REMARKS ON DIGITALIS.*

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It is generally stated in text-books and also in the United States and other pharmacopœias that the digitalis leaves of the second year's growth are preferable to those of other years, and that the cultivated ones are inferior to the wild ones. Recent observations do not seem to support this statement. F. H. Carr, in the *American Journal of Pharmacy*, states that the first and second year's growths have proved identical in their activity, and the cultivated leaves are at least as active as those wild grown. Hatcher, who in his "Text-book of Materia Medica," by Hatcher and Sollmann, indorses the preference of the second years' growth, has since, in a recent article (*Drug. Cir.*, 1914), claimed equal value for first and second years' leaves, as well as for cultivated leaves in comparison with wild ones. Lloyd's observations also confirm this view, and he attributes the erroneous statement about the second year to the fact that formerly also the root was used, which in the first year is insignificant and sappy, while the second year's root is larger and heavier and more pronounced in quality. There may be another reason, however, for adhering so long to the second year's leaves as better. The statement in the text-books is followed by the other one, "gathered at the commencement of flowering." Now, digitalis does not flower till the second year, and leaves could not be gathered in the first year at the commencement of flowering. As the flowers were also used formerly, and are used today in Japan, it can be understood how the statement of the second year's growth originated, flowers and leaves being gathered at the same time. According to the best investigators, this statement should therefore be changed to "leaves of the first or second year's growth should be used."

Professor Hivohashi, of the University of Tokio, Japan, who made extensive investigations in digitalis, states (*Apoth. Zg.*, 1913, vol. 28, p. 9) that digitalis *flowers* probably contain more of the active constituents than do the leaves, and the buds are more active than are the expanded flowers.

As to the preservation of the gathered leaves, all kinds of more or less complicated directions are given in the various pharmacopœias. According to recent literature, however, foxglove leaves do not differ materially from most other vegetable drugs; that is, they will deteriorate if kept carelessly, and keep almost indefinitely if properly stored in air-tight containers in dark places. The changes that do undoubtedly happen take place in the time between gathering and marketing, according to the manner in which the drying is done.

There are four pharmaceutical preparations of digitalis official in our pharmacopœia, viz.: The extract, the fluidextract, the tincture, and the infusion, of which the first one is but rarely and the second one not often used. According to all authorities, the tincture and infusion are the two most reliable preparations,

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but there is a vast difference of opinion as to the relative value of the two. Herzfeld states that:

"I believe that in this country the tincture is the least reliable of all preparations of digitalis, particularly since, for the sake of convenience, it is frequently prepared by diluting the fluidextract, which in itself may be inferior."

Other authorities also dwell on the improper preparation of tinctures from fluidextracts. It is well worth while to stop a minute to investigate this charge. I myself have in former years, when physicians made this remark, asked them how many pharmacists, to their positive knowledge, made their tinctures from fluidextracts. Generally the answer was: "Well, of course, I do not know, but conclude, from the fact that sometimes tinctures do not produce the desired effect, that they are made improperly." And when I replied: "Doctor, are you sure that in such cases you always ordered the right medicine?" the answer would be: "Of course I did; I diagnosed the case myself." In other words, whenever the patient does not respond to the treatment the fault lies with the pharmacist, but not with the physician. The unbiased observer will say, if men are apt to make mistakes there will be as many mistakes made by physicians in diagnosing as by pharmacists in dispensing. I personally do not believe that the practice of making tincture from fluidextract is general; it may prevail among lazy and indifferent druggists, who hardly have any prescription trade for this very reason.

Coming back to our subject, there is besides Doctor Herzfeld no other authority to reject the tincture. As a rule, the tincture is preferred to the infusion, so far as reliability is concerned, and whenever the full cardiac effect of digitalis is required. As a diuretic, in cases of faulty circulation of blood through the kidneys, the infusion is preferred by probably 95 percent of all practitioners. An exception is Doctor R. A. Hatcher, who in a recent paper states that:

"As a matter of fact, a properly-made infusion, as well as the tincture, contains all of the therapeutic active principles of digitalis."

He tries to prove this statement by saying that the marc left after making the tincture is inert, and if an infusion be made with this marc and tested on a frog, the truth of this statement becomes apparent. It is to be regretted that he did not also examine the marc left after making the infusion. Later on, in the same article, he says:

"An infusion from a fluidextract might be unsightly, but it would probably be more active than the official infusion which one would obtain from the nearest pharmacy. This practice is distinctly not advocated, but pharmacists should understand the fact."

We ask: Why not advocate it if it makes a better infusion? And if the tincture and infusion are of equal value, why not make the infusion from the tincture, or why not delete one or the other?

In direct contradiction to Hatcher's results we will cite Herzfeld:

"According to the methods of Keller-Fromme, no digitoxin or digitalin could be detected in an infusion prepared according to the U. S. P., while in an infusion, made after my method, as high as 0.02086 percent digitoxin could be found."

Doctor Herzfeld's method is as follows: The leaves are finely broken up and

freed from the stems and ribs. They are then covered with the entire quantity of boiling water and allowed to digest upon the water-bath at 50° C. for one hour. When cooled down to about 32° C. an amount of alcohol corresponding to 10 percent of the finished infusion is added and the whole permitted to stand for twelve hours. The resulting product is then filtered, the leaves expressed, and the necessary amount of water added to restore the volume. Later on he says that this "infusion" (it is rather a weak tincture) should always be prepared fresh. This would compel the patient to wait about fourteen hours for his medicine, a rather long wait for cardiac patients.

In an editorial of the *American Druggist,* 1913, vol. 16, p. 12, the statement is made that:

"According to Henry Beates, not one physician in ten can tell the difference in the effect produced by an infusion of digitalis made from a fluidextract and that produced by one made from the assayed leaf."

This may be interpreted that physicians are not able to tell the effect of their medicine, or that Doctor Hatcher's statement of infusions made from fluidextract is correct.

As to the reliability of the fluidextract itself, we quote J. D. Riedel:

"Fluidextract of digitalis U. S. P. VIII was found to vary in specific gravity from 0.945 to 0.991, and in extract content from 10.30 to 17.41 percent."

And Puckner (*Jour. Amer. Med. Assn.,* 1913) claims:

"Examination of twenty samples of fluidextract of digitalis confirmed the generally-held belief that commercial digitalis preparations vary most widely. The most active were found to be nearly four times as active as the weakest."

Against this statement protests were afterwards printed in a number of pharmaceutical publications.

In the coming pharmacopœia the formula for the infusion of digitalis will remain the same while the alcohol in the tincture will be increased to 60 percent and the fluidextract to 70 percent. It is claimed that this large amount of alcohol is necessary to preserve the preparation.

I regret that the formula for the infusion will remain unchanged. It is now made with the boiling water and 10 percent of alcohol is added after straining. For what purpose is the alcohol added? The properly prepared infusion without alcohol will keep long enough to be taken, and for a longer preservation the amount of alcohol is inadequate. The alcohol should be omitted and the remark: "To be freshly prepared, when wanted," added to the formula. As it stands now, the presence of alcohol misleads many thoughtless pharmacists to think that the infusion may be kept in stock.

Prolonged medication with tincture of digitalis often produces nausea and other untoward effects. It is stated that a certain fat or fixed oil present in the leaves is the cause. As this substance is soluble in petroleum benzin, the leaves can be freed from it by subjecting them to the action of benzin before making the tincture. The general verdict of the medical profession is in favor of this fat-free tincture, although Hatcher and others deny its preference.

According to Hatcher's experiment, isolated fat from digitalis proved harmless. This probably is true, but would be no proof that even a small amount of this fat in the presence of various alkaloids may not influence their action.

As to the source of the best leaves of foxglove not much literature is available. It is stated that the plant grows in England, Middle Europe, and also in America, and here and there the timid statement is made that soil containing iron is best adapted for its growth. According to Gehe (*Handelsberichte,* 1913, p. 84):

"Digitalis is found generally on soil containing iron and manganese, and does not occur in Switzerland on this account. It is assumed that manganese is essential for the life of digitalis."

In contradiction of this, Hatcher says:

"Another curious misconception regarding digitalis which is hard to explain is that the leaf grown in certain regions is more active than that grown in other localities."

This is probably the most remarkable statement in Hatcher's excellent paper. Whosoever has paid attention to the development of agricultural chemistry, the introduction and first results of which have made Liebig immortal, would rather say: "It would be hard to explain if the leaf grown in certain regions were not more or less active than that grown in other localities." I do not think that a plant of powerful and characteristic properties is known that does not change its nature nor produce its constituents in a larger or smaller quantity when transplanted to a new soil. Every farmer in France and Germany knows that the same potato planted in a marshy soil will produce a different tuber than when planted in a sandy soil. Grape vines brought from the Rhine or Garonne to California will flower and bring fruit, but the grape differs in flavor and amount of alcohol produced. The same vine even differs in different parts of California. Many European aromatic flowers, like chamomile, mullein, and others, grow abundantly in America, but lack the ingredients that make them valuable; and they even differ in aromatic properties in different parts of the home country. Why should digitalis be an exception to this general rule? Doctor Thoms, of the Pharmaceutical Institute of Berlin, one of the best and most careful pharmacologists living, states in the last volume of the *Arbeiten aus dem Pharmazeutischen Institut,* 1914, p. 202, speaking of the difficulties of cultivating certain medicinal plants:

"How important, for instance, it would be to have digitalis, which in different parts of Germany is subject to such extraordinary variations in respect to its active principles, under proper scientific cultivation and discover the conditions which for the growth and production of the active principles of digitalis are most favorable."

The chemistry of digitalis is still more confused than its pharmacy, and so far every new assayer has discovered—or claims to have discovered—new principles of various nature. The number of so-called active constituents of the plant is growing daily. Merck & Co., in their annual report of 1911, mention 92 different articles, with their discoverers and properties, and the number has been increased considerably since then. Many of these are identical, and a good many are mentioned only in the papers published by their authors, but were never isolated or brought in the market. Among these many names four stand out prominently, namely, digitalin, digitonin, digitoxin, and digitalein.

The oldest one of these, digitalin-Nativelle, was isolated by the French chemist Nativelle, who claimed it to be a pure substance, while Schmiedeberg, who made

an extensive examination of the plant, pronounces Nativelle's digitalin a mixture of several substances, and gave the name digitalin to another chemically uniform, amorphous body for which he presented a formula. Another digitalin was isolated by Kiliani, another by Homolle-Quevenne, another by Lancelot, another by Lebourdais, and so on. In Merck's list the name of digitalin appears thirty-seven times, each time denoting a different article. No wonder that a confusion prevails and that prescribers and dispensers are at a loss what is meant by digitalin. It is not the object of this paper to enter into the merits of these numerous glucosides for each of which the discoverer or manufacturer claims a certain superiority over others. But in view of these different results obtained by men of great learning, long experience, and renowned ability, we are led to the question if there is not a reason for this disagreement and if perhaps some fundamental facts or principles have been overlooked.

Now, in trying to bring the various results into some classification, we notice that nearly all agree on the fact that some of the products are soluble in water, some insoluble in water but soluble in alcohol. Kiliani states that digitoxin is insoluble in water, Hatcher makes the same statement, while Cloetta separated a soluble digitoxin, to which the name of digalen was given. It is further stated that, while digitoxin is insoluble in water, it becomes soluble in water, best in hot water, in the presence of a certain saponin that is also present and which, according to some authorities, is identical with digitalein, according to others with digitonin. The presence of a saponin is also claimed by a number of other investigators, but by no means by all. It is on this basis that Hatcher makes the claim that the infusion contains all the active ingredients of digitalis held in solution by saponin. He therefore supposes that no change takes place when the infusion cools, although every druggist knows that a slight precipitate forms, and he also must suppose that this saponin and the insoluble digitoxin are present always in the right proportion,—that is, enough saponin to dissolve the digitoxin. As a matter of fact, however, the presence of saponin is still in doubt, and even those who claim its presence do not agree on the quantity, some speaking of a trace only. But nearly all investigators agree on the instability of the various digitalis preparations and the ease with which the one is changed into the other. Some doubt the presence of any pre-existing digitoxin in the plant, believing that it forms, after the leaves are gathered, through the influence of this saponin. We are reminded of bitter almonds, where the amygdalin, through the action of a ferment, is changed into benzaldehyde, hydrocyanic acid and glucose. Might there not be a similar cause in digitalis that would account for the evasiveness of the various chemicals? It cannot be doubted that a soil containing iron and manganese is most favorable to the development of the plant, and, if the claim that manganese is necessary for the production of digitoxin is correct, what hinders us to suspect a certain relationship between manganese and this complex body? To the adherer of the infallibility of the theory of elements such a thought may appear like the outgrowth of a disordered imagination. But other apparently impossible theories have been proved to be founded on facts, and a chemical genius may come some day and upset many of our pet theories. The inadequacy of the chemistry of digitalis should certainly lead the investigators to consider the plant as a harmonious total, and not take out its chemistry as a

part that can be studied and understood without reference to its whole life and development and productions.

It would be wrong to write a review of digitalis without mentioning the physiological tests to which this plant has been subjected in the last two decades. Here the same confusion reigns as in its chemistry. Naturally so. How can we successfully test a chemical before we have absolute knowledge of its properties? Frogs, mice, rabbits, dogs, cats, have been used to establish what is called a standard. But no two investigators agree. These physiological tests are beyond the scope of the pharmacist and physician, as they require especially-arranged biological laboratories that cannot be established without considerable expense. In the same way the physiological chemist requires special training and long experience. Consequently these laboratories are, as a rule, constructed by large manufacturing houses who employ the best talent that they can find. It is natural that these men work in the interest of the firm that employs them and that their researches always confirm the superiority of the preparation that their employers prepare. This is no adverse criticism of their activity. The commercial houses that go to the expense of establishing and maintaining such laboratories try, without doubt, to produce the best articles in every line, and as each and every digitalis preparation has some advantages and characteristics of its own, it is but natural that these advantages are exploited in preference to others. But science gains but little by these efforts, and the skepticism that many entertain in reference to biological tests is justified. This became evident some years ago in New York, when the representatives of a large German manufacturing house undertook a crusade against the sins of certain druggists, as stated, in reality, however, to push and advertise a certain proprietary article. Numerous prescriptions were written by their physicians and then analyzed by chemists of repute, and incidentally a result was obtained that was not looked for. Among the prescriptions were a number for tincture of digitalis. The dispensed articles were sent to a biologist of a good name, who conducted the physiological laboratory of a manufacturing house. He tested them *secundum artem,* without prejudice, and his report was published. It now happened that some of the samples had come from his own house, and had been tested by him, and a certificate as to the strength had been attached to the containers. In his report he declared some of these same tinctures worthless, others too strong. Guaranteed assayed tinctures from other firms shared the same fate. No greater discredit could have been thrown on biological assaying by its worst enemy than by these careful, conscientious examinations. When they were introduced into the pharmacopœia it was stated that they were needed on account of the inadequacy of the chemical test; but, far from solving the problem, they have only added to the confusion and uncertainty.

Before closing I wish to refer again to Thoms' *Arbeiten aus dem Pharmazeutischen Institut.* On page 204 L. Rosenthaler is quoted as follows:

"I am of the opinion that plants produce some of their constituents as a protective weapon against vegetable or animal attacks; but as their enemies do not always have the same geographical distribution as the plants themselves, these protective principles are not needed where the respective enemies are lacking, and consequently are not produced. This supposition explains the fact that the

amount of digitalin of cultivated digitalis is less than that of the wild-grown plants."

This is not a new theory. It has been shown that the cinchona tree produces quinine as a protective against the attacks of certain insects and bacteria, and whenever the tree is transplanted to countries where it is not attacked by these enemies the production of quinine gradually decreases. I also refer to Doctor R. C. Eccles's paper on "Pharmaceutical Bacteriology" in the *Proceedings of the American Pharmaceutical Association,* 1894.

Many other instances of self-protection of plants against surrounding enemies, be they of vegetable or animal nature, or conditions of the atmosphere, could be mentioned. Here, then, is an unexplored field. We generally do not grant self-consciousness and individuality to plant organism, but the few observations that we have made seem to indicate that there is in these low organisms far more foresight and judgment in action than we admit. They may not think, but their work and productions could not be more correct and logical if they had been planned by the most highly developed mind. Nobody ever expects to discover the thoughts of a human being by dissecting his body after death and analyzing the various parts. Can we expect to explore plant life in its conception and its influence on surrounding Nature by dissecting the plant and analyzing what is left after its death?

LITERATURE.

A. A. Herzfeld, M. D.: Remarks on the Use of Digitalis.
R. A. Hatcher: Digitalis and its Preparations.
J. W. Lloyd: A Treatise on Digitalis.
Merck & Co.: Digitalis Glucosides and Allied Drugs.
Doctor H. Thoms: *Arbeiten aus dem Pharmazeutischen Institut,* Berlin.
Gehe & Co.: *Handelsberichte,* 1913.
Schmiedeberg: Pharmacologie.
H. Kiliani: A Review of the Chemistry of Digitalis.
C. E. Vanderkleed: Proc. Pa. Pharm. Assn., 1913.
S. Hirahuschi: Yahngakuasshi No. 369.
Am. J. Pharm.: 1913.
J. Am. Ph. A.: 1913-1914.
Am. Druggist: 1913.
Apotheker Zg.: New York, 1913.
W. A. Puckner: J. Am. Med. Assn., 1913.
O. Cockayne: Leechdoms, Wortcunning and Starkraft, before the Norman invasion.
J. Gerarde: The Herball of General Historie of Plantes, 1597.
F. A. Fluckiger: Pharmacographia.
L. W. Rowe: Proc. Am. Ph. Assn., 1914.
Britton & Brown: Illustrated Flora.
E. R. Eccles: Am. Ph. Assn., 1894.
H. K. Mulford: Pamphlets on Digitalis, etc.
Hoffmann-La Roche: *Originalarbeiten,* 1913, 1.