so that it was admitted by the authorities, with the result that practically inert preparations were placed upon the market.

Veratrina and Veratrum.—Family *Melanthaceae.*

POSOLOGY.

The posology of the Pharmacopoeia is in special need of revision, a fact that I realized upon the occasion of a recent examination of my students in this subject. Most of the men taking this examination have had considerable experience in the pharmacy and are familiar with the doses usually prescribed. When called upon for the average doses of a number of articles, those given were in most cases conspicuously larger than the average doses given in the Pharmacopoeia. The incident merely served to show, what I think is generally recognized among medical men, that most of the doses of the U. S. P are too small.

A more serious defect is that of inconsistency between the doses of drugs and their preparations, the ratio between such doses differing widely from that between their respective strengths. The same want of uniformity is seen between two preparations of the same drug.

It would take too long for me to review here all the doses of the book as to this feature, but I submit the following as typical illustrations:

Balsam of Tolu and Balsam of Peru.—The principal active constituent of these two drugs is benzyl-benzoate, of which balsam of Peru contains from six to ten times as much as does balsam of Tolu, the inert resin of the latter being nearly three times that of the former. In spite of these facts, the U. S. P. assigns the same dose for both.

Senna.—The dose of the syrup is the same as that of the fluidextract, notwithstanding that the latter is four times as strong.

Logwood.—The extract is nearly eight times as strong as the fluidextract, yet the dose is half as large.

Myrrh.—Tincture of Myrrh is of 20 percent strength; that is, it is only one-fifthas strong as myrrh itself, yet its dose is only twice as great.

Aconite.—The dose of this drug is half a grain; that of the extract, one-sixth of a grain, or a third as large An eighth of a grain would bear the proper relation to the dose of the drug.

Camphor—The spirit is one-tenth as strong as the drug, but its dose is only five times as large.

Cimicifuga—The dose of the extract is a little more than a fourth that of the drug, but it is not likely that the yield of extract is in so large a proportion.

Regarding these solid extracts, it would appear to be high y desirable that they should be reduced to the powdered form and so adjusted that they shall bear a fixed ratio to the drug itself.

SUBSTITUTES FOR ALCOHOL IN MEDICINES.

BY H. C. FULLER.*

Some two years ago it was suggested to the writer that it would be worth while to investigate the possibility of developing some substitute or substitutes for alcohol as solvents and preservatives in medicinal preparations. The investi-

* Institute of Industrial Research, Washington, D. C.

gation appeared to be timely on account of the rapidly increasing restrictions accompanying its use, and because of the misapprehension of its purpose in medicines, by the laymen and officials of reform movements.

Alcohol possesses a combination of solvent and preservative properties shown by no other solvent heretofore in general use, a comparatively weak toxicity, and a reasonable cost when not burdened with excessive taxes. Furthermore, it imparts no disagreeable flavor or odor to the preparation containing it.

There are two broad classes of liquid medicinals in which alcohol is employed, those for internal and those for external use. In the former the alcohol has, of late years, functionated in amounts of seldom over 20 percent, but in the latter, owing to the presence of essential oils and resinous constituents, it may run from 35 percent up to 80 or 90 percent.

In developing non-alcoholic formulas certain essentials have to be borne in mind. The finished product must contain the therapeutic agents on which its efficacy depends, it must be palatable or at least it must not be repulsive to the patient, it must resist the usual forms of spoilage, it must withstand extremes of temperature without damage either to itself or its container, and it must hold its appearance on standing over a prolonged period of time.

The fundamental idea in this problem is to develop finished products which are non-alcoholic, but in discussing it with others it has been noted that there is often a misconception as to what is involved. The use of alcohol in the different stages of manufacture leading up to the finished product is often necessary and desirable. The broad statement is sometimes made that medicines cannot be prepared without the use of alcohol. This is partly true, but the statement is misleading, because while it is often necessary to use alcohol in the development of a formula, it is not always necessary to have it remain as an ingredient of the finished medicine.

In the researches which we have conducted, covering a vast number of different products, it has been demonstrated that no hard and fast rule can be applied for developing non-alcoholic formulas. What happens in the case of one combination may be, and usually is, entirely different from what happens in the case of another. Often the presence of one ingredient in a formula will prevent the application of the results previously obtained with other combinations, and necessitates a long series of researches and experiments to develop a set of conditions which will subdue the refractory element, or perhaps it would be better to say, which will yield a properly adjusted finality in which the element functionates.

In some medicines of low alcoholic content it has been found that glycerin as a partial solvent and a partial preservative, is a satisfactory and readily available substitute. Its employment in most cases, however, must be reinforced by other agents, both for keeping certain ingredients in solution, and to keep the product from spoiling.

There are certain types of reconstructive tonics and elixirs containing strongly combined metallic salts and alkaloidal salts, from alcohol which can be easily eliminated, and glycerin substituted, and in some cases the addition of other preservatives is unnecessary.

When we come to the vast legion of formulas containing vegetable drugs, the problem becomes complex, and, as has been already stated, each combination

is a research in itself. There are several ways of bringing about the solution of the essential ingredients and the incorporation of the extract into a finished product. With some formulas direct percolation with relatively strong glycerin menstrua, augmented perhaps with the addition of mild alkali or weak acid, depending on the nature of the drugs, will effect the desired results, and the glycerin extract can be combined with the other ingredients of the formula and the whole adjusted to the desired proportion. With others a preliminary percolation must be made with alcohol, using perhaps number one specially denatured, and the solvent recovered, the syrupy extract being taken up in the glycerin and then diluted. Again the alcoholic percolate must be mixed with glycerin and the volatile solvent recovered, on the theory that it is easier to keep something in solution than to bring it down to solid form and then try to dissolve it again.

It has been surprising to note how many vegetable drugs will yield the great bulk of the valuable constituents on which their therapeutic activity depends to water alone, and when the solvent action of water is combined with that of glycerin and other common agents, to observe how many will yield good medicines without the presence of any alcohol.

As a general proposition glycerin alone in a liquid medicine compounded with mixed drugs cannot be depended upon as a preservative. Of course, if it were used in amounts of 50 percent or more perhaps this generalization would not apply, but products containing this quantity would in few instances be practicable, and would usually differ so in appearance from the original formulas that the trade in them might be affected.

Mixtures containing sugar are difficult to preserve with glycerin, and the presence of certain drugs will support spoilage organisms even when 35 percent or more of glycerin is used. When sugar is used to give "body" to a product as well as a certain sweetness, it can be eliminated or reduced considerably by the addition of the glycerin, and where a certain degree of sweetness is essential, any reduction in this quality due to the lack of sugar can be made up by a minute amount of saccharin.

Glycerin solutions of certain drugs will often inhibit the growth of spoilage organisms for a considerable period, and then from no apparent external cause, support a healthy growth of mould. This is probably due to the production of some favorable media during aging, perhaps the hydrolysis of complex tannoids or gums and the liberation of sugar molecules, because the evaporated residues of such mixtures have an entirely different appearance from residues of the same products when freshly made.

Where the mixture contains drugs which have antiseptic properties, such as the aromatic balsams or methyl salicylate, the preservative action of the glycerin is usually sufficiently reinforced, but unless this is the case, it is often essential that benzoates, salicylates, chloretone or some other well-known preservatives not incompatible with the mixture, be added. Furthermore, pasteurization has been found efficacious in rounding out the manufacture of a product to insure its keeping qualities.

When we come to the substitution of alcohol in products where it has been necessary to use 35 percent or more of the solvent, an entirely different set of conditions is presented. There are very few of the well-known substances which will

dissolve essential oils, camphor, menthol and the like and still mix with water. Acetone mixes with water and has been used successfully in external remedies such as liniments and pain killers where the odor has been masked by the presence of highly aromatic oils. But there is a prejudice against its use in any remedy which might be capable of internal use owing to its supposed toxicity. From experiments recently conducted and still incomplete it would appear that the toxicity of acetone has been exaggerated, and that the reports of its toxicity may have been due to the fact that it is found in the excretions accompanying certain diseases, rather than to any actual proof of deleterious effects caused by ingestion.

The evolution of substitutes has proceeded apace. Most of the new products proposed have been discarded, because they do not measure up to the requirements. Several derivatives of glycerin appear to answer some or all of the necessary conditions such as solvent power, miscibility with water and lack of pungency, odor and toxicity. Special mention should be made of those wherein one or more of the glycerin hydroxyls have been esterified by certain inorganic acids especially the halogen acids, and by certain organic acids of the acetic series. Some of the most promising are those obtained by introducing a side chain group into the glycerin molecule, the side chain being a halogen derivative of a lower organic acid of the acetic series.

It has been asked whether the results of these researches have any practical application or value. It can be answered that they certainly have. We have on our shelves samples of several different types of liquid medicines and toilet preparations, ranging all the way from simply tonic formulas and blood purifiers where the alcohol previously functionated from 8–20 percent, to bay rums, hair tonics, mouth washes, etc., in which it was formerly necessary to use from 35–75 percent alcohol, all of which are non-alcoholic. Non-alcoholic formulas are already on the market and some manufacturers are in a position to switch to a non-alcoholic basis at their pleasure.

Many interesting side problems have arisen during the progress of the work, especially those concerned with the therapeutic efficiency of the mixture, made up with the new solvents and preservatives. Several of these problems are now being worked out in the physiological and pharmacological laboratory, supplemented by actual clinical observations. Enough has been accomplished to demonstrate the real importance of the work and its economic significances to the manufacturer of medicines.

PHARMACOPOEIAL NOTES.*

BY JOHN K. THUM,[1] PH. M.

Without a doubt pharmacists have always appreciated and realized the importance of alcohol and the large part it plays in their vocation, but it remained for the exigencies of the Great War to make them focus their attention on it and give the matter of alcohol more serious consideration. Thoughtful pharmacists are beginning to think that the thing to do under present circumstances is experimentation with the end in view of curtailing the use and importance of alcohol

* Read at February Meeting, Philadelphia Branch, A. Ph. A., 1920.

[1] Pharmacist of the Lankenau Hospital, Philadelphia, Pa.