NOTES ON THE U. S. P. IX AND N. F. IV.*

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The ninth revision of the Pharmacopoeia and the N. F. IV have now been in our hands for nearly a year and pharmacists and chemists are rapidly adapting themselves to the many changes that have been made, in what I may term, official drugs, chemicals and preparations. I say this reservedly, as I understand there is a question whether or not the courts still recognize the U. S. P. VIII and that in order for the ninth revision of the Pharmacopoeia to be recognized, it may be necessary for Congress to pass a law to that effect.

To one who has found it necessary to perform analytical work under the U. S. P. VIII and the U. S. P. IX, it is apparent that there is a decided improvement in the chemical assays of the latter, and although there is no doubt considerable room for improvement with many, there are but very few chemical methods which will not admit of some change, when closely scrutinized. A method which may appear to be ideal to one chemist may contain, in the mind of another, serious errors, which in his opinion may vitally affect his results.

A few years ago I had occasion to examine some resin jalap according to the U. S. P. VIII. The requirements for resin jalap under this revision were, among others, that not more than 35 percent should be soluble in chloroform. After making many different determinations I was led to the conclusion that the amount of chloroform-soluble of resin jalap depended entirely upon the method used, and that from the viewpoint of this requirement, one could decide that the resin either did or did not meet the U. S. P. requirements, according to whether or not he was a "bull" or a "bear."

I called this to the attention of the Revision Committee and was pleased to read the following in the U. S. P. IX, concerning the method for determining the chloroform-soluble:

> "Add one gramme of powdered resin to ten mils of chloroform in a stoppered flask and shake the mixture occasionally during one hour; then filter, evaporate the filtrate in a tared dish and dry the residue to constant weight at 100° C. It weighs not more than 0.3 Gm."

Surely, I thought these directions so explicit that no further difficulty would be experienced with the chloroform-soluble of resin jalap. However, in the May issue of the JOURNAL A. PH. A., I read the following from the pen of an exceptionally competent chemist:

> "*Resin Jalap.*—The method for determining chloroform and ether-soluble matter are lacking in details. We are directed to add one gramme of the powdered resin to ten mils of chloroform (or ether) in a stoppered flask and shake the mixture occasionally during one hour, then filter, evaporate the filtrate, etc. The operator is left in doubt as to the washing, size of filter to use or any precautions to be observed."

I did not consider these details necessary, but considered them simply a matter of technique, and presumed that no one would attempt to filter the entire mixture, but would take an aliquot part, filtering through a 9 to 11 cm. filter, rejecting the first five or ten Cc. However, this chemist evidently finds the method lacking

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in these details a serious objection, which goes to show the difference of opinions that may be held concerning the same method.

I shall endeavor to point out some of the difficulties which we have had with the pharmacopoeial tests and some of the ways and means we have adopted to overcome them.

The Pharmacopoeia directs in the determination of bromides, iodides and chlorides that after the addition of a definite amount of silver nitrate to the weighed sample that the whole be titrated back with potassium sulphocyanide. The latter salt has become exceptionally scarce and at present it is practically unobtainable. We have, however, substituted the sodium salt for the potassium, and so far this has given excellent results in our hands, and I would recommend to any who are unable to obtain the potassium salt that they use the substitute.

Fluidextract Ipecac: The new low alcohol menstruum of the U. S. P. IX is not nearly as satisfactory for exhausting the drug as the menstruum of the U. S. P. VIII; in fact, the former fails to extract but little more than 75 percent of the alkaloid, and with an expensive drug like ipecac, this becomes a very important item. Excessive percolation and consequent concentration produces a large amount of precipitate, which keeps coming down for several months. The standards of at least 1.75 percent for the drug and from 1.8 to 2.2 Gm. per 100 Cc. of the alkaloids for the fluidextract, do not agree. Since no difficulty is experienced in obtaining a drug which will contain at least 2 percent alkaloids, the standard for the drug might be raised to this amount; in fact, I would advise very strongly against accepting any drug that did not at least assay this much.

Crude Drugs: The standard for crude drugs has been raised in both the U. S. P. and N. F., which should lead to a better grade of drugs being offered. Considerable difficulty is experienced in having collectors obtain the part of the drug which is official. They are particularly prone to gather the entire herb, when leaves and flowering tops are specified. In fact, at present, lobelia which meets the U. S. P. description, is unobtainable and only recently we examined a parcel of eupatorium that contained 40 percent stem.

Tincture Ginger: The U. S. P. directs that the tincture should not contain more than 2 percent solids and that when treated with 20 mils of cold distilled water, not more than 15 percent dissolves. The amount of water-soluble from practically every tincture made from U. S. P. Jamaica Ginger is higher than 15 percent. The U. S. P. does not state the length of time the ginger solids should remain in contact with the water, and as the results obtained vary with the length of time the solids remain with the water, it is extremely important that this test should be revised; also the statement that it should not contain more than 2 percent solids, invites adulteration, as it is possible to have a tincture containing $1\frac{1}{2}$ Gm. of solids in each 100 Cc. and to add an equal volume of alcohol, which would reduce the solids to 0.75 and still have them meet the U. S. P. test. The following would probably be good standards and comply with the results of many investigators:

Solids from 1.25 percent to 1.75 percent.
Alcohol about 90 percent.

It may be possible to drop entirely the water-soluble solid test, as the informa-

tion obtained from this is of no practical value if the alcohol is in the neighborhood of 90 percent.

Beef, Iron and Wine: The N. F. gives lengthy tests for solid extracts of beef but gives no test for beef, iron and wine. The Internal Revenue Department requires that the proteid content of beef, iron and wine be at least 1.4 percent. Since the N. F. directs that ammonia be used in making beef, iron and wine, when making the proteid determination it is necessary to take this into consideration and first make an ammonia determination, when calculating the proteid content.

Calcined Magnesia: There appears to be very little upon the market that will fulfill the U. S. P. requirements, as most of it contains an excess of moisture, assays low and yields more calcium than is permitted in the official salt.

Indicators: The Pharmacopoeia also recognizes methyl red in addition to cochineal. Our experience with methyl red is that with practically all alkaloids, results four or five percent low are obtained. However, the end point is much sharper than when using cochineal.

Physiological Assay: The admission into the U. S. P. IX for the first time of biological assays is undoubtedly a step in the right direction and while these assays are, no doubt, far from perfect and will be subject to severe criticism, eventually much good must come from the criticism and we will obtain much better methods for physiological assay.

I wish to point out one thing that is probably peculiar to the State of New York concerning the physiological assays, and which may avoid some difficulty and save money for those who are occupied making physiological tests.

The Pharmacopoeia directs that the frog method be used for determining the activity of several of the preparations—digitalis, strophanthus, etc., but the State of New York has a closed season on frogs, from March 1st to June 1st, and it is unlawful to kill them or possess them during this time without a permit from the Conservation Commission. This may be obtained by applying to the proper authorities and filing bond. The Pharmacopoeia has made two biological methods official, *viz.*, Cannabis and pituitary extract, and has given provisional methods for digitalis, squill, strophanthus, suprarenal glands and aconite. Much criticism has been given the U. S. P. cannabis assay, by several workers who state that the dose is too small to produce incoördination. This should be thoroughly investigated. From our experience we are inclined to believe that a larger dose is not necessary.

For standardizing pituitary, the isolated uterus method is directed and a standard histimine is given with which to compare the extracts. This salt is practically unobtainable except in solution, put up in ampuls or in tablet form, and the activity of different salts vary to a considerable extent. I have received an ampul and a tablet which were claimed to contain the same amounts, which showed over 100 percent difference in activity. Furthermore, it has not been shown that histimine is not subject to deterioration. Histimine is evidently not as satisfactory a standard for pituitary extract as a solution made from dry, defatted gland, as histimine does not possess the well-known physiological property of raising the blood pressure.

For the digitalis series, the Pharmacopoeia directs that the one-hour frog method be used and which yields in the hands of experienced operators good

results. The standard ouabain is also practically unobtainable at present in the United States and it is claimed that it is not uniform. The use of conical glasses and a pipette are unnecessary, as the use of a hypodermic syringe, graduated in 1/100 Cc. is much more convenient and accurate for measuring the preparation.

In the N. F. IV, under Fluidextract Apocynum, we read the following:

"For a method of assaying fluidextract apocynum, see biological assays U. S. P. IX, Part II."

However, in the U. S. P. IX there is no standard given for apocynum, and no reference is made to it. I have been given to understand by one of the members of the Pharmacopoeial Committee, to whose attention I called this, that the committee intended that apocynum was to be standardized by the frog method. He, however, did not know what the standard was to be.

Aconite Preparations: In addition to the chemical assays, the drug and preparation may be physiologically tested upon guinea pigs. No precaution, however, is to be taken to standardize the pigs, and since these animals show a seasonal variation to ouabain, is it not possible that they also do the same toward aconite alkaloids? The *Epitome of the U. S. P. and N. F.*, prepared for the use of physicians, under the authorization of the Council of Pharmacy and Chemistry of the American Medical Association, states that physicians should specify aconite preparations that have been assayed biologically, since the alkaloidal assay is not a reliable index to activity.

Suprarenal Glands: The blood pressure method is recommended and gives very satisfactory results. The method of using both femoral veins instead of one, does not yield as close checks as when the injection is made into the saphenous vein. The standard laevo-methylamino-ethanol-catechol is extremely difficult to obtain.

Ergot: It is to be regretted that the U. S. P. has not provided a biological assay for this drug, as very good results are obtained by the blood pressure method and there is considerable drug upon the market which has very little pressure activity.

THOSE WHO CONTEMPLATE GOING TO PHARMACY SCHOOLS SHOULD NOT CHANGE THEIR MINDS ON ACCOUNT OF THE WAR.

President Wilson has clearly pointed out that those who are at work in the school-rooms are serving their country just as surely as those who are already in training camps, or are on the field of battle or are giving their country the benefit of their service as experts. The country at war, and afterward at peace will need the technically trained men more than ever. The cry that the colleges and technical schools shall maintain all their courses and that there should be no falling off in the enrollment at the technical institutes applies to schools of pharmacy with equal force.