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DIGITALIS AND SOME OF ITS DERIVATIVES[1]

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Ladies and Gentlemen: I WISH first to acknowledge the honor conferred upon me by the New England Heart Association through the invitation to address you this evening. The opportunity to discuss the subject of digitalis in the city of Boston, steeped in the traditions of cardiovascular research and rich in eminent leadership in cardiological practice, is indeed a great privilage. I feel doubly honored to have this opportunity on the occasion arranged as a tribute to the memory of one of New England's most distinguished physicians.

I have planned to present the results of experiments and to discuss briefly lines of evidence having to do with various phases of the nature of the action of digitalis and its glycosides. Some are based on experiments performed on animals, others directly on human subjects. The account is not intended to exhaust the subject. It represents for the most part explorations in this field carried out during the past few years by a group of collaborators in our laboratory and clinics.[2]

One of the popular formulations regarding the mechanism by which digitalis abolishes heart failure is based on the view that the essential action of digitalis is an action on the "tone" of the heart muscle. There is no general agreement as to the nature of the

[1] Annual Jackson Lecture of the New England Heart Association, delivered at the Boston Medical Library, April 24, 1942.

[2] From the Department of Pharmacology of Cornell University Medical College and the Cardiac Services of the Beth Israel Hospital and the Hospital for Joint Diseases in New York City. Chief collaborators: Drs. McKeen Cattell, Nathaniel T. Kwit, Janet Travell, Harold Otto, Milton Kramer, Theodore Fox and William Zahm.

property called "tone," but it is usually measured as the resting length of the muscle or the diastolic size of the heart. The work of Dr. Alfred Cohn and his collaborators, Harold Stewart, Steele and others,[3] has presented strong evidence of a change in the "tone" of the heart muscle after digitalis, but the complex nature of the mechanisms prevailing in the intact animal or human makes it impossible to obtain in them entirely satisfactory evidence as to whether the change in "tone" is primary or secondary. We have devised experiments with a simpler preparation of the mammalian heart muscle.[4] These are made with the papillary muscle of the right ventricle of the cat. It is a very small muscle, usually about 8 to 12 mm in length, and weighing about 15 to 20 mg. It is set up on an isometric lever which measures the tension the muscle develops. It is driven at a fixed rate. The tension changes are recorded photographically. In such an experiment the systolic force of the papillary muscle declines until it reaches a low level. Then the introduction of a digitalis glycoside in a concentration similar to that likely to prevail after therapeutic doses in man promptly restores the failing systolic force.

Fig. 1 shows the results of an experiment in which we recorded both "tone" and systolic force. The lever is adjusted to allow the muscle to lengthen or shorten,

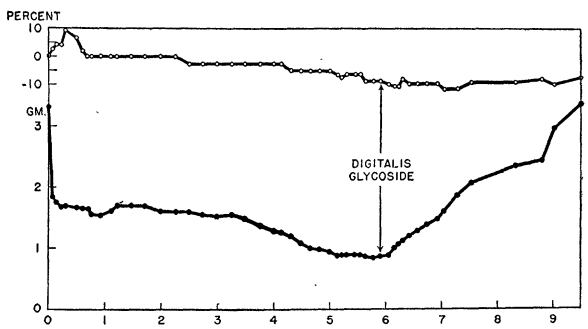

FIG. 1. Effect of digitalis on heart muscle "tone" and systolic force. The upper curve shows the percentage changes in the resting length or "tone" of the isolated papillary muscle of the cat. The lower curve shows that force of contraction of the muscle which is stimulated by a condenser discharge. The muscle length was measured at a constant resting tension. Note the increased force of contraction which occurred after digitalis, without change in "tone."

whenever it indicates a disposition to do so by a rise or fall of its diastolic tension. The record of these adjustments gives an account of the changes in resting length or changes in "tone" throughout the experiment. The upper line in this figure represents "tone" changes, and the lower line represents the changes in systolic force. It may be noted that there are variable changes in the "tone" of the muscle throughout the experiment, and the systolic tension falls off at first rapidly and then more gradually. When a fairly level period is reached, ouabain is introduced into the chamber and within five to ten minutes the systolic force begins to rise, but the "tone" remains unchanged.

This is an experiment in which all secondary mechanisms which might influence the resting length or the "tone" of the muscle have been excluded. The rate is constant. There is no coronary circulation. There is no peripheral circulation nor return flow. When all factors which can indirectly influence the diastolic size of the heart are eliminated, digitalis does not shorten the resting length of the heart muscle.

From such experiments we conclude that digitalis does not exert a primary action on "tone," but a primary action on systolic force of the heart, and that any changes in size or "tone" of the heart must represent secondary adjustments. Visscher and his collaborators[5] have recently expressed a similar view on the basis of experiments of another kind.

Another view concerning the primary mechanism of digitalis action which has gained some recognition in the past few years is based on the experiments of Dock and Tainter,[6] who found that digitalis causes constriction of the hepatic veins in the dog. The result of this constriction is a rise of the portal pressure, enlargement of the liver, fall of the venous pressure and pooling of blood in the liver. Louis Katz and his co-workers[7] ascribed to this pooling of the blood in the liver the primary action by which digitalis abolishes heart failure, the pooling of blood in the liver being analogous to venesection, relieving the burden on the over-distended heart. We recorded the portal and carotid pressures during the slow intravenous injection of dilute solutions of digitalis in the dog and the cat.[8] We found that whereas the portal pressure rises to fairly high levels in the dog, it does the opposite in the cat. The constriction of the hepatic veins by digitalis, therefore, does not occur in the cat and appears to be a phenomenon peculiar to the dog. Bower, Dale, Poulsson and Richards[9] have shown that the liver of the dog possesses a special sluice mechanism not present or poorly developed in other species.

[3] H. J. Stewart and A. E. Cohn, *Jour. Clin. Investigation*, 11: 917, 1932; A. E. Cohn and J. M. Steele, *ibid.*, 11: 871, 1932.

[4] McK. Cattell and H. Gold, *Jour. Pharmacol. and Exper. Therap.*, 62: 116, 1938.

[5] H. Kabat and M. B. Visscher, *Proc. Soc. Exp. Biol. and Med.*, 40: 8, 1939.

[6] W. Dock and M. L. Tainter, *Jour. Clin. Investigation*, 8: 467, 1930; M. L. Tainter and W. Dock, *ibid.*, 8: 485, 1930.

[7] L. N. Katz, S. Rodbard, M. Friend and W. Rottersman, *Jour. Pharmacol. and Exp. Therap.*, 62: 1, 1938.

[8] H. Gold and McK. Cattell, *Arch. Int. Med.*, 65: 263, 1940.

[9] W. Bower, H. H. Dale, L. T. Poulsson and D. W. Richards, *Jour. Physiol.*, 74: 343, 1932.

There is a heavier muscular coat in the hepatic veins of the dog than in those of the cat. They observed that "the hepatic veins in the human liver resemble those of the cat rather than of the dog." Arey[10] has recently summarized the anatomical evidence on this subject. These results are also in harmony with the observations of Cohn and Steele,[11] who were unable to find any evidence to the effect that digitalis causes significant pooling of blood in the liver of man.

At this point we may note that both the "tone" and the "liver" hypotheses of digitalis action involve the prevailing view that in heart failure the heart muscle is overstretched. Starling's law of the heart describes stretching of the muscle as an adaptive mechanism by which it boosts its energy output. In accordance with this law, there is a critical point, however, beyond which stretching is unfavorable. Heart failure is assumed to represent a state in which the distended condition of the heart embarrasses its systolic contraction. With this view, it becomes a legitimate objective to try in some way to reduce the distension of the heart. The view that heart muscle in clinical failure is overstretched gets into serious difficulties when subjected to critical analysis. It is extremely difficult to overstretch heart muscle. It requires a stretch with a force of the order of the systolic force to overstretch it. Such forces rarely, if ever, exist in the living animal. Even such high venous pressures as 15 cm of water represent only about one fourth of the systolic pressure in the right ventricle, and only about one tenth of the systolic pressure in the left ventricle.

We carried out experiments on cats in an endeavor to learn something of the possibility of overdistention of the heart in the intact animal. We recorded intra-auricular and intraventricular pressures by the use of the Frank capsule. We occluded the aorta close to the heart. As the result, the intraventricular pressure, as well as the venous pressure, rose markedly, diastolic pressure in the auricle to as high as 100 cm of water. The heart became very much distended by these pressures. When the heart began to fail as a result of overwork and impaired circulation, both the systolic and diastolic tensions fell. Considering the failing heart as "overstretched" in that state in which a reduction of the stretch would increase the force of contraction, we noted that even under these extreme conditions of failure and high venous pressure, the heart did not behave like an overstretched muscle. This failing and distended heart obeyed the same law as it did in the normal state. With a lowering of the venous pressure, the force of the contraction declined, and with a raising of the venous pressure, the force increased. There are recent studies on man,[12, 13] the results of which point in the same direction. It has been shown by Stewart and his co-workers,[14] and others, that in clinical failure, the heart is disproportionately large for the work it does, but it is another matter to take the stand that it is larger than necessary for the work required of it in its weakened state. As far as we can see, there appear to be no adequate reasons for assuming that the muscle in clinical heart failure is overstretched, or that making the muscle smaller by means of digitalis will improve its function. The reduced size of the heart after digitalis in heart failure is not the cause but chiefly the result of the improved systolic force.

We now come to a series of observations carried out on human subjects with auricular fibrillation, in a study of the mechanism of cardiac slowing by digitalis. Opinions differ regarding the mechanism by which digitalis slows the heart rate in patients with auricular fibrillation. Cushny,[15] in 1912, maintained it was chiefly an action exercised directly upon A–V conduction. About ten years later Lewis[16] took issue with the view and concluded that it was chiefly an action through the vagus, and after another interval of about ten years Elsie Porter[17] expressed the belief that the action was entirely through the vagus.

Fig. 2 shows two extreme types of results obtained when patients with auricular fibrillations are digitalized and then receive a dose of atropine intravenously sufficient to block completely the vaginal endings. A dose of 2 mg by intravenous injection is sufficient; less than this may fail to produce complete blocking; more produces no greater effects on the vagus. Here were two patients, after a control period of rest in bed, almost identical in their clinical features. Each had advanced congestive failure with rapid ventricular rate. Each received a large dose of digitalis. In both, the rates declined to rather low levels. In one the atropine abolished the slowing completely; in the other it had very little effect on the slowing. In the first case (case 3), therefore, the slowing was the result of a predominantly vagal action. In the second case (case 1) it was predominantly an extravagal action. In the further investigation of these results it was found that neither individual peculiarity nor the degree of heart failure determines the mechanism by which the rate was slowed. In one and the same individual the mechanism of the slowing may be at one time vagal and at another time extravagal (case 9). The

[10] L. B. Arey, *Anat. Rec.*, 81: 21, 1941.
[11] See reference 3.
[12] J. McMichael, *Quart. Jour. Med.*, 7: 331, 1938.
[13] J. McGuire, R. Shore, V. Hauenstein and F. Goldman, *Arch. Int. Med.*, 63: 469, 1939.
[14] H. J. Stewart, J. E. Dietrick, N. F. Crane and C. H. Wheeler, *Arch. Int. Med.*, 62: 569, 1938.
[15] A. R. Cushny, H. F. Marris and M. D. Silberberg, *Heart*, 4: 33, 1912.
[16] T. Lewis, A. N. Drury, A. M. Wedd and C. C. Iliescu, *Heart*, 9: 207, 1922.
[17] E. Porter, *Quart. Jour. Med.*, 2: 33, 1933.

amount of digitalis is the deciding factor. The subject may pass from the vagal to the extravagal form of slowing as the drug is increased, and in the reverse direction as the drug is eliminated.

We are now in a better position to understand the differences in the views of Cushny, of Lewis and of Porter. We obtained the results of Lewis and Porter when we gave the smaller doses, and the results of Cushny when we gave the larger doses to the same individual.

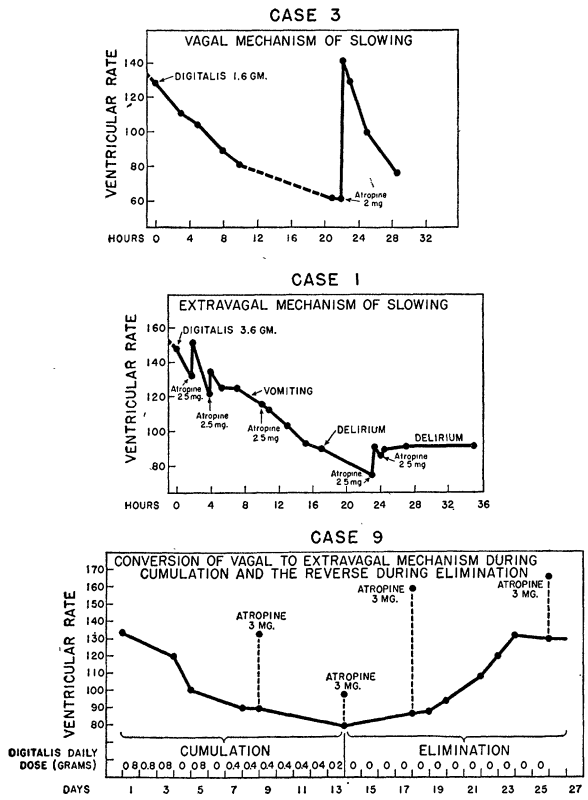

FIG. 2. Vagal and extravagal mechanisms of cardiac slowing by digitalis. Patients with auricular fibrillation and congestive heart failure were confined to bed. The digitalis leaf was given orally. The atropine sulfate was given intravenously.

The extravagal factor represents a direct action of digitalis presumably on A–V conduction. How is the vagal factor, the increased vagal activity, brought about? It is usually stated to be by direct stimulation of the vagus center. But the evidence from experiments on dogs and from observations in humans as related to amounts of the drug in customary use is almost entirely against it. The indications are that the vagus is stimulated reflexly indirectly as the result of improved myocardial function. To assemble the various lines of this evidence would increase unduly the length of this discussion.

The double mechanism by which digitalis controls the ventricular rate in patients with auricular fibrillation has a practical bearing on the problem of the control of heart rate in these patients during free physical exercise. Some of these patients who appear to be satisfactorily digitalized and maintain a slow rate when they are at rest, show extreme acceleration of the heart with effort. It is well known that the sense of palpitation resulting from the high rate is a source of discomfort, and it is likely that such a rapid and irregular rhythm is not an economical form of compensation for circulatory demands. Can it be prevented? We obtained an answer to this question in a group of experiments in patients with auricular fibrillation in whom the effect of atropine was compared with physical exertion during three stages: (1) without digitalis; (2) after moderate doses of digitalis; (3) after large doses of digitalis. The peak rate after an intravenous dose of atropine sufficient to block the vagus completely was compared with the peak rate reached as the result of climbing stairs to the limit of the patient's endurance. The effect of this physical exertion proved to be practically identical with the effect of atropine in all three stages. In the typical case, both factors accelerate the rate to about 180 a minute when the subject is without digitalis, and after moderate doses (vagal digitalization). However, after large doses of digitalis, neither factor raises the rate significantly above 100 a minute. Extravagal digitalization, therefore, prevents the exaggerated acceleration of the heart during physical effort in most patients with auricular fibrillation. In this state free physical exercise will not often accelerate the ventricular rate above 100 a minute. Again, dosage is the deciding factor. In some cases the amounts which establish the extravagal mechanism are quite close to those which induce impairment of appetite and nausea.

We may turn to another matter. It is well known that the potency of different specimens of digitalis varies. About 35 years ago Edmunds[18] assembled preparations of digitalis on the American market. He tested them biologically in frogs and found that the strongest was about 3 times as potent as the weakest. Biological standardization of digitalis was not in general use at that time. As a result of these and other observations, the U. S. Pharmacopeia adopted the frog method for the assay of digitalis. The object was clear, namely, to insure digitalis of uniform potency in man.

Many other methods for the assay of digitalis have since been devised. The cat method of Hatcher and Brody became very popular in this country and several outstanding preparations were assayed by this method. The experiment which Edmunds made with market

[18] C. W. Edmunds, *Jour. Am. Med. Asn.*, 48: 1744, 1907.

preparations in 1907 was repeated in 1940 in our laboratory[19] in order to determine whether digitalis tinctures at this time were in fact more uniform than they used to be. In these tests the cat method was employed. The results were rather startling. They showed that the outstanding tinctures at this time varied widely in potency, and that the strongest was still about 3 times as potent as the weakest. These were all labeled U.S.P. XI Tincture Digitalis, hence supposedly of similar potency by the frog method, with the approximately 40 per cent. range allowed by the Pharmacopeia. This brought into focus a fact which had long been known, namely, that the frog and the cat method do not always give similar answers in the comparison of digitalis materials. Abundant evidence accumulated which showed that two specimens may be of the same potency by the cat method, while one may be twice as strong as the other when tested by the frog method. Which method gives results applicable to man?

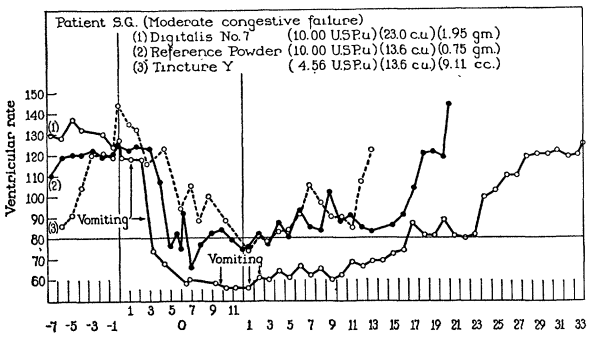

FIG. 3. The cat method reflects the potency of digitalis in man, while the frog method does not. The patient was confined to bed with auricular fibrillation and moderate congestive heart failure. The points to the left of the first vertical line represent the average ventricular rate determined from a count made at the apex three times daily during the control period; the dose of digitalis was given at one time at the point on the first vertical line; the points between the two vertical lines represent single counts at intervals of an hour or less; those to the right of the second vertical line are obtained in the same way as in the control period. Curves 1 and 2, which show different effects, represent the same number of U.S.P. XI (frog) units, but a different number of cat units. Curves 2 and 3, which show similar effect, represent dissimilar doses in U.S.P. XI (frog) units, but the same number of cat units.

This was put to the test in a series of experiments in which the two methods of assay were related to humans, in patients with heart failure and auricular fibrillation.[20] Fig. 3 is a typical example of these experiments. The patient was put to bed in the hospital. The apex rate was counted three times daily, and the average recorded as a point on the chart, during a control period of a week or longer until the rate reached a fairly constant level. He then received a single full dose of the digitalis preparation. Apex counts were made at intervals of approximately one hour throughout the day. In the subsequent days the record was made in a manner similar to that in the control period prior to the dose. A period of three weeks or longer elapsed for the elimination of the drug, after which the patient was redigitalized with the next preparation.

(To be concluded)

FOOD AND NUTRITION AS RELATED TO THE WAR[1]

By Dr. CHARLES GLEN KING

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THOSE of us who are working in the field of foods and nutrition these days feel varying degrees of embarrassment when we hear the phrase "Food Will Win the War." It sounds a bit out of balance. War is essentially a fight to the death; and so far as I can see, we have no substitute for the men who face, and fight with, guns and bombs. The first credit is theirs.

I have no quarrel with the phrase "Food Will Help Win the War" or better still, "Food Will Be a Major Factor in Winning the War." We do have a critically important job to do. If we neglect doing it quickly and well, we shall prolong the war and certainly would cause great injury to all humanity.

First, let us look at our No. 1 and No. 2 weapons—the airplane and the tank. To be sure, research and production must not be neglected in either of these fields, but no matter how good the machines may be, there is still need for the utmost protection of the soldiers who run them. In both types of service just referred to, the problem of fatigue is of critical importance. The machines literally wear out the men.

One of our Allies is said on good authority to have practically eliminated a major source of aviation accidents by a surprisingly simple change in food

[19] H. Gold and McK. Cattell, SCIENCE, 93: 197, 1941.

[1] Address given at the National Chemical Exposition, Chicago, Ill., November 27, 1942.

[20] H. Gold, McK. Cattell, N. T. Kwit and M. Kramer, *Jour. Pharmacol. and Exper. Therap.*, 73: 212, 1941.