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THE U. S. P., NINTH REVISION, AS A WORKING UNIT FOR THE DRUG CHEMIST.*

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I have been asked to discuss the ninth revision of the United States Pharmacopoeia from the standpoint of a chemist. I presume that in presenting my observations I may be permitted to give expressions to the thoughts which come to one who has been associated with the chemical features of drug problems in a broad sense including analytical, standardizational and forensic. I feel that I am pretty well acquainted with the Pharmacopoeia as a working unit after over fifteen years of almost daily contact with the seventh and eighth editions, and from the study I have already made of the ninth and latest edition of the work. My association with the Pharmacopoeia is not a literary or a second-hand, critical, chemical study, but an intimately practical one in everyday work, and during the last nine years I have been able to see at first hand its applicability in relation to chemico-legal problems.

I know nothing of pharmacopoeia politics and am not, and never have been, concerned with anything but the finished work and what it embraces. Hence I can look at it from that standpoint. As a result of my experience the test of the Pharmacopoeia is an intensely practical one. It is the signal test of usage. This test lies entirely in its working value—as it elucidates the definite problem of the moment, either analytical or descriptive. In proportion as it is thus applicable and serves to indicate or clarify the immediate method of procedure or the description of the substance under investigation, in such measure is it a significant factor in my work, and I think I can state with authority, in such measure is it of real and lasting value to the pharmaceutical and medicinal chemist.

The Pharmacopoeia is the authority to which one turns both for standards and for methods of analysis. It is the working unit for the drug and medicinal chemist. Now what is the scope of the ninth revision from the point of view of the drug and medicinal chemist? Let us consider first its scope as to the substances recognized in the text and second as to the standards, analytical tests, and methods of analysis.

The Food and Drugs Act states "that the term 'drug' * * * shall include all medicines and preparations recognized in the United States Pharmacopoeia or National Formulary for internal or external use and any substance or mixture of substances intended to be used for the cure, mitigation or prevention of disease of either man or other animals." Now the first thing that strikes the critical eye of the chemist in looking over the 782 articles recognized in the text of the new edition of the Pharmacopoeia is the fact that about 10 percent of these articles do not answer the definition of drug as given above but are more strictly speaking

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chemical reagents, intermediates, condiments, flavoring agents, perfumes, mechanical solvents, vehicles and binders. Thus we have well-defined standards for sulphuric, hydrochloric and nitric acids, aqua regia, sodium indigotinsulphonate, zinc metal, cochineal and red saunders; for lead oxide, bleaching powder and silver oxide; for sugar, caraway, coriander, fennel and mustard seeds, cinnamon, vanillin and nutmeg; for orange flower water, rose water, lemon peel, red rose petals, tincture of lavender and oils of orange, caraway, coriander, fennel, lavender, lemon, spearmint and rosemary; for benzine (petroleum ether), water, acetone and paraldehyde; for starch, gelatin, glucose, honey, paraffin, suet, talc and infusorial earth. Others might be mentioned. The drug chemist asks himself if any one of these substances comes within the scope of the definition of drug as given in the law. It is doubtful if any of the above substances have any extended use as internal or external mitigants or preventatives of disease. Objection will at once be raised to my attitude because of the fact that some of the chemicals mentioned above are employed in the preparation of other chemicals used in medicine, but the manufacture of chemicals is a commercial proposition, and the maker of ammonium chloride, for instance, is not concerned with the employment of a strictly U. S. P. standardized hydrochloric acid. Furthermore, one of the general principles laid down by the committee of revision was to the effect that the standards of purity and strength prescribed in the text of the Pharmacopoeia are intended solely to apply to substances which are used for medicinal purposes. Standards for condiments and flavoring oils have been adopted by the authorities administering the food sections of our National and State Acts, hence the user of these commodities is now amply protected from any sub-standard or spurious articles.

Now please do not misunderstand my position with regard to the inclusion of a considerable number of reagents, intermediates, condiments and flavors in the text of the Pharmacopoeia. I am not objecting to their being included but the significance of including all these substances which are not drugs and medicines is somewhat obscure when a much greater number of important and valuable drugs have not been recognized or have been deleted. If substances such as sulphuric acid, nitric acid, bleaching powder and metallic zinc are included, why omit aniline and benzol which are the basic substances of a vast number of medicinal chemicals as well as iron oxide which is used in the coating of dark-colored tablets?

Again, since there have been included so many reagents, intermediates, condiments and mechanical agents, why was such a large number of botanical drugs of well-established therapeutic value omitted or deleted? For one who uses the Pharmacopoeia as a working unit this is a question of important and serious moment. Let us examine the list of deletions of this class of drugs. Among them are included:

Anthemis	Chirata	Cypripedium
Apocynum	Coca	Euonymus
Berberis	Conium	Eupatorium
Calamus	Convallaria	Ficus
Calendula	Corn silk	Geranium
Cassia fistula	Cotton root bark	Hamamelis leaves and root
Chimaphila	Cusso	Hedeoma

Horehound	Phytolacca	Santonica
Krameria	Prunum	Sassafras pith
Lappa	Quercus	Savine
Leptandra	Quillaja	Scoparius
Lupulin	*Rhus glabra*	Scutellaria
Matico	Rubus	*Viburnum opulus*
Pareira	Salvia	

What percent of the total deletions do these products and their preparations represent? Thirty-five percent.

These botanical drugs have been used as medicinal agents for a great many years. Their value has been demonstrated over and over again by medical usage. The fact that they and the popular remedies containing some of them have withstood the test of years, and, in spite of the derogatory campaigns directed against them, have continued to grow in popular esteem, is in my mind a significant point in their favor. Nature in her omnipotence has supplied mankind with everything he needs for his comfort and advancement; development only has been needed to make it available. Why should we doubt that nature would fail to supply man with the agents for combating the diseases to which he is subject? The development of drug chemistry during the past decade has demonstrated that the botanical drugs, which have been used more or less empirically for many generations, possess new and hitherto unexpected chemical individuals and the discoveries in the field of phytochemistry are destined to assume greater and greater importance. In the case of our natural drugs it has been demonstrated over and over again that no one ingredient is the cause of the therapeutic activity of the individual conglomerate. The classical work of Dr. F. P. Power and his associates has increased our knowledge of the chemical composition of many well-known botanical drugs. The work of unraveling the constituents of our North American drugs has hardly begun, and as Dr. Power recently stated at a meeting of our chemical society, this field is one of the most attractive to the organic chemist at the present time.

It would appear that one of the principles in the compilation of the present Pharmacopoeia was to base its scope on the therapeutic ideas of a limited number of individuals rather than on medical usage, and this brings me up to a very important subject to which I want to refer at this point—namely, the constitutionality of the clause in the Food and Drugs Act making the Pharmacopoeia a standard for drugs. The argument has been advanced that this part of the law is unconstitutional because by it, Congress improperly delegated legislative authority. The decision of Hough on this point in the Lehn and Fink case is based on common sense and is comprehensive for the case in hand. Unfortunately his decision was not passed upon by the Circuit Court of Appeals or the Supreme Court. He quotes: "The legislature cannot delegate this power to make a law but it can make a law to delegate a power to determine some fact or state of things upon which the law makes or intends to make its own opinion depend. To deny this would be to stop the wheels of government. There are many things upon which wise and useful legislation must depend which cannot be known to the law-making power and must therefore be subject to inquiry and determination outside of the halls of legislation;" and on the point at issue he concludes that "to me there

could not be a plainer instance than this act of the legislature's having made a complete and perfect criminal statute, not dependent at the time of its passage on the act of any other power or person and of them providing for changes in the meaning of the word 'adulterated' a word which, in the nature of things, may and should change its signification with advancing knowledge or increasing civilization." It seems to me that, in the light of Judge Hough's decision, a dangerous situation has arisen because the wholesale deletions in the new edition must have been brought about for reasons other than medical usage or chemical discovery. We all know the attitude of the courts towards controversies where the merits of the case depend upon therapeutic opinions, and if it should happen that the question of the constitutionality of that clause in the law making the Pharmacopoeia a standard for drugs, should arise in the course of carefully planned litigation where the parties had made themselves thoroughly familiar with the methods of revision, it is to be feared that the courts would not hold in especial favor a standard which might, at one whim or another, every ten years, delete a hundred or more valuable therapeutic agents and carefully provide for the standards of a number of chemical reagents, foods and condiments under the caption of drugs.

I realize that the answer to this will be that the National Formulary adopts what the Pharmacopoeia deletes, but this is hardly fair to the National Formulary, and furthermore, the legality of this work has not been passed upon by the courts. From my study of the new edition I think that the National Formulary is a more tolerant standard than the Pharmacopoeia. It includes 789 articles in the text, 7 more than are recognized in the text of the Pharmacopoeia. It presents in Part I a set of excellent formulas of galenical preparations and in Part II it provides standards for a large number of chemical salts and botanical drugs, all of which might just as well be recognized by the ninth revision of the Pharmacopoeia as the salts and drugs which are recognized. To one like myself who depends upon the Pharmacopoeia as a working basis, it seems a little incongruous to have two books of standards of drugs and medicinal chemicals. As the situation now exists, neither is a complete book of standards. I think that instead of deleting well-established medicinal agents, the Pharmacopoeia ought to recognize more and more drugs and medicinal chemicals, and in this respect the Homeopathic Pharmacopoeia has much to commend it.

The examination of the text indicates to the chemist that there has been lack of coördination in the relations between some of the substances admitted and deleted in the ninth revision. Attention is called to the fact that pimento is not recognized though several other well-known condiments are included and the oil of pimento is included; santonica, which is often used in veterinary remedies, is not present but santonin is recognized; distilled extract of witch hazel is an official preparation but witch hazel leaves have been discarded; coca has been deleted and cocaine left in; hops find a place but lupulin is missing; honey is given a place at the official table while invert sugar remains unrecognized; zinc metal is featured but bismuth metal, the purity of which for preparation of medicinal chemicals is as fully important as that of zinc, has not been recognized.

From the standpoint of the analytical chemist, the ninth revision contains much material worthy of commendation. The descriptions and the distinctive and purity tests are good, and in general they are sufficient. The relegation to

the mythical past of some of the old pharmaceutical prejudices is gratifying. Thus we see that Digitalis, to be official, is not limited to the two-year old leaf, and that *Cannabis sativa* can grow somewhere else besides the "East Indies." As a matter of fact, by far the larger quantity of the imported article has, in recent years, come from Greece. The compilers might well have gone one step farther and removed the sex limitations of this drug, for I can state with authority that the tops of the male plants possess physiological properties of the same character and to the same degree as those possessed by the pistillate tops. Methyl salicylate is no longer recognized under three headings, the chemically identical oils of Betula and Gaultheria being omitted. This is real progress.

The microscopic and macroscopic tests and characteristics of botanical drugs have been carefully revised and leave little to be desired. I think, however, for consistency, the microscopic characteristics of buchu should have been included.

The chapter on general methods of analysis should be digested by everyone concerned with the testing of drugs and medicines. Especially is this true of the paragraphs relating to the proximate assaying of drugs. The value of the practical advice contained therein cannot be overestimated. Personally, I think the directions in the text for conducting the proximate assays are too loosely worded. They place too much responsibility on the worker, who unfortunately is often too inexperienced to assume the responsibility. I have conducted a great deal of coöperative work on methods of assaying, and I have found that, unless the directions are precise and complete in every detail, comparative results on which reliance can be placed are almost unobtainable. The personal equation of the drug analyst, even of wide reputation, is, to quote Kipling "beyond the wit of any man, black or white, to fathom." In respect to detail, I think the directions for proximate assays in the eighth revision were more likely to lead to accurate results than those in the ninth. However, I will say this. If the analyst knows something about drug assaying and digests the paragraphs on this subject in the general methods, he ought to obtain concordant and fairly accurate results. But even then, if the results are concordant, they do not necessarily furnish data on the true alkaloidal value of the sample.

The ninth revision has adopted the aliquot assay in place of the total extraction method of the eighth revision. This shortens the time of the analysis and eliminates some of the manipulative features of the old assay, but my experience has shown that an aliquot assay does not give as true an idea of the alkaloidal value of a drug as is given by the total extraction procedure. The weak points of the assay processes of the ninth revision will be the cause of much confusion in the drug trade. In fact this condition has already developed. A dealer offers for sale a drug, the strength of which has been based on an assay which shows the true alkaloidal value. The buyer accepts the goods on that basis and then proceeds to check up the assay with the ninth revision method which gives him lower results. Then he files a claim against the seller. Thus a situation arises which is unfair to the drug dealer, but which can be settled only by some adjustment on his part, unless the two factors are willing to have a joint assay performed in the presence of a referee.

Standards for some of the drugs, based on physiological assay, have been described. This feature is a new one and is to be commended. The standard

for Cannabis is too high and the proper labeling of specimens in order to conform to the Food and Drugs Act will cause some hardship to the legitimate drug trade, because the buyer of drugs is disposed to deprecate any lot that the seller cannot guarantee as strictly U. S. P., even though the former knows that the use of a little more drug will yield an extract of full strength. Buyers are quick to take advantage of any situation like this and on the strength of some insignificant technicality will hold the Pharmacopoeia and the Food and Drugs Act as a club to the detriment of the honest drug dealer. Compilers of standards should never lose sight of the economic bearing of their work when they are developing the scientific features.

The introduction of complex methods for assaying essential oils of a purely flavoring nature is of doubtful expediency. These methods are of value to the buyer of oils in case he wants to know the quality of the commodity, but this subject comes more within the scope of food standards and methods for ascertaining them. However, as long as these flavoring agents are recognized as drugs, it is well to have good assay methods for determining their purity.

Comment will be made on a few individual descriptions and tests. The standard for oil of peppermint is altogether too limited in its scope. Oils of excellent flavoring quality distilled directly from the plant, often contain much less menthol than the ninth revision prescribes. The menthol in these oils is replaced by menthone which has no other effect in the oil than to take the place of the menthol, and in no way detracts from the real flavoring qualities due to the menthol esters which are still present. The chemical tests for cod-liver oil are really characteristic of the oil from the fresh livers of fish in general. The ninth revision limits the source of oil of theobroma to the seeds, but the shells of the cocoa bean contain an oil with practically the same composition, which can be used for the same purposes. Tons of this oil are annually wasted. No assay has been included for Sanguinaria. The reason for this is not apparent to one who has been familiar with methods for assaying this drug for many years. The assay of spirit of camphor is limited to natural camphor. A perfectly good spirit can be prepared with artificial camphor, but the use of the assay in the ninth revision would be of no value in determining its strength. The assay of spirit of nitroglycerin is open to criticism. The conclusions from the results obtained would depend largely upon the personal equation of the analyst, and if the commercial alcohol used in the preparation of the material contained any inert soluble substance in excess of that prescribed for pure alcohol of the text, the results would be erroneous. There are several good methods for determining accurately the percentage of nitroglycerin.

Before closing this review of the ninth revision, I want to include a few remarks concerning some of the drugs which are widely used but which have not been recognized. My acquaintance with drugs and chemicals has brought me in contact with a number of individual medicinal commodities for which I am often in need of standards, tests and descriptions, and which are not recognized. Some of these include:

Pinus strobus	*Chamaelirium luteum*	*Asclepias tuberosa*
Iris versicolor	*Chelone glabra*	*Asarum canadense*
Acorus calamus	*Aralia racemosa*	*Baptisia tinctoria*
Aletris farinosa	*Panax quinquefolium*	Paracotoin

Brauneria angustifolia	*Rumex crispus*	Chinosal
Castanea dentata	*Scrophularia marilandica*	Digitoxin
Cnicus benedictus	Juniper berries	Lecithin
Collinsonia canadensis	Veronal	Novocaine
Coptis trifolia	Ichthyol	Acetyl Salicylic Acid
Dioscorea villosa	Chloretone	Nucleinic Acid
Hydrangea arborescens	Alypin	Coto
Melissa officinalis	Atoxyl compounds	Piperazine compounds

They are all drugs which find a place in the Materia Medica of this country and are of much more therapeutic importance than the flavoring agents, condiments, chemical reagents, etc., for which standards and tests have been carefully provided. I realize that many of the botanical drugs have been recognized and described in the National Formulary for which much commendation is due the National Formulary. I also realize that some of the others are products, the manufacture of which is covered by a patent, but I see no reason why this should prevent the inclusion of a valuable drug among the standards of this country. No chemical can be patented. Its designation under its true chemical name is always free. A method of manufacture can be patented and a fanciful name can be trademarked. But why does this prevent recognition of a drug under its true chemical designation, giving its fanciful name as a synonym if desirable? It may be argued that the manufacturers object. But what is the force of this argument if the drug is well established in our Materia Medica and the control of standards and the traffic in drugs has been recognized by our Congress and the standards for these drugs based on the Pharmacopoeia and the National Formulary. Thus far the compilation of these standards has been delegated to responsible bodies and the results of their work have been vouchsafed by the courts. In this connection I was interested in the report of the Agricultural Appropriation Bill just introduced in Congress, wherein a sum is asked for the purpose of determining standards of drugs not recognized by the Pharmacopoeia.

My work with drugs and medicines brings me in contact with a great many different substances. When I want information concerning them, their description, their standards, how to test them and the methods to use, I want some authority to which to turn. To what extent does the Pharmacopoeia, ninth revision, furnish the data? This is the test of the Pharmacopoeia from the standpoint of the drug and medicinal chemist. The ninth revision as an analytical work and book of standards is going to be a great help as far as it goes, except for the unfortunate circumstance of the introduction of the loosely worded methods of drug assaying. As a standard for drugs it is going to be altogether too limited in its scope. It has devoted too much space to prescribing standards for chemical reagents, food products and substances which are purely mechanical in their application to pharmacy and which do not fall within the definition of drug as laid down in the Food and Drugs Act, and has left out a vast number of very important drugs and chemicals in daily use in medical practice, both in this country and those lands to which our drugs are exported.