Section on Scientific Papers

Papers Presented at the Sixty-First Annual Convention

THE CHAIRMAN'S ADDRESS—THE DETERIORATION OF PHARMACEUTICAL PREPARATIONS.

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The standardization of galenical preparations is such a well worn topic that I hesitate to refer to it in this connection, yet it is the logical starting point in the consideration of their stability.

The adoption of standards for these products marks the most important ad-

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vance which has been made in their manufacture. Before such standards became possible many years had been devoted to the analysis of drugs; and later to the development of assay methods for determining the active principles which had been found. It is almost needless to say that an apparently unlimited amount of work yet remains to be done in both these fields. Our knowledge of the chemistry of many important drugs is so slight that we cannot even attempt

to develop chemical methods for their standardization; other drugs whose chemistry is better understood cannot be accurately assayed because suitable methods for this purpose have not been devised, and moreover, when we examine the assay processes which are in general use we find many imperfections. Steady progress has, however, been made in the development of methods and apparatus for assaying drugs and today the manufacturer may find that he is forced to use a process which he knows to be inaccurate because it was perhaps the best available when the Pharmacopœia gave it a legal standing. It is obvious that standards could not be established until fairly satisfactory assay processes had been agreed upon. The immediate effect of such standards was much greater uniformity in the strength of preparations standardized, for although the methods were not perfect and results not always as accurate as they should have been, yet the first serious attempt was being made to bring about uniformity and variations in strength became almost negligable.

After certain standards and methods had received official recognition the question of the stability of the standardized products began to receive attention. Previous to this time chemists engaged in this line of work had been so busy developing the assay methods, without which, deterioration studies could not be made, that no systematic investigation of the changes which might occur in such standardized products after their manufacture, had been undertaken. Many persons, forgetting the years which had been consumed in acquiring our present knowledge of drugs, seemed to think that it would be a simple matter to determine once for all the degree of stability of these preparations and investigations and discussions of this matter became the fashion. So much has been said and written that it was thought desirable to summarize our knowledge of the subjects, but a review of the literature, so full of contradictory "conclusions," seems to render this impossible except in the most general way. Even the results of investigations in many cases show the widest variance, for instance one chemist finds that some lots of fluidextract and tincture of chinchona show deterioration, while other chemists who have examined many lots of these preparations have found no evidence of deterioration. The occasional precipitation of alkaloids from cinchona preparations may be due to differences in the drug used, or to the conditions of manufacture and storage and only a careful study will determine the cause of this deterioration so that steps may be taken to prevent it. It is safe to say that in more than one laboratory, studies are being made with this end in view. We may confidently expect that whenever products are found to deteriorate every effort will be made to overcome this difficulty, and the fact that most of these preparations are so stable encourages the belief that in nearly all cases deterioration can be practically eliminated. Fluidextract of coca which is fortunately of little importance is the only fluidextract which has been uniformly found to deteriorate. Indeed the only general conclusion which can be drawn after a careful consideration of the literature is, that as a class galenical preparations are surprisingly stable. It is extremely unfortunate that a few writers acting as alarmists have tried to show that the reverse is true and I wish to call attention to some of their statements. We have been told that fluidextract of ergot is worthless after it is six months old, yet the clinical reputation of ergot in this country was probably largely established by the use of a fluid-

extract which the manufacturer aged for one year before bottling. The most careful studies of this preparation have failed to show any loss of strength in two years and it is difficult to say at this time how much longer it can be kept without deterioration as this can only be definitely determined by further aging tests. Very old samples of the crude drug have also been shown to be of average activity despite the more or less prevalent opinion that such drug is worthless. Again a recent writer in one of the pharmaceutical journals making use of the data of various investigators has arrived at some conclusions differing materially from those of the original authors and in no way justified by the data presented. This writer says that fluidextracts of ergot and digitalis should not be relied upon when over six months old, although no evidence whatever is offered in support of this statement. He also states that physicians should discard "as far as possible" all fluidextracts which are over two years old, while the data presented could in no way lead to this conclusion. Some manufacturers also have made capital of reputed deterioration to call attention to special means of preserving drugs from influences which have not definitely been shown to affect them. For instance, patents have been issued on a process for destroying the hydrolytic enzymes which cause the deterioration of digitalis preparations, and other special methods for preserving crude digitalis and its preparations have been exploited; yet Hatcher* has recently shown that fluidextracts at least twenty years old show no evidences of deterioration, while the crude drug preserved with ordinary care has been proven to be perfectly stable, thus rendering unnecessary any of the special methods of drying or preservation. Although Hatcher's results may not be taken as final, his careful work certainly shows how ridiculous it is to try to explain the cause or devise means for preventing deterioration which is not known to take place. This brings us back to the consideration of accuracy in methods of valuing drugs, for other investigators, using methods different from that employed by Hatcher, have fixed upon various rates of deterioration for fluidextracts and tinctures of digitalis. I have reminded you of our scant knowledge of the chemistry of many important drugs and of our imperfect chemical assay methods and these statements apply also, perhaps in less degree, to our knowledge of the pharmacology of many such drugs and in an even greater degree to the physiological assay methods. While we are attempting to study the deterioration of such drugs as ergot and digitalis by diverse methods upon which pharmacologists are not yet in accord we must not therefore allow ourselves to draw too definite conclusions. If conservative in this respect, we can acquire much valuable information from these studies in regard to the methods used as well as to the stability of the preparations. We cannot expect the same degree of accuracy in physiological methods that has been attained in chemical methods on account of the unavoidable variations in the animals used and also from the fact that it is a comparatively short time since physiological methods were first used for the standardization of drugs. No single method should be relied upon and results upon only a few lots should not be accepted as evidenced by the results on fluidextract of cinchona which have been cited. With these facts in mind an impartial study of the literature

*Journ. A. Ph. A., July, 1913, p. 876.

can lead only to the conclusion that there is no positive proof, with one or two important exceptions, that galenicals deteriorate in any serious degree.

Such important advances have been made in the manufacture of galenicals that the members of the pharmaceutical profession may well congratulate themselves upon this fact instead of agreeing with one of our friends who, upon the basis of his studies of ergot deterioration has depicted the situation as "horrible." I would by no means have you infer that I think we should be satisfied, for on the other hand I believe that it is the duty of any one engaged in the manufacture of medicinal preparations to strive with all the means at his disposal to improve both preparations and methods for testing them.

It has recently been very popular to advocate the dating of pharmaceutical products, and certainly no one will deny that this should be done whenever our knowledge is sufficiently exact to establish a period after which the preparation should not be used. Until this can be done nothing could be more illogical than to date such preparations. For example it has frequently been urged that digitalis preparations should be dated, yet Hatcher's work seems to have established the fact that these preparations will keep twenty or thirty years; what can be accomplished then by dating them? Surely preparations older than this will not be frequently used! If the dates of manufacture are placed upon preparations when no definite knowledge in regard to their keeping qualities is available, who shall decide when these preparations must be discarded? One writer who advocates placing the date of manufacture on certain preparations says that while it is very difficult to set a definite time limit on a preparation which deteriorates, yet the dating of such preparations enables the pharmacist to use his expert judgment as to whether or not a preparation is too old to be used. If this knowledge is not available to the manufacturer, where can we expect the dispenser to obtain the information? The answer is clear; the fact of deterioration must be determined from the preparation itself and not from any date appearing on the label. The fact that where deterioration occurs, different lots will deteriorate at very different rates, cannot be too strongly emphasized; this is due no doubt to differences in the preparation itself as well as to conditions of storage. If galenical preparations are not protected from extremes of temperature and from direct sunlight, and are not stored, well stoppered, in amber bottles more rapid changes must be looked for in the preparations. Differences in various lots of the same preparation and even in different bottles of the same lot are seen in a marked degree in solution of hydrogen dioxide, so that any time limit which could be established would, therefore, have the disadvantage of being too near in some cases and too remote in others, and the same condition will be found to exist with other preparations which deteriorate. It might be urged, that until we can absolutely demonstrate that a preparation does not deteriorate at all during a long period of years, we should give the consumer the benefit of the doubt and require the manufacturer to date his packages, but the fallacy of this argument is easily seen when it is considered that most of our information points to the great stability of such products and that if the pharmacist was arbitrarily required to discard preparations of a certain age the consumer would ultimately have to pay for this uncalled for waste. The careful pharmacist will in any event turn over his stock of pharmaceuticals

as rapidly as possible both for the purpose of keeping his stock fresh and to increase his financial gains; in this he is certainly to be encouraged.

Although there can be no doubt that deteriorated products have been dispensed and will be dispensed in the future, conditions are rapidly improving and, indeed, have never been as serious as many writers lead us to believe. It is undoubtedly true also, that improvements in manufacturing processes will keep pace with improvements in analytical and pharmacological methods, so that as fast as the fact of deterioration can be established, steps will be taken to overcome the difficulty. Let us not forget that even though methods are imperfect and preparations may occasionally deteriorate the resulting variations in strength will in most cases be much less than the variations which would occur in unstandardized preparations. We are therefore making good progress and a little patience only is required until the bugaboo of deterioration will be, in one way or another, overcome.

DISAPPEARING DISEASES.

Dr. Guilfoy, the Registrar of Vital Statistics of New York, has recently published some interesting figures from former records showing what modern methods have done in the way of abolishing certain diseases. Asiatic cholera was formerly a frequent visitor to the city, there being 5,000 deaths from this scourge in Manhattan and the Bronx in 1849; 2,500 in 1854; and 1,100 in 1866. During the last thirty-six years there have been only 11 deaths from this disease. Typhus fever was prevalent from the year 1868 onward, there being 200 deaths attributed to it in 1893. If the same death-rate from malarial fever had prevailed in 1912 as in the period from 1880 to 1890, there would have been 1,400 deaths from this cause; the number that actually did die from it was 20. The most striking conquest has been made in the case of smallpox which was practically always prevalent prior to the year 1876. Since that time the epidemics have become milder and of shorter duration until last year there were only two deaths from this disease in a population of over 5,000,000 people.—*Journ. A. M. A., V. LX*, 842.