chloroform or ether, but the solvents extracted also some glycerin and sodium chloride unless the proportion of acetone in the solvent was reduced to such an extent that it no longer possessed any advantage over alcohol.

In the following method which was found to yield the most satisfactory results it will be noted that no account is taken of the essential oil which the official elixir contains, as the error occasioned by it is too small to be significant. If, however, it is desired to avoid the presence of the volatile oil in the residue it can be readily removed by a preliminary extraction with petroleum ether in which terpin hydrate is insoluble. The method is as follows:

Dissolve 20 grammes of common salt in 100 Cc. of water, or if more convenient add 1 volume of water to 3 volumes of a saturated aqueous salt solution. To a convenient measured volume of the sample of elixir add the prepared salt solution until the alcohol content is from 10% to 15% by volume. Shake out with four portions, one-fourth volume each, of chloroform containing 5% to 7% alcohol by volume. Wash each portion of the solvent successively through 5 Cc. of the prepared salt solution. Filter through a pledget of purified cotton into a tared beaker or small crystallizing dish, finally rinsing the cotton and the tip of the funnel with a little alcohol. Evaporate with the aid of a blast and without the application of heat. Wipe off any moisture that may have collected on the outside of the dish and allow to stand fifteen minutes before weighing.

Ten Cc. of a sample of elixir of terpin hydrate prepared in accordance with the formula of the National Formulary with the exception of the essential oils when assayed by the proposed method yielded 0.1764 Gm. of terpin hydrate instead of 0.1750 Gm., an error of + 0.8%.

While the method was devised primarily for the assay of elixir of terpin hydrate it may perhaps be adapted to other preparations of this drug, which do not contain other ingredients extractable by the immiscible solvent used or which can be freed from interfering substances without loss of terpin hydrate.

TINCTURE OF DIGITALIS AND THE INFUSION IN THERAPEUTICS.*,[1]

BY SOMA WEISS AND ROBERT A. HATCHER, M.D., NEW YORK.

Our knowledge of the pharmacology of the digitalis group is increasing rapidly, and its therapeutic use now begins to approach an exact science more nearly, perhaps, than that of all excepting a few drugs. But there are still many minor points, and not a few major ones, that require further study.

Clinicians have long held the opinion that the action of the tincture of digitalis differs qualitatively as well as quantitatively from that of the infusion. This difference is usually explained on the ground that the several active principles found in the leaf are not extracted in the same relative amounts by the menstruum used in making the tincture and the water used in making the infusion.

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*From the Laboratory of Pharmacology of Cornell University Medical College.

[1] This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association. Reprinted from *Journal A. M. A.*, February 19, 1921, p. 508.

Pharmacologists have shown a disposition to give too little consideration to the views of the older therapeutists when these appear to be in conflict with the deductions drawn from the results of modern experiments, even as many therapeutists have a tendency to dismiss pharmacologic deductions when they fail to support opinions based on clinical observations. Obviously, we can accomplish no more through the clinical use of a drug, however extensive our knowledge of its pharmacology may be, than was accomplished formerly by one who chanced to discover the correct way of employing it, and it is probable that William Withering used digitalis with success equal to that of many of the clinicians of to-day.

Nothing could be farther from our purpose than to attempt to belittle exact pharmacologic investigations; but it is true that pharmacologists and chemists are responsible for much of the misunderstanding that exists to-day regarding this drug. On the other hand, many of the older clinicians were acute observers; and while their deductions may have been faulty at times, these were often founded on fact. This should serve as a warning to us against dismissing long established clinical opinions without attempting to understand the basis for their existence, and to explain wherein the error lay when such is proved to exist. With the clearing away of misconceptions, the use of the drug will approach the state in which the general practitioner will be able to use it even more wisely than Withering employed it. We shall, therefore, discuss briefly the basis for the view that the constituents of the infusion of digitalis differ in kind from those of the tincture.

It is not our purpose to discuss the chemical nature of the active principles of digitalis, or their solubilities, except as may be necessary for an understanding of the question of the composition of the tincture and the infusion.

COMPOSITION OF THE TINCTURE OF DIGITALIS.

Digitoxin, digitalin and digitalein, the three principles generally supposed to represent the activities of the leaf, are soluble in alcohol, and all of these (if, indeed, they exist in the leaf) are present in the tincture; and it may be stated at once that the official tincture represents the activity of the leaf completely, that is to say, that the tincture contains all except traces of the active principles of the dried and powdered leaf from which it is made.

There is no way of estimating the total amounts of the several active principles in the leaf or in the tincture directly; therefore the following method was used in order to determine whether the tincture represents the leaf fully:

A tincture was prepared according to the directions of the United States Pharmacopoeia, and the marc (the drug left in the percolator after extraction) was dried and weighed. The dried marc weighed just half as much as the drug weighed previous to extraction; this was odorless and tasteless, or nearly so. This in itself points strongly to the removal of all the active principles during percolation, for all of them are very bitter, and nothing is destroyed during the simple process of extraction with the menstruum consisting of three volumes of alcohol and one of water.

An infusion was then prepared by pouring 1000 Cc. of boiling water on 7.5 Gm. of the dried marc, representing 15 Gm. of the original digitalis from which the tincture had been made, and this infusion was tested in order to determine whether it contained any active substance.

The intravenous injection of 150 Cc. of this infusion of the marc per kilogramme of body weight was without perceptible effect, though this dose was equal in volume to about twenty-five times that required of an infusion of this specimen of digitalis to cause death. The cat then received a further intravenous injection of the full average fatal dose of ouabain before death

resulted, showing conclusively that the infusion of the marc (and the marc itself) contained not more than traces of water-soluble active digitalis principles.[1]

The presence of saponin-like bodies (digitonin or digit-saponin) in digitalis has given rise to much discussion. These substances are devoid of the therapeutic action of digitalis, but, on the other hand, they may be deleterious when large amounts are injected intravenously, and their significance in digitalis therapy is frequently misunderstood. The gastric disturbance which sometimes follows the oral administration of tincture of digitalis has been attributed largely, but erroneously, to these substances, though Cushny[2] states that the tincture contains less of these than the infusion. Presumably Cushny means the tincture made from a given weight of drug contains less than the infusion which represents an equal weight of the drug.

We are not aware of any direct experimental evidence on which this statement is based, but one frequently sees it coupled with the explanation that these saponin bodies are insoluble in alcohol. This deduction is misleading in that while they are insoluble in absolute alcohol, the official tincture is made, as previously stated, with a menstruum of about 70 percent alcohol. We have therefore attempted to determine whether the marc left after preparing the official tincture contains saponin-like bodies or not, and if so, the approximate amount as compared with that present in the official infusion, though the matter did not appear to us to be of great practical importance, because it is well known to pharmacologists that the leaf contains only small amounts of these bodies, and even these amounts are not absorbed readily from the gastro-intestinal tract, nor do they cause local irritation in amounts at all comparable to those that can ever be administered during the therapeutic use of digitalis.

PRESENCE OF DIGITONIN.

Kiliani,[3] who is probably the greatest living authority on the chemistry of digitalis, states that digitalis leaves contain only traces of digitonin, and he also says[4] that Boehm found that digitonin causes gastric irritation in dogs only after the oral administration of enormous doses. These results attributed to Boehm have been confirmed for experiments in this laboratory. Unfortunately for the cause of scientific therapy, the fallacy regarding the supposed rôle of digitonin in the production of gastric disturbance following the administration of the tincture of digitalis in therapeutic doses appears to us to have been kept alive largely from motives of financial interest; at least, we have been unable to discover any evidence to support the theory mentioned, and an advantage sometimes claimed for proprietary substitutes for the official preparations of digitalis is that they lack the irritant or disturbing effect of these saponin-like bodies.

[1] The use of ouabain in this experiment is based on what is termed the "combined ouabain" method for the estimation of small amounts of digitalis bodies, which was described by Hatcher and Brody (*Am. J. Phar.*, 82, 360, 1910). This method consists in determining the difference between the average fatal vein dose of ouabain for the cat per kilogram of weight and that required to kill after the previous injection of a dose of any digitalis body. The difference represents the percentage of the fatal dose that is attributable to the digitalis body under investigation.

[2] Cushny, "Pharmacology and Therapeutics or the Actions of Drugs," 1918, p. 399.

[3] Kiliani, *Arch. d. Pharm.*, 243, 7, 1905.

[4] Kiliani, *Ibid.*, 230, 260, 1892.

We undertook to compare the laking action of an infusion prepared from the powdered lead with that of one made from the marc of the tincture, but the laking action exerted on partially washed corpuscles (obtained by mixing blood with 100 parts of physiologic sodium chloride solution and allowing the corpuscles to settle to the bottom of the vessel) was so feeble in both cases that we abandoned further effort in this direction.

We found that the intravenous injection of digitonin (Merck's) in doses of 20 mg. per Kg. of body weight caused hematuria in three experiments on cats, and, on the other hand, the intravenous injection of an infusion of the marc of the tincture in doses of 150 Cc. per Kg. of weight produced no perceptible effect. From this we may conclude that very little digitonin remains in the marc of the tincture and whether or not the tincture contains more than traces of it, the difference between the amounts of it present in the tincture and in the infusion of corresponding amounts of the drug are of no therapeutic or toxicologic importance.

The subject does not seem to us worth further consideration in view of what has been said, especially since we have such high authority as Kiliani for stating that the leaf contains only traces of digitonin.

The Pharmacopoeia gives directions for the biologic assay of digitalis with the standard of activity required for the leaf, the fluidextract and the tincture, but none for the infusion; it is far more important to the clinician, therefore, to know to what extent the infusion represents the leaf from which it is made than to know whether the tincture contains more than traces of saponin bodies.

DIGITALEIN AND DIGITALIN.

Digitalein is very soluble in water, and it may be accepted that any that may be present in the leaf passes into the infusion. Digitalin (the true digitalin of Schmiedeberg and of Kiliani) is also extracted by water, possibly with the aid of the saponin bodies; but neither digitalein nor digitalin is absorbed readily from the gastro-intestinal trace of animals or that of man.

Oral doses of digitalein equal to the fatal vein dose were administered to cats daily periods for a week, and it was then found by means of the combined ouabain test that there was little persistence of action. Amounts of digitalein equal to four or five times the single fatal vein dose were administered to each of several cats through a stomach tube in single doses without inducing perceptible effects.[1]

Schmiedeberg[2] states that the absorption and behavior of digitalein are such that it is difficult to obtain therapeutic effects with it, and that digitalin is absorbed slowly and irregularly from the gastro-intestinal tract. Naunyn[3] states that Ger-

[1] Unpublished experiments performed in this laboratory some years ago and recently confirmed by us in part. The digitalein of commerce is said to consist of a mixture of glucosides from Digitalis purpurea, prepared according to the process of Schmiedeberg, and containing digitoxin, digitalin and digitalein (New and Non-official Remedies, 1920, p. 88); and since the proportions of these three appear to vary in different specimens of commercial digatalein, we do not pretend to say that all specimens show the same behavior. In fact, it is our opinion that digitalein has no place in the materia medica while it remains so uncertain in composition and activity.

[2] Schmiedeberg, *Arch. f. Path. u. Pharm.*, 62, 305, 1910.

[3] Naunyn, *Therap. d. Gegenw.*, 1, 193, 1899.

man digitalin (which consists of true digitalin in part) exerts only a weak and uncertain action after its oral administration to man; and Eggleston[1] found that both digitalein and digitalin are absorbed so poorly from the gastro-intestinal tract of man (as judged by the lack of therapeutic effects) that they are unsuitable for therapeutic use.

ABSORPTION OF DIGITOXIN.

Digitoxin is practically insoluble in water, and it is commonly stated that the infusion contains only traces of it,[2] or that it contains more or less of the digitoxin held in suspension by the saponin bodies. Sollmann[3] states that a 1 : 10 infusion (note that this is not the official) contains two-thirds of the digitoxin of the leaf.

The evidence that is available to us appears to show incontrovertibly that digitoxin is absorbed from the gastro-intestinal tract of man with a far greater approach to uniformity than is either digitalin or digitalein. It is only proper to state that Schmiedeberg[4] states that the insoluble digitoxin is absorbed even less regularly than digitalin, the administration of a given amount causing pronounced effects in one case and none in another. This is apparently an example of erroneous deduction, following the view so commonly held that insolubility in water exerts a profound influence on the absorption of even those drugs which are given therapeutically in doses of a milligram. Solubility does play an important rôle in the absorption of drugs which are given in doses of a gramme or more, but this factor is of minor importance with reference to the absorption of such minute amounts as one gives of digitoxin.

Naunyn[5] used digitoxin, and states as the result of clinical experience that it is absorbed completely, despite its insolubility (in water). Huchard[6] comments on the frequent lack of therapeutic success with different specimens of digitalis and says that he always gives the preference to crystalline digitaline (digitoxin) because it is uniform in its therapeutic effects. Eggleston[1] also found the absorption of digitoxin from the gastro-intestinal tract of man to be more nearly uniform than that of digitalin or digitalein; at least, he found the dose required to be less variable.

AMOUNT OF DIGITOXIN IN THE INFUSION.

Having submitted evidence that appears convincing to us that digitoxin is absorbed from the gastro-intestinal tract of man, with a far greater approach to uniformity of action than is the case with digitalein or digitalin, it is increasingly important to determine whether the infusion contains only traces of digitoxin, as Cushny[2] states, or much larger amounts, as Sollmann[3] claims, for it is evident from the foregoing that the therapeutic value of the infusion must depend on the presence in it of digitoxin, if there are only these three active principles in the leaf in important amounts, or on the presence of some other readily absorbable principle not described heretofore.

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[1] Eggleston, Cary, "Digitalis Dosage," *Arch. Int. Med.*, 16, 1 (July 1915).

[2] Cushny, "Pharmacology and Therapeutics or the Actions of Drugs," 1918, p. 399.

[3] Torald Sollmann, Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1917, p. 383.

[4] Schmiedeberg, *Arch. f. path. u. Pharm.*, 62, 305, 1910.

[5] Naunyn, *Therap. d. Gegenw.*, 1, 193, 1899.

[6] Huchard, Les maladies du coeur, 1908, p. 164.

There is no way of separately estimating the several active principles of the infusion, and we have approached the solution of the question in the same way that we determined that the tincture represents the leaf completely, that is, we examined the marc left after the infusion had been made.

VARIOUS METHODS OF MAKING INFUSION OF DIGITALIS.

Before presenting the results of these experiments, we wish to discuss the several methods that we have employed in making the infusion, including that official in the United States Pharmacopoeia, and a modification that we have used in this laboratory for several years for the preparation of infusions for use in experimental studies.

United States.—The United States Pharmacopoeia directs that the infusion shall be prepared by pouring 400 Cc. of boiling water on 15 Gm. of bruised digitalis and allowing it to macerate for one hour, after which the liquid is strained, 500 Cc. of cinnamon water is added to the strained liquid, and enough water is passed through the strainer (and the marc) to make 1000 Cc.

It would be interesting to know why the Pharmacopoeia directs that the drug be "bruised" instead of directing that the powdered digitalis be used. According to the pharmacopoeial requirements, the leaf must be "carefully" dried, but there is no statement as to the amount of moisture allowed. The lamina of digitalis is brittle, when properly dried, and one does not speak of "bruising" a brittle substance; it is only the tough and useless midribs that resist trituration and their presence serves to prevent the reduction of the lamina to a uniform powder, unless the trituration is prolonged; hence the degree of fineness of the "bruised" digitalis will vary widely, depending on the interpretation put on the direction to bruise the drug, and also on the amount of the contained moisture and the relative amount of midribs.

It will be observed also that only 500 Cc. of water is used in the extraction of the drug in making 1000 Cc. of the official infusion, since the cinnamon water, constituting half of the total volume, is added to the strained liquid and not passed through the marc on the strainer. Furthermore, not all of the infusion held in the marc is removed by the water which is passed through the strainer to make up the required volume.

British.—The British pharmacopoeia directs that the infusion be prepared by pouring 1000 Cc. of boiling water on 7 Gm. of digitalis in No. 20 powder, allowing it to stand for fifteen minutes, and straining while hot. It will be observed that this process involves the use of less than half as much drug as that of the United States Pharmacopoeia; that a uniform powder is directed; that the solvent action of all of the liquid is utilized, though for a shorter time, and that the finished infusion is not diluted by passing water through the strainer.

Author's Method.—The infusion that has been used so frequently in this laboratory for experimental purposes has been prepared essentially as follows: One thousand Cc. of boiling water is poured onto 10 Gm. of digitalis in No. 60 powder in a flask or beaker, which is allowed to stand for one hour in a boiling water-bath with frequent stirring of the infusion, in order to expel the air from the cells, thus facilitating extraction, water being added to replace that lost by evaporation; the infusion is cooled, and filtered through paper, or filtered while hot, when it is desired to maintain it in a sterile condition.

PRACTICAL TESTS OF VARYING METHODS.

Infusions were prepared in the official way and in that just described, after which the marc was washed free of the adhering infusion, or this was gotten rid of by pressing the marc between layers of filter paper, adding a small volume of water and again expressing. The marc was then dried and weighed, after which tinctures were prepared and examined for their activity by testing them on cats. We are aware that the washing of the marc with about 200 Cc. of water involves a slight error; but if 1,000 Cc. of boiling water fails to extract the active principles, we do not believe that the error involved in washing this marc with 200 Cc. of cold water

is of any importance. In some instances we estimated the activity of the infusions directly, in order to compare the activity of those prepared in different ways.

RESULTS.

The results of these experiments may be presented briefly without giving the protocols in detail.

An infusion made according to the official (U. S. P.) formula was not quite so active as one made in the same way except that 1000 Cc. of boiling water was poured on the "bruised" leaf. The activity of the official infusion was such that 6.3 Cc. was required for each Kg. of body weight of the cat to cause death (average of two fairly concordant experiments), while an average of 4.4 Cc. was required of the second infusion per Kg. of weight (average of two fairly concordant experiments). It will be seen that the activity of the official infusion was only about 70 percent of that of the second, which represented about 90 percent of the activity of the leaf; at least, the tincture prepared from the marc of the second specimen was about one-tenth as active as an average tincture, while the tincture prepared from the dried marc of the official infusion was about one-fifth as active as the average tincture of good quality. These tinctures were evaporated to expel the alcohol, after which they were diluted with physiologic sodium chloride solution before being tested on cats in the usual manner.

When the infusion was prepared by pouring 1000 Cc. of boiling water on 15 Gm. of digitalis in No. 60 powder, its activity, indicated by the direct tests on cats, was equal to that of the tincture prepared from the same amount of this specimen of drug, and, since we have seen that the tincture exhausted the drug completely, it would appear that the infusion also represented the full activities of the powder in this case. However, the activity of the tincture made from this marc was equal to about 4 percent of the activities of the leaf, the discrepancy being within the limits of error, so far as the direct test of the infusion (two experiments) is concerned; but the test of the tincture of the marc showed conclusively that at least a very small part of the active principles actually remained in the marc.

The infusion made by pouring 1000 Cc. of boiling water on 10 Gm. of the No. 60 powder represented the drug even more completely than in the case just mentioned, and the tincture prepared from the dried marc of this infusion was practically inert; at least, the injection of the tincture (after evaporation of the alcohol) representing the marc of 3 Gm. of the drug was without effect, and the animal then required 90 percent of the average fatal dose of ouabain to cause death, indicating that the marc was about one three-hundredth part as active as the drug before infusion. This affords satisfactory evidence that 100 parts of boiling water suffice for the extraction of all of the active principles of the drug in No. 60 powder when maceration is continued for an hour.

In one case the drug was used in the form of No. 80 powder in the proportion directed by the Pharmacopoeia, 15 Gm. for 1000 Cc. of infusion, after which the activity of the marc was equal to about 3 percent of that of the original powder. This indicates that the finer powder is somewhat more nearly exhausted by that volume of water than is the coarser, since the activity of the marc of 15 Gm. of No. 60 powder was slightly greater than this;[1] but when a smaller proportion of drug is used, the fine powder is not necessary, and an infusion made from the latter is tedious to strain or filter.

VARIABILITY OF OFFICIAL INFUSION.

It hardly required the present study to arrive at the conclusion that the official infusion lacks uniformity. The long standing and extreme diversity of competent clinical opinion alone would suggest this strongly, and the method of completing the required volume of the finished product by passing water through the strainer must result in some variation in the activity of the infusion, even

[1] We have found that the removal of air from the cells of the drug by means of a vacuum pump facilitates extraction with water. The particles of a No. 60 powder have a diameter of 0.23 mm., and those of a No. 80 powder, 0.17 mm.; hence the latter are less than half as large as the former.

though the formula were faultless in other particulars. A given volume of infusion is made from 15 percent of the weight of the drug that is used in making such a volume of the tincture, but the activity of the average infusion is probably equal to less than 10 percent of that of the tincture, as indicated by the biologic test, and the difference in therapeutic effectiveness is probably much greater as a rule, because the deficiency in extraction in making the infusion falls wholly on the least soluble but the most absorbable fraction, the digitoxin or the digitoxin-like substance.

From this a somewhat paradoxical situation arises. It is well known that many druggists prepare a so-called infusion by diluting the tincture or fluidextract, while those who take pride in their profession make the infusion according to pharmacopoeial directions, and it may happen frequently that the so-called infusion prepared from the fluidextract will contain more of the digitoxin than a strictly official infusion prepared with great care, and the preparation that should be condemned by all rules of scientific pharmacy will then give better therapeutic results than the one prepared conscientiously. This is in no sense an argument for slipshod pharmacy, but is an argument for improvement in the official formula for preparing the infusion.

ADVANTAGES OF INFUSION PREPARED BY METHOD HEREIN DESCRIBED.

The infusion prepared in the manner described, in which 1 part of digitalis in No. 60 powder is treated with 100 parts of boiling water and kept for one hour in a boiling water-bath with frequent stirring, contains all of the active principles of the leaf. When this infusion is filtered and used therapeutically, the effects are the same as would be induced by the tincture in doses just one-tenth as large. If one desires the cinnamon flavor, this may be secured by adding 1 Cc. of oil of cinnamon to 10 Gm. of the powdered digitalis previous to the addition of the boiling water. Very little of the volatile oil is lost during the process of preparing the infusion.

An infusion thus prepared has these advantages over one made according to the present Pharmacopoeial method:

1. There is better extraction, whereby the infusion represents the activities of the drug completely.
2. There is uniformity of activity, in place of the variability of the official.
3. With a given degree of activity it contains a larger proportion of the slightly soluble but more readily absorbable, digitoxin or digitoxin-like substance, or substances.
4. The dosage is just ten times that of the tincture in volume.
5. The filtered infusion is transparent.
6. It may be kept indefinitely without loss of activity.

STABILITY OF INFUSION.

We are not at present concerned primarily with the question of the stability of the infusion, but we wish to correct some erroneous views that are prevalent concerning the question, for it is useless to show the way to make an infusion properly if the preparation is valueless, because of the rapidity with which it decomposes, as some believe.

No one denies that the infusion of digitalis decomposes under adverse conditions—like all other infusions of drugs that contain no antiseptic—but the question that concerns the clinician, who, for any reason, prefers to employ the infusion,

is whether it can be prepared conveniently in a reasonably stable form. Hatcher and Eggleston[1] have shown that the infusion of digitalis prepared in the manner recommended here, and filtered while hot, retains its activity with little change for several weeks when kept with reasonable care. We are able to offer evidence confirmatory of this conclusion.

One of us (R. A. H.) prepared an infusion of digitalis in the manner described, using 1 part of the powdered leaf to 100 parts of boiling water, filtering the infusion while hot, putting it into bottles which it filled completely, corking these, and sealing them with paraffin, Feb. 5, 1918. Specimens of this infusion have been tested on cats from time to time, and no perceptible loss of activity could be detected at the time of the last examination. A slight precipitate has formed in every bottle, leaving the supernatant fluid perfectly transparent, and in a few there has been a growth of mold, owing to imperfect sterilization of the corks.

THERAPEUTIC EFFECTIVENESS.

Dr. Cary Eggleston used a specimen of this infusion clinically, July 28–29, 1920, and found the dose required to induce the typical therapeutic effects to be the equivalent of that which he had established for the tincture as measured in terms of cat units. A condensed report of the essential facts are presented here through the courtesy of Dr. Eggleston. The apex rate was 145, and the radial pulse rate was 73, the pulse deficit being 72 after two days' rest in bed; the infusion was then administered at 12 midnight, 6 A.M. and at 12 noon. The apex rate was reduced to 104; the radial pulse rate rose to 86, the deficit being 18, shortly before the last dose. The condition steadily improved and the pulse deficit had nearly disappeared within four hours after the last dose, and on the following morning this deficit had disappeared, completely, the rate being 66.

The condition of the heart, as shown by the pulse deficit, was worse at the time the first dose of the infusion was administered than it had been twenty-four hours before, showing that rest in bed alone was not producing any improvement. The striking improvement that occurred within less than twelve hours hardly leaves room for doubt concerning the therapeutic effectiveness of this specimen of infusion that had been prepared nearly two and a half years previously. The infusion was filtered before being used, showing that the precipitate had not carried down the active principles in an insoluble form.

SUMMARY.

1. Tincture of digitalis was prepared, the marc of which was dried and used in the preparation of an infusion; this infusion of marc was tested on cats and found to be inert, showing that all of the active water-soluble principles of the leaf are extracted during the percolation for making the tincture.

2. This method of testing the marc affords a delicate means of testing the degree to which the active water-soluble principles are extracted during the percolation of the drug.

3. There is no essential difference in the amounts of the saponin bodies present in the tincture, and in the infusion prepared from equal weights of the leaf, and therapeutic doses of digitalis do not contain enough to induce any undesired effects.

[1] R. A. Hatcher and Cary Eggleston, "The Stability of the Infusion of Digitalis," *J. A. M. A.*, 65, 1902 (Nov. 27), 1915.

4. Infusions of digitalis were prepared in different ways. In each case the marc was washed and dried, after which it was used for the preparation of tincture, and this tincture was tested on cats in order to determine to what extent the active principles had been extracted during the preparation of the infusion.

5. The official infusion does not represent the drug completely; hence the standardization of the leaf does not insure uniformity in activity of the infusion. The variability of the infusion is at the expense of the more absorbable of the active principles.

6. The infusion prepared according to the simple method described represents the activities of the leaf completely; hence it permits of uniformity when a standardized powder is used for making it. It may be used in place of the tincture in doses just ten times the volume of those of the latter, and it becomes a matter of indifference, so far as therapeutic effects are concerned, which is used.

7. We have been unable to discover any experimental evidence to support the view, still held by many, that there is a necessary qualitative difference between the actions of the tincture and those of the infusion of digitalis, even when the latter is prepared properly.

8. An infusion of digitalis prepared in the manner recommended, and kept in completely filled and hermetically sealed bottles for more than two years and five months, retained its activity unimpaired, as shown by the results of tests on cats and by the therapeutic effects on man.

DIAGNOSTICAL ELEMENTS IN DRUG ANATOMY AND THEIR NOMENCLATURE.

BY THEO. HOLM, CLINTON, MARYLAND.

For several years the writer has been engaged in studying the morphology and anatomy in general of our native medicinal plants with the purpose of presenting the results in book form. Owing to the present extraordinarily difficult conditions relative to the publication of such work, involving many illustrations and quotations from similar works in foreign languages, there seems, at present, no possibility of securing a publisher to undertake the publication. Meanwhile, a tenth revision of the Pharmacopoeia of the United States is being prepared, and being well acquainted with the botanical part of the ninth revision, I thought that some suggestions relative to the diagnosis of a few drugs might prove useful to the collaborators.

In dealing with anatomical diagnoses of drugs as presented in the Pharmacopoeia I wish to point out that the distinction between root and root-stock (rhizome) is not always correct, causing erroneous statements as to the internal structure. Moreover, the structure itself is very often so poorly defined that it would be absolutely impossible to identify the drug in question by means of the structure quoted. We must, as a matter of fact, bear in mind that plant anatomy has developed to a remarkable extent during the last decennial; thus, structures formerly considered peculiar to certain genera are known now to be common to many others, besidethat several new characteristic structures have been discovered, which *ad interim* are considered peculiar to some few families or genera. In other words, the anatomical characterization offered in the U. S. Pharmacopoeia might be made more helpful to