RESOLUTION ANENT STANDARD FOR CANNABIS.*

WHEREAS, The standards of strength for Cannabis and its preparations introduced and made mandatory in the ninth revision of the U. S. Pharmacopoeia are open to just criticism as at once illogical and lacking in definiteness, and

WHEREAS, Biological assays of much greater merit and importance, although given official recognition in the new Pharmacopoeia, are not made mandatory, and

WHEREAS, Under the new pharmacopoeial standard, Indian Cannabis in all probability equal in activity to that which has hitherto been imported is now practically excluded from the American market on the ground that it does not comply with U. S. P. requirements, therefore

Resolved, That the Pharmacopoeial Revision Committee be requested and urged, 1st to modify the official test so as to eliminate its vagueness and self-contradiction, and, 2nd, to make the biological assay for Cannabis optional as in the case of Digitalis and other drugs for which biological assays are provided.

IMPORTANCE OF THE RESOLUTION.

By Act of Congress, confirmed by enactments of the various State Legislatures, the U. S. Pharmacopoeia is declared to be, within its scope, the supreme legal authority. In the recent revision of this authoritative work multitudes of changes have been made in the endeavor to remove inconsistencies and imperfections, and the work was done with such a sense of responsibility that the instances in which new errors were unwittingly introduced in making the changes have been very few.

The new standards for Cannabis and its preparations are a conspicuous exception. The error that was made after all is one easily rectified. An assay process was described on page 604 of the text to which little or no exception is taken by those who have been accustomed to biological assay methods. But on turning the leaf we find that *this assay process has not been adopted.* The assay consists in a series of tests by which the relative activity of the sample under examination and that of a standard product is determined. The experiments are made on dogs whose reaction to the drug has been previously carefully studied. It is assumed that the susceptibility of the animal is proportioned at least roughly to its weight, but that is not a matter of great consequence in the tests. It is first ascertained with regard to each animal what is the minimum quantity of the standard which will cause signs of "muscular incoördination." Suppose that that quantity is found to be 0.75 mil. The minimum quantity of the sample under examination which will produce an equal disturbance in the nervous system of the same dog is then ascertained in a series of parallel experiments, and so by a simple proportion, the strength of the sample is deduced. If the minimum dose were found to be 0.65, the sample would be known to be stronger than the standard in the ratio of 65 to 75 or 1.00 to 1.15+. The result would be conclusive at least if the experiments were made by an expert although it is obvious that there would be no great exactness in the conclusions deduced.

But the final paragraph of the text turns to confusion all that precedes. It is headed "Standard," but goes on to declare that there *is* no standard for Cannabis, and then immediately proposes to use as a standard "a fluidextract or an extract that has been carefully prepared and suitably preserved." That is to say, the drug is a standard in itself—but then why should one go to the trouble of assaying it? Grant that the real meaning is that an arbitrary standard for the drug must be adopted, which may be a fluidextract (or extract) prepared from an average sample of the drug, *i. e.*, from a score or more of samples of cannabis of recent crop. It is on this principle at all events that the standards adopted by manufacturers who offer products standardized by biological assay have been originally prepared.

Well, a standard has been provided, such as it is, but the Pharmacopoeia makes no use of it. Instead, it introduces an entirely different plan for determining the activity of the drug. Now it is the dog that is to be the standard—or rather a kilogramme of dog—without regard to race,

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* Presented before Scientific Section, A. Ph. A., Indianapolis meeting, 1917, by W. S. Hubbard for A. B. Lyons. The latter desired it to be understood that he did not present the subject as a member of the U. S. P. Revision Committee. The resolution was referred to the Committee on U. S. Pharmacopoeia of the American Pharmaceutical Association.

age, sex or previous condition of servitude. To be sure we have been told on page 605 that dogs "differ considerably in susceptibility to the drug" and that it is best to select animals "which react easily to the drug." Now, however, we are told that a standard fluidextract will produce incoördination when administered to "dogs" in the dose of 0.03 mil for each kilogramme of body weight of dog, and this it seems, constitutes the whole test. Weigh your dog (after a 24 hours' fast) multiply his weight in kilogrammes by 0.03 to find the dose in mils which should produce incoördination. Half that dose might do it, but no matter about that. Precisely what degree of incoördination is to be looked for is not stated—could not well be, in the nature of the case. It is clear that the test as it stands admits of no quantitative interpretation.

I think I have amply justified the statement of the preamble, *viz.*, that the pharmacopoeial requirement is "open to just criticism as both illogical and lacking in definiteness." *The remedy consists in amending the final paragraph of the text to bring it into consistency with that which precedes.* In place of the statement, "As there is no substance of definite composition which can be adopted as a standard, a fluidextract of cannabis or an extract which has been carefully prepared and suitably preserved may be utilized for this purpose," there should be some such statement as the following: "Since we have not been able as yet to isolate any definite chemical compound as the active principle of the drug, an arbitrary standard must be adopted, representing as nearly as possible the average activity of cannabis of recent crop. On account of its superior stability, a fluidextract is to be chosen for this purpose. Such standard is to be provided by—subject to approval by the U. S. Public Health Service. One mil of this standard shall be considered the equivalent of one gramme of standard cannabis or ten mils of standard (official) tincture or 0.1 gramme of standard extract."

This last ratio is different from that implied in the present pharmacopoeial requirement (about 0.133) and is subject to modification. How the blank left should best be filled is not to be settled without due consideration and discussion. Personally, I incline now to think that the responsibility should be assumed by either the American Pharmaceutical Association or the American Drug Manufacturers' Association, perhaps more appropriately the latter.

The responsibility will not end with the preparing of the original standard. It is equally important that the standard be maintained of uniform strength as time goes by. Since a fluidextract suffers more or less deterioration with age it will be necessary to make frequent assays of the standards, employing dogs whose susceptibility has been accurately established—and several of them at that, to guard against possible change in susceptibility—and so from time to time adjusting anew the strength of the standards.

Reasons why the change is imperative. The present pharmacopoeial assay is based on the assumption that all dogs are equally susceptible to cannabis intoxication, exactly in proportion to their weight.

The falsity of such an assumption is so obvious that argument is unnecessary. Even admitting that the dog is one selected as a good subject, there remains the fallacy that an agent producing its effects on the nervous system will act on an animal quantitatively in proportion to its body weight. Here in the outset is introduced an element of extreme variability into the result of the assay. Differences on this account of fifty to one hundred percent might be looked for.

But further, the personal equation will surely enter as a very large factor into the decision whether or not the test animal shows "muscular incoördination." The Pharmacopoeia does not even state that the effect to be produced is a minimum one as it should do, and it is only the expert who is competent to pronounce with certainty on the signs of incipient incoördination. Differences of ten to twenty-five percent are likely to occur from this cause.

Are these sources of serious discrepancy removed by the proposed change in the pharmacopoeial assay? Emphatically, they are. The assay now is simply a matter of comparison of sample with standard. If any reasonable care is used in carrying out the test, any one of average intelligence, after sufficient practice—an essential prerequisite, just as chemical training is essential in a quantitative chemical determination—can fix within a margin of say ten percent the relative strength of sample and standard. Of course, the measurements of the doses administered to the animal which will often be a fraction of a mil must be made with great exactness.

Why the matter concerns you and me. Granted that this particular assay is faulty, why should we give ourselves concern about it? The reason is that the Pharmacopoeia has become

a legal authority, its verdict in any matter is final, so that if a product of mine is condemned as misbranded because not in conformity with pharmacopoeial requirements, my only recourse is to challenge in the courts the authority of the law itself. The chance of winning such a suit is small, and even success would not give one unmixed satisfaction, since it would prove our best friend not infallible and hence liable to be unjustly attacked when its authority happened to be our dependence.

Why a biological assay of cannabis should not be made mandatory. It is hard to understand why it was that the Cannabis Assay was singled out from the list of biological tests to be made compulsory. Biological assays require expert skill which is at present possessed by very few individuals, so that as yet such assays ought not to be made mandatory. There are those who question the value of any tests of this description—unless the experiments are made on a human subject. We have at best learned only the rudiments of an art which we believe has large possibilities. The time may not be distant when there will be established laboratories for carrying out tests of this character, in charge of experts. Clearly, it is not practicable now for the ordinary pharmacist, or even the average drug manufacturer, to attempt work of this character. We favor therefore withdrawal for the present of the requirements that cannabis and its preparations shall be standardized by biological assay.

We have in mind nevertheless one valid reason why some standard for this particular drug should have been provided. As long as Indian Cannabis alone was official, the reason did not exist. The revisers of the Pharmacopoeia, however, have made official American grown cannabis on equal terms with the imported drug. Why this should have been done just at the time when the Harrison Act went into effect, imposing stringent regulations on the traffic in cannabis as a dangerous habit-forming drug, it is not easy to explain. The supply of the imported drug was surely ample for all legitimate uses. It was certainly not a case of developing a new American industry for which there was any known demand.

There has been a great deal of skepticism in regard to the claim that American Cannabis is equal in activity to the imported drug. There is unimpeachable testimony from experts that some samples of American Cannabis do compare favorably with the best Indian Cannabis. But the American Cannabis procurable in the market is reported far inferior in activity to Indian Cannabis.

Certainly the American grown drug as a rule yields far less extractive than the imported, the ratio being on the average about 6 to 10. This means either that the American drug is weaker than the Indian or else that an extract made from the American is much stronger than one made from the Indian. Consequently, the two varieties of cannabis cannot be included under one pharmacopoeial title without confusion.

If cannabis were an important drug therapeutically, or one largely used, it might be worth while to take trouble in order to utilize a home product. The fact is that the chief use actually made of cannabis is in the preparation of corn remedies, in which apparently it is chlorophyll rather than any active constituent that counts. Naturally, the American Cannabis for this use is superior to the imported, but it is its color, not its possible anodyne action, which concerns the purchaser.

However, it does not seem to me necessary to ask the Revision Committee to reopen the question of including American Cannabis under the title Cannabis. It seems to me sufficient to revise the assay method so that it shall give correct, if not very exact, information regarding the activity of any sample examined. For reasons already stated, it is certainly inadvisable to require at present for cannabis or any other drug standardization by biological assay. A few years hence such standardization will be practicable and therefore imperative.