when your solution is made up, it will take but 10 or 15 minutes to store it as directed, and then you will feel reasonably sure that your product will bear careful inspection and that your customers receive what they pay for.

The fact that many doctors do not prescribe spirit of nitrous ether today because they feel that they cannot get a standard preparation, casts a reflection upon the ability and carefulness of the druggist. I believe that the druggist will be more than repaid for the little time he spends in taking precautions to keep his stock under the conditions necessary to insure the best possible preparation, and perhaps in no case are precautions more necessary than they are in the keeping of spirit of nitrous ether.

WHAT IS MEANT BY DRUG STANDARDIZATION?*

F. E. STEWART, PH. G., M. D., PHILADELPHIA, PA.

A visiting physician of one of the large Philadelphia hospitals called me up by 'phone for information regarding the failure of fluidextract of apocynum to relieve dropsy in three patients under his care. Finding that he did not know whether or not the fluidextract had been standardized I suggested the use of a standard preparation. Three or four days afterward my medical friend again called me up to report that the standardized fluidextract procured at my suggestion was promptly effectual, and said, "If standardization means so much for other drugs it is about time for the medical profession to awaken to its importance."

A prominent Canadian physician to whom I was demonstrating the modern methods of drug standardization in the laboratory said, "The medical profession knows in a general way that drugs vary in strength but only few physicians are aware of the wide variations in such important drugs as digitalis, strophanthus, and apocynum demonstrated here today. We know that bicarbonate of sodium is pure and other lots are purer. This is about my limit of knowledge, but that digitalis fluidextracts on the market may vary 300 percent in active constituents, and strophanthus fluidextracts show a variation of 6000 percent is an eye-opener to me."

The importance of drug standardization is so great that all intelligent persons, laymen as well as members of the medical and pharmaceutical professions, should be informed of its value. For without this knowledge physicians do not realize the necessity of discriminating in favor of standardized products when prescribing, pharmacists do not appreciate the necessity of standardizing their products, or purchasing their supplies from manufacturing houses engaged in standard-work; and people ignorant of the fact that preparations of the same name may differ so widely as to be dangerous to life, take prescriptions to drug stores where they can get them compounded the cheapest, without regard to the character, quality and strength of the ingredients that enter into them.

One of the first things of importance to consider in drug standardization is nomenclature. To every drug a name must be given by which it may be in-

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variably known and dealt in. The Latin language is generally employed because it is a dead language and is not liable to change, as in the case of a living language.

The name adopted must belong to the common language of science and not be commercially controlled. So-called trade-mark names or trade names do not meet the requirements of science. If the product is not provided with a scientific name proper standardization demands that the scientific societies should name it, or the government might well do so in connection with the enforcement of the pure food and drugs law.

As for the trade-names, text books are adopting them as general appellations or synonyms without protest from the manufacturers, who, therefore, cannot justly complain if competitors adopt them for describing identical products.

Botanical standardization is absolutely necessary in establishing the identity of vegetable drugs. *Capsicum fastigiatum* is the botanical name for the variety of capsicum designated by the U. S. Pharmacopoeia. Capsicum indicates the genus, fastigiatum the species to which the plant belongs. In relation to medicinal chemicals the U. S. P. gives in the "purity rubric" the amount of permissible inocuous impurities in each case. More than this amount the substance must not contain to comply with the U. S. P. standard.

Preparations of chemical drugs are standardized by chemical assay. The same applies to preparations of vegetable drugs containing active principles susceptible to assay chemically.

But there are a number of important preparations of drugs which cannot be satisfactorily standardized in this manner. I refer to the preparations of digitalis, acontie, cannabis indica, convallaria, ergot, gelseminum, lobelia, squill, strophanthus, and veratrum. These preparations are standardized physiologically by tests on animals.

Physiological or pharmacodynamic standardization is likewise employed for standardization of the adrenal glands, thyroid glands, etc.

Antitoxin and curative sera are also standardized physiologically, bacterins (bacterial vaccines) are standardized by bacterial count. The strength of old tuberculin is approximately determined by clinical tests and the same applies to small pox vaccine, while the newer tuberculin, "T. R." and "B. E." are standardized by determining the content in solid substance.

The Food and Drugs Act of June 30, 1906, made the United States Pharmacopoeia and the National Formulary official standards for interstate commerce in drugs and medicines. Most of the states have enacted similar legislation. Consequently drugs and preparations sold under the U. S. P. and N. F. names, must be made in accordance with the standards laid down by these authorities or they are misbranded and liable to seizure by the government. Manufacturers and dealers who do not follow these standards are amenable to the law.

The national law and the laws of most of the states, permit the sale of products differing from these standards if the differences are plainly stated on the labels. Some of the state laws are more strict and permit no deviation.

By way of illustration let us consider the method of physiologically standardizing fluidextract of apocynum. Apocynum belongs to the group of so-called heart tonics of which digitalis is the chief exponent. I have two reasons for consider-

ing apocynum first, one is, it permits a continuance of my story relating to the use of this drug in the treatment of dropsy in the clinical service of my medical friend; and the other is the opportunity of pointing out the advantage of physiologic tests for a drug not properly standardized botanically.

Fluidextract of Apocynum is the U. S. P. name for a preparation of the "dried rhizome" and roots of *Apocynum Cannabinum,* "or of closely allied species of apocynum," and is made by percolating the dried and powdered drug with a mixture of alcohol, water and glycerin. The Pharmacopoeia directs that each cubic centimeter of a fluidextract shall contain the active constituents of one gram of the drug from which it is prepared. Fluidextract of Apocynum should therefore represent the drug volume for weight. In other words, one minim (drop) should approximately represent in activity one grain of the dried and powdered drug.

Apocynum is commonly known as Canadian hemp, or black Indian hemp, and is also called incorrectly "Indian Hemp." It belongs to the Apocynaceae or dogbane family.

This remarkable family of plants consists of about 130 genera, including more than a thousand species, growing abundantly in most tropical countries, thence decreasing, rare in temperate regions. The plants are trees or erect climbing shrubs, rarely perennial herbs, and are among the handsomest, and many of them among the most fragrant in the vegetable kingdom, and are largely used for decoration. Otherwise, except for a few edible fruits, and the rubber-yielding species (African rubber is chiefly the product of this family) interest is almost entirely in the medicinal and poisonous properties.

So numerous and abundant are these plants, and so generally and intensely poisonous are they that their appearance should be noted by every one to be avoided. A botanical description will exceed our space limit.

The active constituents are glucosides, which may be encountered in any of the plant-parts, but are especially common and abundant in the bark and seeds. These are very common agents of criminal, military ordeal, and legal poisoning among savages, and accidental poisoning by them is not infroquent. Some of the most powerful arrow poisons are derived from this family.

We are in complete ignorance as to the species of *Apocynum* which should yield this drug. Up to a very recent period, five or more distinct species were included under the name *A. Cannabinum,* even in our standard botanical works, and the plants themselves are not distinguished. It is therefore impossible to ascertain which species yields the different drugs whose actions have been reported under that name. This fact doubtless explains, in great part, the conflicting testimony regarding the medicinal activity of the drug.

The drug as it appears on the market is of indefinite length, 1/8 to 1/3 inch thick, cylindrical, wrinkled, fissured, orange brown, becoming gray-brown on keeping, almost inodorous, taste starchy, afterward becoming bitter and somewhat acrid.

The active constituents are the bitter glucosides, apocynin and apocynein. Its effects are similar to digitalis (commonly called foxglove).

Apocynum is usually given in the form of fluidextract, the average dose of which is five minims.

Now it must be very apparent to any thinking person that fluidextract of apocynum when prepared from a drug not properly standardized botanically is a very uncertain preparation. As already stated, we are in complete ignorance as to the species of *Apocynum* which would yield this drug, so we are not sure when purchasing it that we have the species containing the glucosides to which its medicinal value is due. No way is provided by the Pharmacopoeia for determining whether these constituents, and how much, are present. Even though an assayed drug should be employed no directions are given to ascertain whether the finished preparation contains them in proper amount. Unless the finished fluidextract is subjected to standardization the dose of five minims may be too large, or, on the other hand, the preparation inert.

Is there any wonder under such circumstances that the hospital physician who called me up did not obtain satisfactory results from fluidextract of apocynum in the treatment of dropsy?

But a very different report followed the substitution of a standardized fluidextract. The dropsy which threatened the patient's life commenced at once to yield and the heart and kidneys resumed their functions. Let us therefore consider how fluidextract of apocynum is standardized.

Apocynum belongs to the so-called "Digitalis Series" which includes digitalis, or foxglove, apocynum, convallaria—commonly known as lilly-of-the-valley—squill, and strophanthus.

The drugs of this group have the peculiar power of stimulating the heart, and are of enormous value in the treatment of certain diseases of the heart and kidneys.

When given in medicinal doses they cause the heart to contract with greater force and empty itself thus restoring the circulation of the blood to the kidneys and other organs in case of heart weakness.

This property of strengthening the heart's action is invaluable in dropsy in which impaired circulation is a prominent factor. By its action on the heart and arterial system—which is in fact a continuance of the heart on account of its muscular walls and power of aiding the circulation by contracting—such drugs as apocynum, digitalis, and strophanthus, also act as diuretics. Forcing more blood through the kidneys they aid in purifying the blood of urea—the ash of tissue waste—and preventing death from uremic poisoning.

By their use the most severe forms of dropsy may often be quickly relieved, and the weak and dilated heart restored to normal action, and the patient at death's door returned to fairly good health and continued many years in a life of usefulness.

The first step in standardizing preparations of drugs is to assay the crude drugs before purchasing. The manufacturer of standardized drug preparations would soon find himself out of pocket if he neglected this precaution. Drugs are of value in direct proportion to the active principles they contain, and these constituents vary in different lots.

The next step consists in assaying finished products and adjusting the amount of active principles present to fixed standards. This is accomplished either by chemical assay or by physiological tests on animals, or by both methods, one being used as a control for checking results obtained by the other.

A number of the physiological methods for standardizing the digitalis series of drugs are in use, among which is the so-called "lethal dose" method of Reed and Vanderkleed.

The first step in this method consists in determining the lethal dose; this is accomplished in the following manner: A series of guinea-pigs is selected each weighing approximately 250 grams. The preparation to be tested, if a tincture or fluidextract, is then freed from the greater part of alcohol by evaporation, and diluted with water to the desired quantity. Into a series of four of the guinea-pigs this dilution is now injected in amounts equal to 9/10, 10/10, 11/10, and 12/10 of the standard lethal dose. The animals are then placed in cages and allowed to remain for twenty-four hours, when they are examined and a note made of those living and those which are dead.

The result of this preliminary test, in which the range of dosage is quite wide, enables the investigator to form some idea as to the strength of the preparation. Basing the dosage upon these results, other series of guinea-pigs are injected with progressively increasing or decreasing doses, as the case may be, still further diminishing the variations between doses, until the smallest amount is found which will prove fatal within twenty-four hours. The probable minimum lethal (toxic) dose of the preparation, unless it deviates considerably from that of the standard, is generally obtained by one or two series of injections.

In order to express the percentage results it is necessary to adopt for each drug or preparation assayed a standard minimum lethal dose (m. l. d.) with which the preparation being tested may be compared. For example, the m. l. d. of fluidextract of digitalis is 0.1 cc.; that of fluidextract of strophanthus, 0.0025 cc.; that of tincture of strophanthus, 0.025 cc.; that of fluidextract of apocynum, 0.075 cc.

After comparing the preparation to be standardized with the standard m. l. d., it is diluted or concentrated if necessary to bring it down or up, as the case may be.

As already stated, digitalis fluidextract on the market may vary 300 percent in strength. This fact was stated in Bulletin No. 48 issued by the U. S. Bureau of Hygiene, Washington, D. C. Later researches show the variation to be from 30 to 400 percent.

Now digitalis is one of the most important drugs in the treatment of diseases of the heart and kidneys, and conditions often arise in practice when the patient's life is entirely dependent upon its prompt and decided action.

Accuracy in dosage is essential. Unless the dose is large enough to produce the required effect upon the heart and circulation, failure results. If the dose is too large the patient dies of digitalis poisoning.

Imagine the danger resulting from neglect to use standardized digitalis preparations. The patient takes the prescription to the druggist who secured his pharmaceutical education before the advent of the modern drug standardization and obtains a fluidextract or tincture below standard. The dose prescribed fails to relieve the patient and is therefore increased. We will assume that the tincture is prescribed in 15-drop doses. This dose failing to relieve, 20 drops are given, to be rapidly and progressively increased for effect until 60 drops are used per dose and the same administered three times a day.

After a week or more the vial is emptied and the patient sends to the drug

store for renewal of prescription. In the meantime, the druggist has purchased a fresh supply of tincture of digitalis which happens to be three times as strong as the weak preparation first used. The patient goes on with the 60-drop dose as before. But now he is taking three times as much drug at a dose, or an amount equal to 180 drops. The toxic action of the drug soon manifests itself, the patient grows worse and worse, and finally dies in convulsions which are ascribed to uremia, when they were in fact, due to digitalis poisoning.

"How careless the doctor—how careless the druggist"—say you. Nay. Rather say, "How ignorant and negligent are both of the importance of drug standardization."

Or, the physician fearing to give larger doses of digitalis than that laid down in the text books as a maximum, goes on with his ineffectual dosing, and the patient finally dies in uremic convulsions. In either case death is the result, and the cause is the same, namely: Want of standardization of the digitalis preparation employed.

It may be asked why not separate the active constituents and use them for medication instead of trusting to the uncertain fluid preparations of the drug? There are insurmountable difficulties in the matter; in the first place, the active principles of digitalis are only partially known, and the isolation of those with which we are acquainted is attended with considerable difficulty. There appear to be at least four glucosides in digitalis which possess the characteristic action on the heart and circulation, and these are accompanied by one or more glucosides decidedly different in their effect. The therapeutic action is composite and is due to the combination of a number of principles which act and react on one another to produce the characteristic effects of digitalis as a therapeutic agent, therefore the only way to be sure of obtaining the desired effect is to use a physiologically standardized preparation of digitalis itself.

Therapeutic standardization by the cooperative investigations and impartial discussions of competent observers are necessary. Progress in materia medica science is dependent upon it, and public welfare demands it. How can we as physicians meet our obligations in this regard when new products are controlled commercially and introduced by advertising? Until some plan is adopted for the protection of professional interests impartial discussion is impracticable. If reports concerning advertised products are adverse there is a danger of law suits, if they are favorable there are suspicions of purchase. A strong central board of control representing commercial, as well as professional interests, is urgently needed to prevent dishonest exploitation of common interests by selfishness.

One of the problems of standardization is to prevent the finished product from deterioration on account of the action of the air. Preparations of ergot, digitalis, strophanthus, aconite, and several other important drugs soon lose their strength on this account.

It has never been realized until lately that most of the deterioration going on in fluids, owing to the action of the air, is due to the air held in the fluid rather than to the air in contact with the fluid in the container.

For example, a container may be completely filled with a fluid and then hermetically sealed, yet the oxygen of the air in the fluid will continue to act and cause its deterioration.

Researches were made in the Mulford Laboratories by Pittenger and Vanderkleed to determine the influence on deterioration of exhausting the air from fluids and then sealing them hermetically under vacuum.

Fluidextract of ergot was chosen for the experiment. First of all, the fluidextract was tested by injection into dogs, and gave an immediate rise of blood-pressure represented by 44.8 mm. of mercury. The total assay for alkaloids by the process of Meller, gave a percentage of .163. This fluidextract of ergot was then divided into four portions as follows:

A. The first portion was put up in vacuum in tubes specially designed and made for this purpose.

B. The second portion was filled into bottles which were tightly corked, and allowed to remain for one year unopened.

C. The third portion was filled into bottles which were kept loosely corked for one year, this being obtained by boring a small hole in the cork.

D. The fourth portion was tightly corked but opened occasionally throughout the year.

These four samples were tested upon dogs at the end of twelve months, with the result that with A, no loss of blood-pressure raising power was sustained; this was also true of the percentage of total alkaloids. Of the other samples, the tightly corked sample (B) deteriorated the least (about 35 percent). A greater deterioration was noted in C, and D, (tightly corked, but opened occasionally, conditions under which the preparation is commonly kept) showed the most marked deterioration (67 percent.)

These investigations would indicate that with complete exhaustion and exclusion of the air from the container and its contents, practical permanency may be secured.

I hope my paper has proved of sufficient interest to excite your desire to investigate the subject of standardization more deeply, and I am sure if you do so, many astonishing things await you. Among other things you will discover one of the causes of therapeutic nihilism, and you may find out that drugs possess powers undreamed of that can only be revealed by drug standardization.

THE SNEAK THIEF IN PHARMACEUTICAL ETHICS.

The pharmacist who loudly urges Sunday closing and then sneaks back to his store and lets in customers is a sneak thief; so is the one who prates of ethical pharmacy and then substitutes in a most pernicious manner. However, one of the worst sneak thieves in pharmacy is the one who places a large sign over his store which reads "No Cut Rate Druggist," and who still continues to cut right and left. He is first kin to the prescription percentage druggist who has a sign which reads "No Percentage Drug Store." The pharmacist who treats disease violates the ethics of pharmacy as well as medicine and is hence a double offender. Those pharmacists who declare that dishonesty and blindness to professional ethics are necessary to success in business are mistaken and they are very much mistaken at that.—*Pacific Pharmacist.*