2. *Conium Test.* To the substance to be tested for the presence of conium fruits (as anise, caraway or other unbelliferous fruits), add 25 per cent. sodium or potassium hydroxide solution. In the presence of one per cent or more of conium fruits a distinct mouse odor is developed in time (10 minutes to one-half hour). This test is not reliable with old unbelliferous fruits, as many of them develop a more or less marked mouse odor with alkalies.

3. *Lignin Test.* The classic phlorglucin-hydrochloric acid test is useful in making estimates of the amount of lignified tissue present, as in old belladonna root, aconite roots and stems, lobelia herb, fruit products, spices, etc.

4. *Grahe's Cinchona Test.* Drive the moisture from the inner surface of a small test-tube by holding it over a Bunsen burner. Into this dried test-tube place a pinch of finely powdered cinchona bark (No. 80) and heat rather carefully over an alcohol lamp or Bunsen burner. When the bark begins to char, red fumes begin to fill the tube and condense on the side of the tube as a reddish purplish liquid. The intensity of the reaction is approximately proportional (direct proportion) to the percentage of alkaloids present. Some skill and experience is necessary to perform this test well. The tube must not be heated too quickly or too much, and the powder should be uniformly fine.

5. *Beaker Sand Test.* Pour a definite amount of the powdered spice or vegetable drug into a beaker, add water, stir until the sand is washed away from the vegetable particles and settles to the bottom of the beaker. Let a stream of water run into beaker so as to wash out the vegetable matter. The final washing and decanting must be done carefully so as not to lose the sand. Salt brine may be used instead of water, should the vegetable matter have a comparatively high specific gravity. Dry sand and weigh to obtain the percentage of sand present.

6. *Ash Determination.* According to the regulation method. The percentage of the acid-insoluble residue should also be determined. It should be borne in mind that the ash determination gives only approximate results as far as the presence of clay and dirt is concerned, since the organic matter of dirt is combustible. The ash percentage varies extremely in vegetable drugs, especially in herbs and leaves. The sand percentage is comparatively high in those herbs and leaves having abundant trichomes, especially if the drug plants (or herbaceous spices) bearing such trichomes are grown in dry sandy soil. Dirt (and sand) percentage is apt to be high in roots and rhizomes, particularly when rootlets are abundant and when the gathering is carelessly done.

C. H. LaWall and H. A. Bradshaw have prepared a table of ash contents of representative air-dried crude vegetable drugs which will serve as a very valuable guide for micro-analysts, in making ash determinations.

(To be continued)

ON DRUG STANDARDS.

WILBUR L. SCOVILLE, DETROIT, MICH.

The present plan of the Pharmacopoeia of making a minimum standard of a drug the real standard for that drug is not a satisfactory plan. To say that because in certain years it is impossible to get very much stramonium, for instance, which will assay 0.25 per cent. of alkaloids, therefore it is necessary to make this lower quality a standard drug, though in other years it is comparatively easy to obtain the drug containing twice this amount of alkaloid, is not a scientific way of setting standards. It is making commercial conditions the basis of scientific usage. It is placing too much emphasis on commercial variations in drug quality.

Commercial variations must, of course, be taken into consideration, for this is

more a commercial than a scientific question, and one cannot demand impossibilities, but to make these variations the sole, or even the main, consideration is not at all necessary.

The error in the plan lies in the fact that *drugs are not in themselves medicaments, but are the material from which medicaments are made.* The real medicament is the preparation, i. e., the extract, fluidextract, tincture, or infusion or decoction. The drug itself is never used by the great majority of physicians, and but rarely used by a small minority. Even the preparations which still fill the market and contain crude drugs in small quantities, are relics of old-time methods and need revision. I refer here, of course, only to drugs which are standardized.

When a physician wishes in these days to administer aconite, or belladonna or nux vomica, he orders the tincture or extract or fluidextract—not the drug itself. Hence the *preparation,* not the drug, is the real standard of medication. This is true even to opium, when Powdered Opium, itself a standardized *preparation,* is the form used when the powdered form is desired.

So it is entirely rational to make the preparation the basis of standardization, and not the drug. It is the real medicament, and the drug is but the raw material from which it is made.

It is quite as reasonable to demand that if a low-standard drug be employed in manufacturing, enough of it shall be used to produce a satisfactory preparation, as to allow of a high-standard drug being used in a small proportion to produce a low-standard preparation. If a high-quality drug may be diluted, a low-quality drug should be multiplied. And in either case, essentially the same results are obtained in the preparation. So the important question is not whether a high-standard or a low-standard drug is employed for manufacturing, but whether the preparation made for use in medication is of standard quality.

Hence drugs should be considered as manufacturing material, and any grade which will produce standard preparations in any proportion that may be practicable, should be allowed. The Pharmacopoeia may reasonably reduce the requirements for all alkaloidal drugs, and raise the standard for preparations. Economic considerations will limit the minmum standards more effectively than any arbitrary standard.

A standard drug is mostly a hypothetical drug. Nature rarely produces it. If she ever does, it is by accident. But standard preparations are obtained facts, and can be obtained from widely varying material. Adulteration should, of course, be excluded, but natural variations should be allowed to all practical limits. It is not, in fact, necessary for the Pharmacopoeia to place any limits on the alkaloidal contents of its drugs when it establishes standards for the preparations of those drugs. Aconite must be aconite, belladonna must be belladonna, etc., but tincture of aconite must not only be made from aconite root, but must contain a stated amount of aconite alkaloids, and extract of belladonna must contain its standard amount of belladonna alkaloids as well as be made from belladonna leaves. The manufacturer deserves the credit that is due him for skill and judgment in producing acceptable results that stilted formulas do not offer him. The *product,* not the formula or method, is the important thing.

Economic considerations will force an operator to decide whether he will make

a fluidextract twice as strong as the drug that is offered, or whether he must reject that drug and insist on one two or three times as strong. But this is immaterial to the physician who desires reliable and standard medicaments, but is little concerned as to how they are obtained.

The elimination of definite standards for alkaloidal drugs would necessitate but little change in the present Pharmacopoeial formulas for preparations of those drugs, and would relieve the Pharmacopoeia from its present assumed responsibility for certain economic losses. The Eighth Revision not only recognizes that there are limits to economic production in fluidextracts and tinctures, but in a number of instances it defines what those limits may be.

For instance, it requires that Nux Vomica shall contain not less than 1.25 per cent. of Strychnine, but the fluidextract need contain but 1 per cent. (w.v.); that is, the fluidextract does not represent even a hypothetical standard drug.

The reason is plain enough. Nux Vomica is a very difficult drug to exhaust, and the Pharmacopoeia definitely recognizes the fact. But it also stands sponsor for the statement that a loss of 20 per cent. of the value of the drug is satisfactory.

Now, economic production depends upon a number of factors, such as facilities, the value of the time of the operator, waste, and personal skill. These will vary greatly. What is economical production in one place may be far from it in another And since the Pharmacopoeia cannot restrict economic factors, it is inconsistent for it to define economic limits. Moreover, it is quite unnecessary. Practically the only attention paid to it at present is to take advantage of the allowance.

But if the Pharmacopoeia makes the fluidextract the basis of standardization and simply directs that it, in this case, shall be made from Nux Vomica of undefined alkaloidal strength (or of hypothetical strength), but must contain a stated amount of alkaloids, and must be made with a stated menstruum, then the operator must be responsible not only for the product, but for economic production. This is simply a law of production which has been hitherto applied to all commercial products except pharmaceuticals. It should now be applied to these. Such a function does not belong to the Pharmacopoeia.

In support of the contention that drugs, in themselves are but manufacturing material, let me call attention to the fact that in the present formulas of the Pharmacopoeia but one alkaloidal drug is used as such. Powdered Ipeca is used in Powder of Ipecac and Opium, and in Compound Laxative Pills. The latter is to be dropped, leaving but one for the next Pharmacopoeia. Besides this, Powdered Jalap—a resin-standardized drug—is used in Compound Powder of Jalap.

Just two preparations for the next Pharmacopoeia in which standardized powdered drugs are used, and both of these are relics of old-time pharmacy and had their reputations established long before standardization came into use. It is indeed a question whether the amount of alkaloids in the Ipecac used in Dover's Powder is of any real consequence.

In other instances in which powdered drugs are used in preparations, by far the greater number are used as flavors, diluents, or excipients. Extracts have in most cases taken the place of powdered drugs in pills, ointments, suppositories, etc., and the tendency is strongly in that direction. It is of advantage to encourage that tendency. The plan here proposed will do that.

In the following lists are given the results of numerous assays of alkaloidal drugs, extending over a period of 6 to 10 years, and which indicate normal variations in those drugs. It is not expected that final deductions will be made from these lists alone, for other similar reports are available. But these are offered as a contribution on which a new plan of standardization may be based. The plan, not the suggested standards, is the real issue.

Aconite.

12 below 0.55%
6 between.....0.55 and 0.65%
6 between.....0.65 and 0.75%
3 above 0.75%

27 assays.
Fluidextract should represent 0.65% w.v.
Tincture should represent 0.065 w.v.

Belladonna Leaf.

12 below 0.26%
43 between.....0.26 and 0.35%
35 between.....0.35 and 0.45%
15 above 0.45%

105 assays.
Extract should represent 1.6% alkaloids.
Tincture should represent 0.04% alkaloids.

Belladonna Root.

10 below 0.36%
32 between.....0.36 and 0.46%
35 between.....0.46 and 0.56%
12 above 0.56%

89 assays.
Fluidextract should represent 0.50% w.v.

Colchichum Seed.

7 below 0.56%
4 between.....0.56 and 0.76%
3 above 0.76%

14 assays.
Fluidextract should represent 0.60% w.v.
Tinture should represent 0.06% w.v.

Hydrastis.

8 below 2.5%
8 between.....2.5 and 3.0%
12 between.....3.0 and 3.5%
6 above 3.5%

34 assays.
Fluidextract should represent 3.0% alkaloids w.v.
Tincture should represent 0.6% alkaloids w.v.

Guarana.

7 below 4%
10 between.....4 and 4.5

17 assays.
Fluidextract should represent 4% w.v.

Hyoscyamus.

17 below 0.05%
20 between.....0.05 and 0.07%
24 between.....0.07 and 0.08%
16 between.....0.08 and 0.10%
11 above 0.10%

88 assays.
Extract should contain 0.30%.
Fluidextract should contain 0.750% w.v.
Tincture should contain 0.0075% w.v.

Ipecac.

14 below 1.75%
31 between.....1.75 and 2.0%
17 between.....2.0 and 2.25%
16 above 2.25%

78 assays.
Fluidextract should contain 2.0% w.v.

Nux Vomica.

Fluidextract should contain 2.0% alkaloids.

Physostigma

5 assays.....0.11 to 0.78%
Extract should contain 2.0%.
Tincture should contain 0.02%.

Pilocarpus.

6 below 0.60%
2 between.....0.60 and 0.75%
5 above 0.75%

13 assays.
Fluidextract should contain 0.75% w.v.

Stramonium Leaf.

9 below 0.26%
57 between.....0.25 and 0.36%
36 between.....0.36 and 0.45%
8 above 0.45%

110 assays.
Extract should contain 1.5%.
Tincture should contain 0.835% w.v.

DISCUSSION.

Charles Caspari, Jr., asked Mr. Scoville whether he leaned to the idea that all standards throughout the world of crude drugs should be abolished in the Pharmacopoeia. Mr. Scoville responded that he thought this would be a wise thing to do. He referred, of course,

to alkaloidal standards only, not botanical. His position was that the process of assay should be continued, but that no standard should be required. Mr. Caspari suggested that it was the purpose of the process to determine the alkaloidal content, and the different processes would yield different percentages of alkaloid. Mr. Scoville agreed to this, but said the process itself should be standardized.

Continuing, Mr. Caspari said he could see where the retail pharmacist would be put in a pitiable condition by the elimination of all standards as to crude drugs for the Pharmacopoeia; that if the Pharmacopoeia gave an assay method, without attempting to apply it to a standard, it would not be used at all by the retail pharmacist. If the Pharmacopoeia did not demand a minimum alkaloidal strength or standard for drugs, any kind of belladonna leaf, for example, might be considered to answer, whether the alkaloidal percentage of the leaf ran down as low as two-tenths or up as high as eight-tenths. Very few retail pharmacists, he said, standardized their preparations. He could see where this would be an excellent plan for the manufacturers, but he thought the minimum standard required by the Pharmacopoeia was not only a safeguard, but an absolute necessity, for those retail pharmacists who choose to make their own preparations. Without a minimum standard, the pharmacist might proceed to exhaust a drug very carefully, and then reason that, as he had done so, he must necessarily have about the required amount of alkaloid in the finished product. This situation, Mr. Caspari said, had been brought forcibly to his attention in the last year, in his new work of drug-control for the state of Maryland, where many pharmacists had been brought before the commission for putting forth preparations too low in strength—laundanum and other preparations. They had not tested their drugs nor standardized their preparations, but thought that if they used a certain per cent. of powdered opium, for illustration, they would get a certain per cent. of the tincture of opium afterwards. The manufacturer, Mr. Caspari said, was already protected, because he had the right, under the law, to buy a two-per cent. drug, if he desired to do so. He expressed the hope that Mr. Scoville would not push this to the point of asking the Revision Committee to abolish all standards. He could see trouble for the retail pharmacist, if this suggestion was carried out. As Mr. Scoville has stated, nature had not been so kind as to produce drugs of uniform alkaloidal strength,—aconite, belladonna, hyoscyamus, and so on,—and if the retail pharmacist was not to be entirely eliminated, a minimum standard for crude drugs was necessary for his guidance. The standardization of preparations was all right, but this did not do away with the necessity for a minimum standard for crude drugs. Mr. Caspari concluded by saying that he could not see the force of the claim that alkaloidal standards for crude drugs should be abolished.

Mr. Frederick T. Gordon said he did not think Mr. Scoville could have been present at the meeting of the Section on Education and Legislation last night and heard Mr. Rusby's address there, in which he showed the vital necessity of the accuracy of the Pharmacopoeial definitions. He said that if there were not Pharmacopoeial standards for the alkaloids of crude drugs, the importation of practically anything in the way of crude drugs would be permissible. As an example of the undesirable proposals to alter the Pharmacopoeial requirements as to crude drugs imported into this country, he instanced the case of colocynth, and quoted from Mr. Rusby's paper to show that it was now being urged by certain interested parties that the word "peeled" be omitted from the definition, so that the Federal authorities would hereafter be required to prevent the importation of this drug, all of which was peeled. Mr. Gordon expressed it as his opinion that it was absolutely essential that a minimum standard for all alkaloidal drugs should be established in the Pharmacopoeia, and that none of these drugs should be admitted into the country below the standard set.

Charles E. Caspari thought that if Mr. Scoville's idea was carried out, the best thing to do was to omit from the Pharmacopoeia all crude drugs. What was the use, he asked, of having belladonna official, if there was no standard for it? If it was not used in powdered form in any galenical or medicine, but only used in the preparation, why have a standard at all? The tendency had been to establish a purity rubric in the Pharmacopoeia, and then determine whether or not the article in question satisfied that rubric. The standard for an alkaloidal drug corresponded to the rubric for purity of a chemical. Mr. Caspari thought,

however, that the legal aspect of this matter was far more important than the value of it to the manufacturing or retail pharmacist. His idea was, that if the standard for the drug was omitted, then the drug should be omitted altogether from the Pharmacopoeia. The statement made by the writer that the minimum quality or standard should be taken as the official one, he heartily concurred in; but simply because from year to year certain plants did not produce a uniform alkaloidal content was no reason, in his opinion, why the minimum should be changed or done away with. He thought the Pharmacopoeial Committee should have the right to state what the standard should be, regardless of fluctuating conditions. Whether the preparation should be standardized, he thought, should depend on whether the therapeutic or pharmaceutical results were the same. Take cinchona, for illustration: There was a standard for its quinine content, but a very loose standard for the other alkaloids present, although it was well known that the therapeutic action of cinchona depended not wholly upon the quinine, nor wholly upon the other alkaloids; it was quite possible that the therapeutic effect of the different alkaloids present might in some way modify the ultimate therapeutic action.

Chairman F. R. Eldred said that while he recognized the difficulties attending the fixing of a minimum standard, owing to the fluctuations of the strength of crude drugs from year to year, nevertheless he regarded it as imperative that such a standard should be established —though it should not be fixed so high that, in some years, we would be utterly unable to obtain the standard drug. He agreed with Chas. Caspari, Jr., that it would do an injustice to the retail pharmacist to deprive him of such standards, as it would open the way to his having any kind of drugs put on him, without any recourse whatever. He likewise believed it would work a hardship on the manufacturer. In some cases it was very difficult to obtain the drug at all, because it was not admitted; there had been great scarcity of certain drugs on that account. This, however, was the lesser of the two evils. The manufacturer would be in worse shape if any kind of drug was admitted to the country, and would find it more difficult to get good drugs than now, when they were in a measure protected by the minimum standard. If a drug were shown to be below the minimum standard, he could reject it; otherwise, he might have to accept it, because while they would buy on sample, sampling as it was carried on today by the dealers was very unsatisfactory, and in many cases the manufacturers received samples entirely too small to represent the lot of drug. He cited a case where the house with which he was connected had attempted to prove forty bales of nux vomica, where all the samples submitted had probably been taken out of one bag. They therefore declined to make use of any samples taken in a way not reasonably safe to indicate the value of the drug. He believed that minimum standards were necessary for the protection of the retail pharmacist.

Chas. Caspari, Jr., emphasized the statement that a minimum alkaloidal standard should be maintained in the Pharmacopoeia. As shown by Mr. Rusby's paper last night, unless a minimum standard was demanded for a crude drug, a miller might purchase a thousand pounds of belladonna, say, grind it and sell it to the retail trade of the country, and if it happened to be a low grade of belladonna,—or a low grade of pilocarpus, for example,— if he had a Pharmacopoeial standard, he could quickly test the drug, and thus get the official preparation. Without such a standard, he was absolutely at sea.

Mr. Scoville might suggest that he assay the crude drug; but he might do that and find it so low grade that it could not be used at all. Mr. Caspari said that though he was not now recognized as a retail pharmacist, he confessed to having a warm spot in his heart for him, and he desired to give him all the protection possible, and he was earnestly in favor of the retention of minimum standards in the Pharmacopoeia.

Charles E. Caspari, speaking again on this subject, said that Mr. Scoville might go a step farther, and suggest the omission even of galenical preparations from the Pharmacopoeia, because, after all was said and done, it was the alkaloid in drugs that produced the therapeutic effect; and, therefore, if it was desired to give aconite, why not give aconitine? And so with opium, and other drugs.

Mr. F. T. Gordon also spoke again on this subject, and said that this whole matter revolved around the question of dollars and cents. He was satisfied that if the Pharmacopoeia

contained no standards for crude drugs, the United States would become a dumping-ground for inferior drugs. The pure foods and drugs laws of the several states were based on the Pharmacopoeia, practically, and if no standard was established, anything would be permissible. He agreed with Mr. Scoville that the standardization of the finished product was highly important, because that was what was used by the patient; but this was not all of it. Those engaged in the wholesale drug business were not in the business for their health, but to make money out of it, and he believed that it was absolutely necessary to retain minimum standards in the Pharmacopoeia for the protection of the retail pharmacist.

Mr. Scoville closed the discussion upon his paper, and defended his position. He said that when he wrote this paper and spoke of it to a friend, he had been warned that he was "liable to get into hot water;" that he had proposed a radical thing, and one that would meet with strong opposition. The discussion this morning had shown that he had failed to make himself clear. First, he had stated that the Pharmacopoeial method of making a minimum standard was not very desirable, and nobody had objected. Second, he had said that crude drugs were not the medicaments used, but the raw material from which they were made, and nobody had objected. Then he had said that the Pharmacopoeia should not have fixed standards for crude drugs, and here was where the trouble had come. This did not mean, he said, that standard drugs would not be sold. They were sold long before the Pharmacopoeia had made such requirement. Standard drugs had been sold for thirty years or more.

Mr. Scoville said that he could not see the logic of saying that the manufacturer or large dealer must be restricted, and the retail pharmacist trusted to do absolutely the honest thing. He did not think the retail pharmacist was any better or any worse than anybody else, on the average. It was the same thing here as if the state of Colorado were to say to a man, "You cannot take any ore out of this mine, unless it shows a certain percentage of gold to the ton, and then you can do anything you like." This was where the standarization of drugs was at fault. The only thing that the public used—that which produced the medicinal effect—was the preparation, and it could not be assumed that because a drug was up to a certain standard the preparation was all right. He was not making any plea for the manufacturers, for they could take care of themselves, but his position meant an elevation in standards. It meant that the minimum standard for crude drugs should no longer prevail, but that the actual strength of the preparation should be found. The whole question hinged upon what the public used. The retail pharmacist would not be hurt, because assayed drugs would be on the market, subject to his order. As to the point that had been made that some drugs might fall as low as one-fifth of the standard now required, Mr. Scoville claimed that it would not be economical to use drugs of that low grade. The idea was for the druggist to control his preparations; if not, he was not protecting the public. As matters stood now, the inspectors were given something to talk about, but that was all. Where drugs could not be standardized, restrictions must be placed around them as far as possible. But where the preparation, the thing used, could be controlled, it could be told whether it was of the proper quality and strength. This was his contention. Mr. Scoville said he did not suppose this would knock the standards out of the Pharmacopoeia, but he believed it would lead to it in time, simply because it was right.

In conclusion, Mr. Scoville said he was not opposing any laws, and not intending to put any obstruction in the way of legal protection. He did not see how it would make any difference to the retail pharmacist, but did see that the drug inspectors might be bothered; "but without that bother," he said, "your pure food inspection does not amount to that!" (a snap of his fingers). To sum up his position, he thought the Pharmacopoeia had better recognize the differences existing in the raw materials of medication, and pay more attention to what the patient was actually taking.