert. Yet this has not proven altogether satisfactory and it may be possible that some other substance may yet be proposed as a substitute for glucose, and suggestions in this respect are invited.

The selection of a proper menstruum for each extract likewise required considerable experimentation. The U. S. P. VIII directed that Extract of Belladonna Leaves be made with a menstruum of two volumes of alcohol and one volume of water. With many samples of the drug, the manufacturers found that if the drug were completely exhausted with this menstruum that the yield was large and the extract was deficient in alkaloidal content. Hence, in the U. S. P. IX, a stronger alcoholic menstruum has been directed, namely, three volumes of alcohol and one volume of water, so as to reduce the amount of extractive and permit of maintaining the alkaloidal standard.

Extract of Ergot, U. S. P. VIII, was a roundabout process copied after the British Pharmacopœia and yielded a small amount of extract associated with

sodium chloride and at a very high cost. The committee was convinced that hydrochloric acid in proper proportion should be added to the alcoholic menstruum used in the extraction of ergot. Several of the samples of ergot worked with by the committee contained relatively large proportions of oil, and, unless this was removed, the resulting extract was granular and oily. Hence, in order to obtain a smooth and homogeneous product, the oil had to be removed from the ergot by purified petroleum benzine before it was percolated with the alcoholic menstruum.

In Pure Extract of Glycyrrhiza two changes are to be noted: The first is the use of chloroform water, following the initial menstruum a mixture of ammonia water and water, to complete the exhaustion of the drug. The purpose of the chloroform water is that decomposition in both the drug and in the percolate before concentration, which is prone to take place in warm weather, may be prevented. The second change is the omission of the five percent of glycerin which was directed in the Eighth Revision. Experience has shown that pure extract of glycyrrhiza made with this small amount of glycerin is apt to become moldy. This is possibly due to the percentage of glycerin being insufficient to act as a preservative, and in this dilution it actually serves to provide a suitable field for the culture of molds.

A small percentage of tartaric acid was found to aid materially in the exhaustion of hydrastis. Hence, in the Powdered Extract of Hydrastis, 5 grammes of that acid is directed for each 1000 grammes of drug extracted.

In the U. S. P. VIII formula for Extract of Nux Vomica, the nux vomica was first exhausted with a menstruum of acetic acid and water, and the concentrated acetic extract then treated with alcohol. In the formula of the U. S. P. IX, the extraction of nux vomica is made with a mixture of three volumes of alcohol and one volume of water, which menstruum extracts the drug and yields an extract which when purified by the removal of the fat, appears to be entirely satisfactory.

Extract of Malt instead of being directed to be evaporated "to the consistence of thick honey," which is not at all definite, is now directed to have a specific gravity of not less than 1.35 nor more than 1.40.

The fluidextracts recognized in the U. S. P. are, in number, greatly in excess of those recognized by any of the other pharmacopœias. In the endeavor to improve on the U. S. P. VIII formulas, the sub-committee made several hundred experiments, trying various menstrua and methods of manipulations. For the first time in the revisions of the U. S. Pharmacopœia, fractional or divided percolation is directed. This process, Type Process C, is now not only permissible, but is officially directed to be employed in the fluidextracts of Aconite, Aromatic Powder and Bitter Orange Peel.

The type samples prepared by several of the committees which had worked with this class of preparations in the previous revisions had been preserved and reports on these were secured. The original samples, wherever available, were carefully inspected and the changes both in amount and character of precipitate noted. The experiments led to the adoption of a number of changes in the menstrua directed and, for several, entirely new formulas were introduced.

In the following fluidextracts an increase in the alcoholic strength of the menstruum directed is to be noted: Bitter Orange Peel, Belladonna Root, Buchu, Guarana, Hyoscyamus, Pilocarpus, Podophyllum, Sarsaparilla, Staphisagria, Sumbul and Uva Ursi.

Numerous complaints showed that it was practically the universal opinion that in the Fluidextract of Buchu of the Eighth Revision, the menstruum of three volumes of alcohol and one volume of water was incorrect, and alcohol is now directed.

A reduction in the alcoholic strength of the menstruum is to be noted in the following fluidextracts: Gelsemium, Ipecac, Senna and Triticum.

The U. S. P. VIII directed that Fluidextract of Cascara Sagrada should be made with a menstruum of four volumes of alcohol and six volumes of water. Our knowledge of cascara sagrada and its constituents now permits us to direct the extraction of the drug with hot water and the addition of the alcohol to the concentrated aqueous percolate as a preservative only. This improvement has been made in both the fluidextract of cascara sagrada and in the powdered extract, in both of which the extraction of the drug is directed to be made with water.

The Aromatic Fluidextract of Cascara Sagrada of the U. S. P. VIII was criticized in several respects. First, the attempt to extract the glycyrrhiza along with the cascara sagrada by the use of magnesium oxide. The proper solvent for licorice is, beyond any question, ammonia water and the extraction of these two drugs should not be made together, as either magnesium oxide or calcium oxide is the required alkali for the extraction of cascara sagrada. The flavoring with compound spirit of orange was likewise criticized. In the formula directed in the U. S. P. IX, these objections have been met by directing the use of pure extract of glycyrrhiza and a change in the aromatics to a combination of the oils of anise, cassia, coriander, and methyl salicylate. Any slight tinge of bitterness remaining is drowned by the further addition of 1 gramme of saccharin to the 1000 mils of product.

In Fluidextract of Cinchona the addition of 100 mils of diluted hydrochloric acid to the menstruum was found necessary in order to exhaust the drug. Without this addition of acid, the resulting fluidextract failed to represent even approximately the total amount of alkaloid in official cinchona bark.

In Fluidextract of Colchicum Seed, while no change is made in the menstruum of two volumes of alcohol and one volume of water, some means had to be adopted to remove the oil which is extracted, possibly largely mechanically, and separates in the fluidextract. Hence, in the formula for this fluidextract, the preliminary treatment of the drug with purified petroleum benzin is now directed.

The Digitalis preparations present an interesting study. It developed that in the preparations of digitalis containing a large percentage of water, deterioration rapidly takes place. Further, that the deterioration in the presence of acids was very much more rapid and that an acetic preparation of digitalis very soon lost its efficiency. This can be explained on the ground that digitalis contains glucosidal principals and likewise an acid constituent, and in aqueous or dilute alcoholic preparations a reaction takes place between these constituents by which the glucosides are decomposed. In the fat-free tincture of digitalis, the acid is neutralized and thus the increased permanency of this preparation is explained.

A material increase in the percentage of alcohol in the official preparations of digitalis was indicated and the fluidextract instead of being directed to be made with a menstruum of diluted alcohol, is now directed to be made with a menstruum of five volumes of alcohol and one volume of water. For the same reason, the alcoholic strength of the tincture has been increased by the use of a menstruum composed of three volumes of alcohol and one volume of water in place of diluted alcohol.

In Fluidextract of Ergot, the U. S. P. IX has returned to the recommendation of Dr. E. R. Squibb and directs in the menstruum the use of 20 mils of hydrochloric acid in place of 20 Cc. of acetic acid of the U. S. P. VIII.

In the Fluidextract of Frangula, the similarity of this drug to Cascara Sagrada has suggested that the same method of preparation should be adopted for both fluidextracts and this was found to be entirely feasible. So Fluidextract of Buckthorn Bark is now directed to be made by hot aqueous percolation and the alcohol added to the concentrated infusion as a preservative only.

In the Fluidextract of Glycyrrhiza, we note an entire change in the formula. The U. S. P. VIII directed the extraction of glycyrrhiza with boiling water, thus obtaining a large amount of inert matter which it was difficult to remove by the subsequent manipulation directed. The new formula directs the extraction of the drug with a menstruum of ammonia water and chloroform water, and completing the exhaustion with chloroform water. The first portion of the percolate is set aside as a reserve. The alcohol is directed to be added only as a preservative. The waste of this solvent in the previous formula is thus avoided.

In Fluidextract of Ipecac, the attempt has been made to produce a miscible fluidextract from which a syrup could be made by simple admixture instead of the roundabout process for the preparation of the syrup directed in the U. S. P. VIII. Instead of extracting the drug with a menstruum of three volumes of alcohol and one volume of water and obtaining in the product resinous and other inert materials which had to be precipitated out in the preparation of the syrup, the attempt was to produce by the use of a menstruum of diluted hydrochloric acid, alcohol and water, a miscible fluidextract. This appears to have been overlooked, however, in the Syrup of Ipecac, as the formula of the U. S. P. VIII has still been retained, and the syrup will unnecessarily contain acetic acid in addition to the hydrochloric acid.

In the Fluidextract of Lobelia, the menstruum formerly directed was a mixture of acetic acid and water. This is now displaced by a menstruum of acetic acid and diluted alcohol, which promises a stable and active preparation.

In the Fluidextract of Nux Vomica, the acetic acid directed in the U. S. P. VIII has been deleted from the menstruum, as a menstruum of alcohol and water in the proportion of three volumes of alcohol and one volume of water directed has been found to be satisfactory. Acetic acid dissolves from nuxvomica substances which later continue to precipitate and cause trouble in the preparations and there appears to be no necessity for any acid in this fluidextract.

In Fluidextract of Squill, we have one of the most important changes made in this class of preparations. Squill presents a troublesome problem. Its large content of mucilage and sugar makes it difficult to percolate with the ordinary solvents. The U. S. P. VIII directed that Fluidextract of Squill should be made by percolating 1000 Gm. of the drug with a menstruum of acetic acid and water until 1000 Cc. of percolate was obtained. No attempt whatever was made to exhaust the drug or to obtain a fluidextract of full strength, even if it were possible to carry out the instructions and percolate the drug with this dilute acetic acid menstruum.

The process now directed was proposed by Dr. J. M. Francis. The squill is first exhausted with a menstruum of two volumes of alcohol and one volume of water, and with a hydro-alcoholic menstruum of this strength squill can be percolated. The percolate is then concentrated and alcohol is added to precipitate out the mucilage and sugars. The alcoholic liquid decanted from the syrupy

residue is again concentrated and made up to the requisite volume by the addition of diluted alcohol. This is necessarily a tedious and an expensive process, but yields a fluidextract of squill which appears to be permanent and fully represents the activity of the drug.

In Fluidextract of Senega, a change in manipulation is to be noted. The alcoholic strength of the menstruum remains the same as in the previous edition, but no alkali is added to the menstruum. Solution of potassium hydroxide is eliminated from the formula and in place thereof ammonia water is added to the finished product until a faint alkaline reaction is produced. The reason for this change in manipulation is that precipitation and gelatinization in fluidextract of senega is prevented by maintaining an alkaline liquid. The alkali that gives the best results is ammonia water, and in order to insure alkalinity being maintained, this is added in slight excess to the finished product.

The Eighth Revision directed that Fluidextract of Senna should be made with a menstruum of diluted alcohol and that the drug should be previously percolated with alcohol to remove the griping principle. This preliminary treatment with alcohol and drying of the drug is very expensive. The U. S. P. IX endeavors to obtain the same results by preparing the fluidextract by using a weaker alcoholic menstruum composed of one volume of alcohol and two volumes of water and omitting the preliminary extraction of the drug with alcohol.

In the Tinctures, several changes are of special interest. In Tincture of Arnica, in order to insure the exhaustion of the drug, *interrupted percolation* is directed.

In Tincture of Cantharides, a process of maceration with warm alcohol is directed. The cantharides directed (10 percent) can never be fully extracted by the alcohol and all we can succeed in doing is to make a saturated alcoholic solution of the active constituent, and this is attained by macerating at a temperature of 50° to 55° C.

In Compound Tincture of Gentian, the addition of glycerin and the reduction of the alcoholic strength to that of diluted alcohol is to be noted.

In Tincture of Iodine, in order to insure the solution of the iodine, 50 mils of water per liter is added.

Tincture of Kino of the U. S. P. VIII was not a satisfactory preparation. The addition of glycerin and the attempt at filtration meant a long exposure with associated contamination which engendered enzymic action and the early gelatinization of the product. The U. S. P. IX directs the extraction of the kino in a flask with boiling water, the alcohol being added to the cooled decoction and the tincture decanted and strained. By this simplified process, exposure of the kino is avoided and a more permanent preparation is secured.

Tincture of Nux Vomica is now directed to be made directly from the powdered drug by percolation with the menstruum and then assayed, the standard being fixed at total alkaloids .25 Gm. in 100 mils instead of strychnine 0.1 Gm.

In Tincture of Sanguinaria, hydrochloric acid is directed in place of acetic acid, with the alcoholic strength of the menstruum remaining the same as in the previous revision. One has but to try the use of hydrochloric acid in the extraction of sanguinaria to note its value for this purpose.

In the Tincture of Strophanthus, we note a decided improvement over the formula of the U. S. P. VIII. Strophanthus is a drug that is very difficult to extract and its large percentage of disagreeable fat is another troublesome factor. The U. S. P. VIII directed that the tincture be made with a menstruum

consisting of 65 volumes of alcohol and 35 volumes of water without previously defatting the drug. The resulting tincture was cloudy from separated oil and was exceedingly nauseating because of the presence of the fat.

The medical use of strophanthus is such that this nauseating tendency of the preparation should be eliminated. The formula of the U. S. P. IX is a decided improvement over that of the previous edition in that the drug is first defatted by preliminary treatment with purified petroleum benzin. The use of alcohol 95 percent as the menstruum is likewise to be commended as more nearly extracting the drug and yielding a more definite preparation.

UNUSUAL METHODS OF SMUGGLING NARCOTICS.

Authorities of the Chicago house of correction have discovered that quantities of narcotic drugs are smuggled constantly to prisoner-patients in the "dope" cure hospital and that morphine, heroin and cocaine are introduced by mysterious underground channels. It was only after long vigils that kisses were discovered to be one agency which enabled patients to get such drugs, the morphine being in capsules transferred from mouth to mouth.

For a long time the smuggling of contraband drugs into the Bridewell has threatened to render ineffective the famous Sceleth drug cure in use there. The authorities have been powerless to stop the contraband traffic. Crude methods have been detected and suppressed.

Oranges arrived in such notable quantities as to arouse suspicion and an analysis revealed that most of the oranges sent to the prisoners contained from fifty to sixty grains of morphine. The fruit had been impregnated by means of a hypodermic needle stuck through the skin.

HELP WANTED.

Don't get scared out of your boots. The evils that threaten pharmacy are not big enough to overthrow it; not by a long shot. But if the practitioners of pharmacy are going to limit their defense of the calling to the resoluting, orating, vociferous condemning, and the like, with which they have so long "fought" their battles, it will not take more than a fortieth-rate evil to give pharmacy the deathblow. Get this in your head: It isn't the strength of pharmacy's enemies—they are pitifully weak—that bodes ill for pharmacy; it is the weakness, the lethargy, the internal bickering and suspicion of pharmacists. (From *N. A. R. D. Journal*.)

TEAM-WORK.

The good will of members is a valuable and essential asset of an association. Ill-wishes constitute an hostile invading force—active microbes that infect the confidence of those who might otherwise be induced to affiliate with an association.

Judgment on the results of a baseball game is largely based on the man in the box, but victory is usually dependent on team-work. The success of an association is dependent on coöperation; we all have an important part to act.