APPROVED METHODS OF PHYSIOLOGIC STANDARDIZATION OF DRUGS.*

HISTORICAL SKETCH.

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The general subject of standardization of drugs, from the chemical standpoint, is too well known to this body of scientific men to require more than the mere statement. The author of this paper does so, chiefly for the purpose of correlating it with the subject of this paper.

That there was once a need of standards, at the time of the beginning of the publication of the Pharmacopœia, almost a century ago, also goes without saying. To be historically exact, it may be stated that the Pharmacopœia was born in 1817, and that Dr. Lyman Spaulding was its historical father. The narrative touching its infancy and early days and growth, as found in the early part of its introduction, must always prove very interesting reading to the members of your profession.

The thought at the date mentioned, no doubt, was that polypharmacy had held sway long enough. Times even at that long-ago date had advanced sufficiently so as to exact more scientific and less slip-shod methods; more science and less empiricism. Once started, the work of improvement and perfection grew apace, each succeeding decennium adding its moiety of art and of science toward the attainment of a better and still better "book of standards."

At the outset the medical profession appears to have been much in evidence in its development and promulgation. Later and even at the present day your profession has led the way with acceptance and profit. Both professions, however, it is pleasant to remark, have shown during the last two decennial periods a better spirit toward each other, a spirit of "getting together" in this important work. As a result a composite work is clearly developing, made up of contributions from every available source.

In the foregoing brief historical sketch of the Pharmacopœia it is interesting to note that not until the Revision of 1890, the seventh in order, did there appear specific direction as to establishment of "standards of purity." So interesting and so important as well does this point seem to your essayist that he craves your indulgence of a somewhat lengthy quotation from the introduction of the Revision mentioned. As touching this point it declared as follows, "It was recommended by the Convention that assay processes should be appended to the United States Pharmacopœia, descriptive of the "energetic," or "otherwise important" drugs, and to such galenical preparations as the Committee of Revision of the Pharmacopœia should deem wise, especial care being taken that assay processes for *Opium* and *Cinchona* should be attended with as little manipulative difficulty as possible; that the standards of purity of drugs should not be above the point of practicability, etc." The deductions your essayist makes from these statements, which seem to him to be important, are two-fold, namely, first, that a beginning to set "standards of purity" should have been made at so recent

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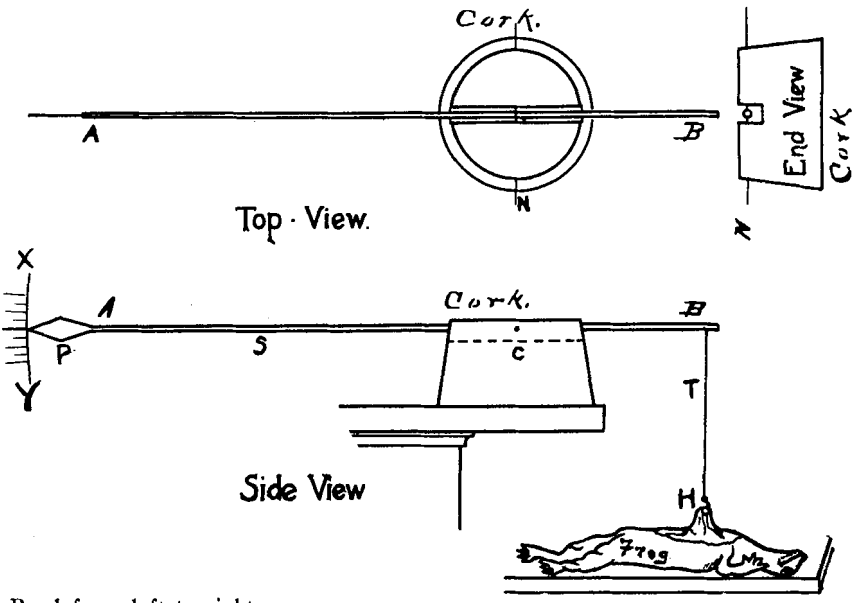
a date; and, secondly, that a few years later (1900) the second step, "physiological standardization," should have been suggested; "suggested" only, to be sure, without recommendation to make use of such process. It is with much satisfaction, however, may it be hoped we all agree, that the last Revisional Convention, that of 1910, created a large Committee with full power to act, touching this among other matters. At the date of preparing this paper your essayist understands the Revisional Committee will make processes of pharmacologic assaying optional with the pharmacist in the forthcoming revision.

PRACTICABILITY OF PHARMACOLOGIC ASSAYING.

That galenicals are more likely to be efficient when standardized by any ac-



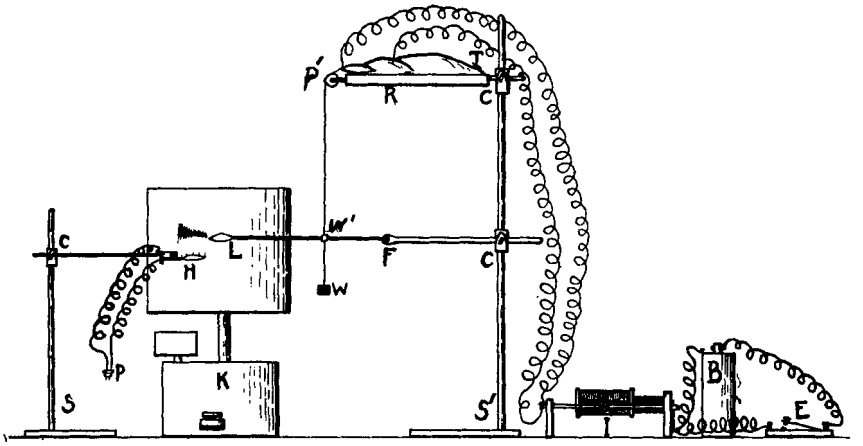
Read from left to right:
Top view.
A.....B.....long straw (soda fountain straws answer purpose).
Cork
N.....needle piericng cork through slot as shown in "End-View."
Side View.
A.....B.....long straw, same as shown in "A.....B" in top view.
B.....H.....cord leading from end of straw to heart of frog.
P.....pen made of stiff card board, moving through arc, "X-Y."

cepted process is practically axiomatic. Indeed nearly all crude drugs of importance, whose active principles can be isolated and estimated without destruction by chemical assaying, are required by the present Pharmacopœia to be so treated. A few, however, notably those containing glucosides, which are of the greatest importance in practice, can not be so treated. Digitalis, strophanthus, squill, and almost all of the so-called, "digitalis bodies," are of this class. Ergot may likewise be included in this classification, for it is also practically non-assayable by chemical processes. Under former pharmacopœial direction it was evidently assumed the crude drugs must have been, perforce pure, whatever that term may have meant, and "void of offense" (intentional at least). Under the "New Plan," as it might well be called, the drug, with its galenical preparations, is to be challenged at every step in its journey toward "certainty of actions," as

shown by its assay. Could more be desired? Should less be accepted, where the issues are, life or death?

Pharmacy, as an art has all along kept even pace with its sister arts; but, as a science has it or has it not lagged sadly behind? Who, though, can challenge its splendid modes of encapsulating disagreeable and nauseating drugs? Who does not welcome the ampoule and the spiret as sure means of preventing deterioration of active principles? Who can fail to commend the skillful methods of preparing for use vaccines and sera, so skillful, indeed, as to make infection in their use almost impossible? Much more could be said, much more deserves to be said in praise of your profession along these lines.

But to be more specific in this discussion is it asked, "how" and "to what



Reading from left to right:
S.....stand to which is fastened signal magnet support (C).
P.....plug to electric battery.
H.....marker (made of cardboard pen.)
K.....kymographion (machine run by clockwork carrying smoked paper.)
S'.....tall stand writing pen for drum.
C.....clamps.
R.....support for specimens.
F.....hinge for writing-pen arm, F.....L.
T.....tack through specimen.
P'.....pulley carry, thread to weight (W), fixed by wax to F.....L (W').
I.....inductorium.
B.....cell conveying electrical stimulus to specimen on support.
E.....electric key for regulating current.

extent" may pharmacology be an aid to the pharmacist? Let the reply be, first, as to "how it may be." It can be a help in almost every way, and a hindrance in none. Does one question whether, for instance, digitalis, or any member of its group of drugs, or ergot also, if standardized physiologically, the only way most of them can be standardized at all, the result in their use would not meet with instant approval? Surely those who prescribe and those who must use these drugs would do so. The uncertainty as to the strength of supposed active principles in these drugs, affecting so vital a process as circulation and its control, has been too long a reproach upon the professions of medicine and pharmacy. This reproach, fortunately, has been very largely removed by the large and scientific manufacturing houses of our own and other countries, to their great credit may it not be declared.

Secondly, "Is the process feasible or practicable?" it may be asked.. This query might be considered as practically a corollary to the two immediately preceding propositions. To whom, "feasible?" For whom "practicable?" To the pharmacist, wholesale and retail, in reply to the first. For the physician and his patient, in reply to the second inquiry. Is the "process" one to be easily learned by the former class? Can it be acquired by one long out of school and in business? Are "short courses" possible in schools, if one desires to avail himself of such means of information? Has the subject been taught in schools of pharmacy, and, if so, with what degree of helpfulness? These and many other questions suggest themselves at once to the progressive mind, and deserve careful and thoughtful answer. The wholesale manufacturing houses already alluded to are daily answering some of these questions with great acceptance. An attempt will be made to answer them as applied to the retailer, especially those who manufacture their own galenicals from crude drugs, later. As to the "teachableness" of the subject to undergraduate students, or graduate students as well, the best reply is to submit a concrete case in which it has been done.

The essayist as long ago as 1905 was impressed with the thought that the pharmacist more than the physician should be trained in pharmacology. He introduced it, therefore, in his course in materia medica in the College of Pharmacy of the University of Iowa. He provided, however, for an antecedent course in physiology, covering about the same ground as is suggested by the Pharmaceutical Syllabus. With this course as his foundation the student was led through a purely didactic course in materia medica, the action of drugs being strongly emphasized. Following this a purely laboratory course was given, illustrating by means of animal experimentation all the points made in the didactic course. Especial attention was directed to the glucoside-containing drugs. An opportunity was also made use of in illustrating toxicology, by means of pushing drugs beyond their therapeutic limit and requiring the application of suitable antidotes in each case.

No more interested or enthusiastic classes were found than those whom the essayist was required to teach in the institution named. These consisted of students in the medical and dental colleges therein. The courses differed in the three colleges in no essential detail, only in the amount of work required. The "evidence from the field," also during the years that have passed since the work began has been uniformly supportive and in justification of it. Many of our graduates have pronounced it helpful to them beyond their belief when taking it. Some of them, indeed, have equipped their laboratories quite elaborately with expensive apparatus with which to carry on this mode of assaying as well as the modes they have for so long a time been accustomed to.

PRACTICABILITY FOR THE RETAIL PHARMACIST.

Probably no statement made in the present paper will be more quickly challenged by the retail pharmacist, especially by those who have had no opportunity to observe the practical working in a laboratory, than this particular division of the subject. Is it really possible for one not thus trained to undertake to familiarize himself with it? The essayist considers it easily possible. He believes, further, that no class of pharmacists will more enjoy the actual laboratory

work than these. The processes are no more difficult and much less intricate than many of those laid down for chemical assaying.

At the risk of being prolix I cannot refrain from presenting somewhat in detail at this point methods used by my own students in their laboratory work. Among many excellent processes for standardizing drugs the essayist selected that of Famulener and Lyons, known among pharmacologists as the "One Hour Method." It consists, briefly, first, in carefully selecting the frogs required by the method. They should average in weight from 20 to 30 grammes. They should be kept in a cool place, in ice during the summer months. When possible they should be procured as fresh as may be, from near-by brooks, or from swampy fields. When needed for experimental purposes they should, first of all be pithed in the brain, thus rendering it insensible to pain, as well as immobilizing the animal; next exposing its heart by cutting away a small diamond-shaped portion of the skin over the same. Thus prepared, with the animal lying upon its back, a pin bent to resemble a fish-hook is passed through the apex of the heart and connected by means of a thread to the short arm of a straw lever. (The method of constructing this piece of apparatus, as well as a more elaborate and expensive one will be shown with this article.) Thus exposed and attached the test as to efficiency of drugs of the cardiant type is easily made. The drug to be tested, usually a fluidextract with its solvent driven off by heat over a water-bath and water in sufficient quantity added to bring it up to its original volume, is allowed to drop continuously upon the exposed heart until its pulsations are observed to cease. The dose which accomplishes this is known as the L. F. D. (Least Fatal Dose). It is customary to prepare several frogs of about the same strength and weight, and as many doses of the tested drug. Thus a frog and its dose of the drug will be found in which the pulsations will cease in *exactly one hour.* This dose should be considered the L. F. D. sought and should be carefully noted. Corroborative tests should be made and averages struck, as in volumetric chemical analyses. From the findings thus obtained the dose suitable for the human patient is easily computed.

A second illustration of testing a drug physiologically is found in ergot. This drug is known to possess, if potent, strong vaso-constrictor action. So powerful is this action that an animal like a cockerel is usually selected for testing purposes. The white leghorn is best, because of its prominent comb and wattles, both of which are highly vascular. The preparation of the drug usually selected is its fluidextract, and the mode of its application is by hypodermatic injection into the muscles of the breast. If the drug is potent a very marked discoloration will appear within an hour or so, shading from a simple bluish to a bluish-black color. The duration of the discoloration will depend, usually, upon the strength of the specimen tested. The normal color will return ordinarily in a short time, and the animal can be used again. This method is the one used and recommended by the Bureau of Public Health at Washington, D. C., and is submitted, therefore, as the one to be preferred in practical testing for this particular drug.

It will be observed in Fig. 1 that the apparatus may be very simple and inexpensive. In Fig II it is more complicated and expensive.

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