THE EFFECT OF THE DIGESTIVE SECRETIONS ON THE ACTIVITY OF DIGITALIS AND ALLIED DRUGS *

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As is well known, the glucosids in general are comparatively unstable chemical substances and are easily broken down into a sugar and some other substance. A number of factors are operative in splitting up the glucosidal molecule, but chief among them, especially in the presence of heat, are certain enzymes, the alkalies, and the mineral acids.

In view of these facts it is not at all surprising to find that certain of the digitalis glucosids have been reported to be broken down to a greater or lesser degree, either by the enzymes of the gastric or pancreatic secretion, or by the acids or alkalies added to these enzymes to make them active. Three researches may be noted as specifically showing this deterioration.

In 1896 Deucher observed clinically in cases of heart disease and dropsical conditions that digitalin verum was almost invariably much more potent when given subcutaneously than when given by the mouth. As this difference was much greater than is common when other drugs are thus administered he came to the conclusion that the digitalin was probably changed either in the stomach or in the intestinal tract into partially inert compounds by the action of the hydrochloric acid of the stomach or by the ferments found in the stomach and intestine.

In an effort to prove whether this hypothesis was correct or not Deucher[1] carried out a series of experiments in which definite amounts of digitalin verum were subjected, with certain exceptions, for twenty-four hours to the action of artificial digestive secretions. For the purpose of subsequently determining the changes, if any, which were produced, frogs were injected with equivalent amounts of the digitalin, subjected to artificial digestion, and an undigested control, the time of appearance of the systolic stoppage of the exposed hearts being noted as an end reaction. From these experiments he came to the conclusion that the digitalin was partially broken up into inert compounds by the action chiefly of dilute hydrochloric acid, 0.2 per cent., although the presence of pepsin seemed to accelerate the breaking down to some extent. The pancreatic solution employed by him was found to be inactive.

Deucher further suggested the possibility that the other glucosids of the digitalis group might be broken up by the action of the digestive agents, but he seems to have only made experiments with digitalin verum.

In 1907 Löwy[2] supplemented Deucher's work by investigating the effect of acid, acid pepsin, and alkalies, on the infusion of digitalis, and on the pure principles helleborein and strophanthin. He found that in the presence of heat, after twenty-four hours, hydrochloric acid and acid pepsin solutions reduced the activity of the infusion and of helleborein. He concluded, however, that the 0.2 per cent. acid at the body temperature alone caused the deterioration noted and that the pepsin was without effect. Löwy also noted that moderately strong alkali solutions (0.5 per cent.) decreased the activity of the infusion.

The activity of strophanthin was not found to be changed by acid pepsin digestion.

As opposed to this latter view Hatcher,[3] in working with strophanthin, came to the conclusion that both acid peptic and alkaline pancreatic digestion for two hours caused some diminution in the toxicity of the strophanthin. In considering the opposed finding of the two investigators, however, it is to be noted that strophanthin is an indefinite term and it is quite possible that the two observers worked with different strophanthins, one of which was more easily attacked by the digestive agents.

As a fact of considerably more importance, it was found by Hatcher and Bailey[4] that the toxic dose of strophanthin for cats by the stomach was five or six times that by intravenous injection, and after a lengthy series of experiments they came to the conclusion that the lessened activity of the drug when given by the stomach depended only to a small degree on the destructive action of the digestive secretions, and that the chief factor in decreasing its toxicity depended on a delayed absorption.

Findings such as these with digitalin verum, with the infusion, and with strophanthin, raises the very important question of proper dosage of these bodies. With a drug so powerful as digitalis, no therapy can be regarded as safe unless the exact strength of the drug employed is known, and if deterioration goes on in the stomach and intestines before absorption these facts should be known.

To this end a number of further experiments along this line were deemed worth while, not only as confirmatory of the findings above recorded, but also to test the rate of deterioration by making use of an exact assay method for determining the degree of change of the substances in question, after subjecting them to the action of the digestive agents for a time more nearly analogous to the conditions found *in vivo*. These were accordingly tested to determine the degree of deterioration when subjected to the action of hydrochloric acid, with and without the addition of pepsin, and of alkali with pancreatin, and in certain instances of emulsin, a glucosidal-splitting ferment found in bitter almond and other seeds.

For the purpose of assaying the preparation before and after digestion the one-hour frog-heart method was used. This, in brief, consists in determining the least amount of the drug which will just produce permanent systole of the ventricle of the frog *Rana pipiens* at the end of one hour. The drug is injected in solution into the anterior lymph-sac, and a temperature of 22 C. is maintained throughout the experiment, the heart being exposed at the end of one hour.

DIGITOXIN

A control was first established for digitoxin by dissolving a weighed amount in 30 per cent. alcohol. The assay value by the method briefly described above was found to be 0.008 mg. per gram of frog weight.

To test the effect of the gastric secretion on digitoxin, a weighed amount placed in a cylinder was subjected to the action of an artificial gastric juice containing 0.25 per cent. hydrochloric acid and 0.1 per cent. scale pepsin. The undissolved digitoxin was placed in an incubator

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1. Deucher: Deutsch. Archiv. f. klin. Med., 1896, lvii, 1; 1896-7, lviii, 47.
2. Löwy: Wien. klin. Wchnschr., 1906, xix, 1157.
3. Hatcher: Am. Jour. Physiol., 1908, xxiii, 303.
4. Hatcher, R. A., and Bailey, H. C.: Tincture of Strophanthus and Strophanthin, THE JOURNAL A. M. A., Jan. 2, 1909, p. 5.

at 38 for three hours, and was then taken up with enough alcohol to just form complete solution. This solution assayed 0.011 mg. per gram frog weight. A second weighed amount similarly treated assayed after three hours in the incubator, 0.010 mg. per gram frog weight. Eighteen hours later this solution of digitoxin which was kept at room temperature assayed 0.013 mg. per gram frog weight.

A weighed amount of digitoxin was then subjected to the action of 0.25 per cent. hydrochloric acid for three hours at 38°. At the end of this time it assayed 0.01 mg. per gram frog weight; at the end of eighteen hours at room temperature it assayed 0.014 mg. This decrease in activity, approximately parallelling that of the acid pepsin digestion, would indicate that the acid alone was the active agent in breaking down the digitoxin molecule, and that the pepsin was inactive.

Pancreatic secretion containing the pancreatin 0.1 per cent. dissolved in 0.15 per cent. sodium carbonate was allowed to act at 38° on weighed amounts of digitoxin for periods of three hours, and also eighteen hours at room temperature. At the end of three hours the assay gave 0.008 mg. per gram frog weight in duplicate experiments, thus showing no decomposition from pancreatic digestion. When subjected to digestion for eighteen hours, however, there was some deterioration, the assay value being 0.010 mg.

FRENCH DIGITALIN

French digitalin, consisting mainly of digitalin verum, was tested, the undigested control assaying 0.012 mg. per gram of frog weight. A weighed amount was subjected to the action of an artificial gastric juice for a period of three hours. It then assayed 0.013 mg. per gram weight. After eighteen hours at room temperature the assay showed further deterioration, 0.016 mg. per gram frog weight being necessary to produce systolic stoppage of the heart. Hydrochloric acid alone was approximately equally effective in causing deterioration as the combined acid and pepsin.

No deterioration was obtained under treatment of weighed amounts of French digitalin with an artificial pancreatic secretion.

DIGITALEIN

Digitalein was assayed, the effective dose being 0.024 mg. per gram of frog weight.

In a weighed amount, 0.25 per cent. hydrochloric acid and 0.1 pepsin were added. After digestion at 38° for three hours the assay showed a deterioration, the amount then necessary to produce systolic stoppage of the heart being 0.032 mg. Hydrochloric acid, 0.25 per cent., without the pepsin caused deterioration so that at the end of three hours at 38°, 0.030 mg. was required to bring the ventricle into permanent systole.

Under artificial pancreatic digestion very little, or no deterioration, was observed. A value of 0.026 mg. was obtained, but owing to incomplete absorption in a large number of assays this result is to be questioned.

Digitalein was tested to determine the effect of emulsin, the glucosid-splitting ferment of bitter almond seeds. The assay value after three hours at 38° gave 0.028 mg. as the amount required to produce systole of the ventricle, thus showing a slight decomposition.

TINCTURE OF DIGITALIS

Having found by the above assays that the chief glucosids found in digitalis were less active after digestion with an artificial gastric juice, experiments were carried out with the tincture. As the glucosids digitoxin, digitalin, and digitalein, are all represented in the tincture, these experiments would also be expected to give analogous results and to be in the nature of duplicates.

The first tincture to be assayed gave a value before digestion of 0.010 c.c. per gram of frog weight. After evaporation of the alcohol, 0.25 per cent. hydrochloric acid and 0.1 per cent. pepsin were added and kept at 38° for three hours. At the end of that time the assay value was found to be 0.014 c.c.

A second tincture assayed 0.008 c.c. per gram of frog weight. An evaporated portion was subjected to artificial gastric digestion for three hours at 38°, and then gave an assay value of 0.012 c.c. After standing eighteen hours at room temperature the assay value was 0.016 c.c.

This tincture was subjected also to the action of an artificial pancreatic juice made up with 0.2 per cent. alkali and 0.1 per cent. pancreatin. In two experiments there was about 25 per cent. deterioration after three hours at 38°. Whether this is invariable cannot be stated, but in view of the fact that none of the glucosids showed deterioration, it may be questioned. It also brings up the point that in the crude tincture, enzymes natural to the digitalis leaf may become especially active with an alkali present, and thus explain the discrepancy in results. This point will be further investigated.

STROPHANTHIN

The discrepancy in the dose of strophanthin is so great by stomach and intravenously that, it was hoped in view of the deterioration with the digitalis glucosids, an investigation of the changes going on under artificial digestion might throw some further light on the question.

The control assay of strophanthin gave a value of 0.00055 mg. per gram of frog weight.

A weighed amount of strophanthin under artificial gastric digestion assayed 0.00065 mg.; thirty-six hours later the assay showed marked deterioration at room temperature, the value being 0.0015 mg. A second weighed sample after three hours' digestion assayed 0.0007 mg., and at the end of twenty-four hours at room temperature, 0.0010 mg. Pancreatic digestion showed much less action on strophanthin. A sample subjected to alkaline pancreatic juice for three hours assayed 0.0006 mg.; twenty-four hours later the assay was still 0.0006 mg. A second sample under pancreatic digestion for three hours showed no deterioration, nor when tested after twenty-four and thirty-six hours at room temperature.

Emulsin had a very slight effect, reducing the activity after three hours in the incubator, to 0.0007 mg. per gram frog weight.

That strophanthin might also be destroyed in the liver is a possible conclusion, but experiments with minced cats' and frogs' livers showed that no decomposition took place after two hours at 38°.

From this series of experiments it is to be noted that the acid of the gastric secretion invariably causes some diminution in the action of the glucosids of digitalis and strophanthus. It is not believed, however, that an exact determination of the degree of decomposition in practice can be made, for in all probability the rate is somewhat more rapid under actual conditions, owing to the motility of the stomach and the comparatively greater dilution of the glucosids. The rate of deterioration, however, appears to be about the same for the various glucosids, about 25 to 35 per cent. in three hours, so that

this fact need not be taken into notice in therapeutics. The further factor, however, of the action of the decomposition products of these glucosids must be considered, and it is possible that certain of the untoward effects of digitalis medication may be due to them. At any rate in so far as is possible it would seem advisable to prevent such decomposition, and it is suggested that this might be done by requiring the official galenical preparations to be neutral, and in practice, by prescribing an alkali along with digitalis. Ignoring the specific irritant action of these bodies on the intestinal tract also, it would seem advisable that the drug should be given between, rather than at meals, when the gastric acidity is at the maximum and such a procedure might possibly not cause undue irritation if a large quantity of fluid were taken at the same time.

SOME FACTORS IN THE TREATMENT OF MYOCARDIAL LESIONS *

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The difficulty of arriving at a positive conclusion as to the exact nature of the tissue changes existing in the cardiac muscle of patients presenting undoubted evidences of heart disease makes it prudent to discuss the following cases under a clinical title rather than one based on morbid anatomy, for few, if any, can distinguish between the signs of chronic myocarditis and those of degeneration, or can say when the molecular disturbance consequent on febrile or other intoxication ends and the congestion with small-cell infiltration of a myocarditis begins. It is true that the physician draws his own mental picture of the changes in each case, but he will have difficulty in describing it in words that will stand the criticism of his audience.

The teachings of Dr. James MacKenzie and other members of the English school have done much to increase our knowledge regarding diseases of the heart, and have given additional impetus to original research in this particular branch of medicine, but, up to the present time, this advance does not appear to be accompanied by any corresponding progress in methods of treatment. It may be an erroneous impression on my part, but it would appear as if the tendency were to give exclusive attention to remedies which influence the mechanism of the heart and to neglect or to discuss superficially treatment that might alleviate or arrest changes in the cardiac muscle itself. Only too often do cases present themselves in which all treatment seems to have ceased after a successful or unsuccessful effort has been made to whip a heart into compensation by means of some member of the digitalis group, and although in many instances this is the result of the patient ceasing to present himself for advice just so soon as he feels well enough to attend to his daily vocation, nevertheless this would be very greatly modified if from the commencement the patient were made to understand that after his apparent recovery it would be necessary for him to follow certain rules of life or to continue some particular line of medication if he wished to retain his restored health.

My object in considering "some factors in the treatment of myocardial lesions" is to emphasize the benefits that very often accrue from the systematic and persistent use of these remedies, generally described as alteratives, which in some direct, but imperfectly understood manner, influence the nutrition of the myocardium. I have no new agents to suggest; all of them are familiar to every practitioner, but in the majority of books they are mentioned so cursorily in comparison with the prolonged discussions on digitalis, strophanthus and squills that very often their value is underestimated, no fair trial is given them and consequently many cases that would have been benefited by their early and persistent administration are allowed to go along unchecked until the patient becomes a chronic sufferer, to whom death comes as a merciful relief.

When we are brought in contact with a weak myocardium the first endeavor is clearly to depict the case, to decide whether the condition is associated with a valvular lesion, as in combined endocarditis and myocarditis, or if it is secondary to a valvular lesion, as in failed compensation; to satisfy ourselves whether it is due to lack of nutrition, as in aortic and coronary disease and anemia, or is the result of toxins such as we find in influenza, syphilis, uterine fibroids, habitual constipation or disordered metabolism. Is it not possible that, while it is fully realized how much all the organs of the body depend on cardiac efficiency for their functional activity, it is not so constantly borne in mind that disturbance in any part of the body may have a deleterious influence on the heart? I mention this because much of the recent literature on disease of the circulatory system conveys the impression that individual study of diseases of the heart is liable to lead to the same results as specialization in the study of other organs; it narrows the clinical horizon; and while this may not be fraught with much danger to the man who is treating only the organs of special sense, it is absolutely inadmissible to the internist who is dealing with viscera which are so mutually dependent on one another for the normal performance of their functions.

One of the first criticisms that might be made regarding the use of such constitutional remedies as the iodids in the treatment of myocardial disorders is the fact that very frequently their administration is not continued for a sufficient length of time to obtain results. In cases of syphilis the physician does not hesitate to keep his patient taking these remedies for weeks, or, it may be, months, without any interruption; but in the treatment of myocardial inefficiency he very frequently stops after ten days or two weeks because he has not obtained the same brilliant results that so often follow the use of digitalis for the same length of time; he seems to argue that because digitalis often restores compensation in a case of valvular disease within two weeks, therefore, the iodids, if they are going to be of any service, must in the same length of time restore to full activity muscular fibers which have been poisoned and in which the toxic process is still going on; he seems to forget that he is not dealing with a cardiac stimulant, but that some form of malnutrition or imperfect elimination has to be corrected before the muscle can recover so as fully to respond to stimulation, and it is this correction that the iodids accomplish.

The following case was one that impressed me very much with the benefits that may sometimes arise from the prolonged use of iodids:

CASE 1.—Mr. A. W. consulted me in August, 1904. For some weeks he had suffered from dyspnea on exertion and hardly a night passed without an attack of cardiac asthma, so that latterly he dreaded going to bed and always slept in an armchair. He was of spare build, had led a good life,

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