

# THE PHARMACOLOGY OF DIGITALIS.\*

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The suggestion of this title for a paper was held to imply considerable latitude, since even a single phase of the pharmacologic action of digitalis could not be treated comprehensively in the time allowed to a single paper.

I shall attempt, therefore, only a brief review of the principal actions of the drug with a few remarks on the individual peculiarities of certain pure principles having a digitalis action, together with some observations bearing on the therapeutic use of the crude drug, its preparations and these isolated principles.

The digitalis action is most briefly defined as consisting in the characteristic slowing, followed by systolic stand-still of the frog's heart. As Heinz has said, this does not seem like a happy choice of definition, since it merely states a toxic action without even indicating how it is brought about, but it is useful since almost any drug which produces this effect may be used in the same way that digitalis is employed for the human heart.

Withering published a book on digitalis in 1785, since which time the drug has been the subject of considerable study. The diuresis which it caused was at first the only effect noticed or utilized, and it was about fifty years later that Blake (in 1839) reported the characteristic effect on blood pressure. Some years later (1851) Traube undertook to explain the cause of this action, but he did not define sharply the relative effects of digitalis on the heart and blood vessels.

About thirty years ago Schmiedeberg and his followers observed the action on frogs' hearts, and concluded that the blood pressure effects were attributable solely to the action on the heart, which was of a specific nature. Kobert, however, showed that the vessels undergo constriction, and therefore participate in the rise of blood pressure.

When Williams devised his celebrated apparatus, and Herring and Bock evolved their method of perfusing the mammalian heart, the way was opened for the more exact study of the action of digitalis.

The literature of this subject is so vast that I can not attempt to mention all the sources from which our information is drawn, but will merely select a few bearing on the practical application of the drug in therapeutics.

It will be most convenient perhaps to consider the subject in the following order:

1. Pure slowing. Its cause and effects.
2. Pure general muscular actions and their effects.
3. Pure vascular actions—causes and effects.
4. The net circulatory effects.

The central action will be considered mainly with reference to its peripheral effects.

## SLOWING OF THE HEART.

Slowing occurs in the atropinized frog's heart from the action on the muscle causing a veratrin-like condition, whereby the systole is increased at the expense of the diastole. Obviously, this alone would cause but little improvement in the circulation, save possibly at the

very first, when the increased contraction may result in expelling more blood, particularly if the irritation of the muscle partially or completely overcomes the tendency toward slowing due to the increased systolic phase. Without atropin, the peripheral vagus mechanism participates in the cause of slowing in the frog, but not in the mammal to an appreciable extent, according to later observers.

In the intact mammal the vagus center is effectively stimulated, and causes slowing through an influence directly opposite to that of the muscular action, since vagus stimulation causes a true muscular inhibition, hence diminution of systole or an increase of diastole at the expense of the systole. In a high-grade stimulation of the center, the diastole may be increased to many times its normal duration. Ackermann did not observe any slowing or increased dilation after atropin, and Gottlieb and Magnus found the slowing in the Langendorff heart negligible, while vagotomy produces almost the same result.

Pure slowing must tend to lessen circulation and to cause a fall of blood pressure, which must actually occur if the slowing be sufficient to counteract other influences, but the lengthened diastole permits an increased volume of blood to enter the heart and also affords longer periods of rest. Slowing lessens the coronary circulation if the systolic phase predominates, but each separate contraction squeezes out the venous blood, permitting a fresh supply of arterial blood during each diastole; on the other hand, a lengthened diastole affords a longer period during which blood may flow through the coronary arteries, and if this phase predominates the longer period of free circulation may compensate for the more frequent renewal obtained by a faster heart. Another advantage obtained by pure slowing is the better opportunity for the great vessels to empty enough of their contents to lessen their distension and the subsequent resistance against which the heart must contract, and the substitution of resilient for more nearly rigid tubes of liquid.

## CARDIAC EFFECTS.

The purely muscular effects are much alike in all animals and have been most frequently studied on the frog's heart. Primary quickening, due to muscular irritation, is often seen before vagus stimulation in experiments, but this soon gives place to slowing from the causes mentioned.

Certainly the most typical muscular action is seen in the tendency to remain contracted, which at first causes only lengthened systole and shortened diastole and later systolic stand-still. The capacity of the muscle for rhythmic contraction is not impaired or abolished at this time, as Schmiedeberg showed by distending it by force, when normal contractions ensued for a short time, soon giving place to paralysis of the function, the heart remaining contracted.

Schmiedeberg considered the chief effect of digitalis on the muscle as leading to an increased elasticity, a larger volume of blood entering the ventricle, which then resumed its normal systolic position. He was unable to perceive any increase in the total capacity for work or maximum strength, but supposed that digitalis merely made the energy more available. While it seems that this must be true for the latter statement, it has been found that the heart is capable of contracting more forcibly (maximum increased) under isometric conditions, and that a larger volume is expelled under isotonic conditions. There is, therefore, practically an

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increase in the total maximum force, as well as the total energy because of the action of digitalis on the heart.

Heinz was unable, however, to get an increase in the absolute strength of the mammalian heart.

François Frank obtained an increased maximal force of contraction, and Gottlieb and Magnus, using the most perfect methods whereby they eliminated such disturbing factors as changes of temperature and alterations of coronary circulation, found that, when under the influence of digitalis, the heart would support a higher column of liquid.

The improved systole, whereby the ventricle is more nearly emptied, following the lengthened diastole, which permits of the increased distension by a greater volume of blood, must result in an increase in the volume of each pulsation, in some cases to the extent of 50 per cent., and this is usually more than sufficient to compensate for any slowing that occurs, hence there is an increase in the total output in a unit of time.

This single fact must mean an increase, if not improved, circulation. This will be mentioned later.

#### VASCULAR EFFECTS.

The vascular effects of digitalis and its isolated and related principles have been the subject of much dispute since Kobert showed that vasoconstriction occurs.

The several obvious proofs of vasoconstriction are afforded by the microscopic observation of the vessels in the web of the frog's foot; by a rise of mammalian blood pressure before the cardiac effects are produced; by oncometric measurement of certain organs; and by the fact that the circulation time in excised organs is increased by digitalis.

The latter experiment demonstrates that the action is in part at least peripheral, and since it occurs after the nervous elements are supposed to have ceased to function it is attributed to muscular action. That the center participates in the action in the intact mammal is not denied, and the reflexes appear to play a very important rôle in the case of certain of the pure principles to be mentioned presently.

The three principal points of therapeutic interest in connection with the vascular effects are: The general rise of blood pressure which occurs, the want of participation in the constrictor action on the part of the pulmonary circulation, and the different effects of the various principles on the coronary circulation. The coronary circulation is commonly lessened by digitalis in perfusion of the isolated heart, since the vessels are constricted.

#### CIRCULATORY EFFECTS.

These constitute the summation of all the actions just considered.

As previously stated, the total output of the heart must obviously control the amount of blood which passes through the arteries. Cushny specifically states that digitalis causes more blood to be driven out of the heart in the therapeutic stage, owing to the predominance of the systolic phase (cardiac effect). But he also states a few lines further on that digitoxin (and that may be considered as having the same action as digitalis) retards the outflow from all the arteries. It is incredible that the output of the heart for a unit of time, which amounts to 50 per cent. in some cases, can be attended with a slower circulation, but Sollmann also states that the velocity is diminished.

A slight increase over the therapeutic dose may cause the inhibitory phase to prevail and the output of the

heart per unit of time will be diminished because the heart is greatly slowed, while the systole and diastole are altered but little.

A high blood pressure at the beginning of the systole will evidently increase the work of the heart which in turn must receive increased nutrition or become exhausted. If the systole persist until the aortic pressure has fallen materially, there will be less pressure to drive the blood through the coronary circulation during diastole, and the three factors—slower pulsations, constricted coronary vessels and inability to utilize the maximum blood pressure—must prevent as perfect nutrition of the heart as will occur if they do not coöperate.

On the other hand, more perfectly aerated blood displaces the venous blood, because of the more thorough squeezing out of the arteries and capillaries at each stroke, partially compensating for the disadvantages mentioned.

While the vasomotor center contributes to the rise of blood pressure, it appears that the musculature of the arteries is a more important factor in digitalis and some of its principles.

#### DIGITALIS, AND ALLIED, PRINCIPLES.

But little was known of the active principles of digitalis until Schmiedeberg's celebrated investigation was published about thirty years ago. He studied the seeds and extracted digitoxin from the leaves. Since then very small amounts of digitalin and digitonin have been found in the leaf. Keller was unable to find digitalein, which he considered as merely a mixture of digitalin, with a little digitonin. He worked with very small quantities of the leaf, which may account for his failure to find the digitalein.

Digitalin was investigated pharmacologically and clinically and bade fair to come into general use, but at the present time it is of little practical importance.

Digitoxin more nearly represents the leaf, but the presence of traces of digitonin in the latter tend to counteract the vasoconstrictor action of digitoxin and probably modifies it to a considerable extent.

Despite the numerous disadvantages of digitoxin, it bids fair to displace digitalis in therapeutics. Among these disadvantages are: Its insolubility in water and consequent irritant action, slowness to act and tendency to cumulative effect; its proneness to decomposition, whereby toxiresin is formed; the narrow margin between the effective dose and that which causes accumulative effects on continued use; and its marked vaso-constrictor effects, which may, or may not, be objectionable, dependent on the case in hand.

The irritant action is responsible for the gastrointestinal and cardiac effects, and it precludes its subcutaneous injection. This insolubility also seems to be responsible for the delay of forty-eight hours or more in inducing the cardiac effects, the rapidity of action of those principles appears to be proportional to the readiness with which they combine with the sensitive apparatus in the heart, while the cumulative effects seem to be in proportion to the stability of the combination.

It has been urged that the ease with which digitalis may be washed from the heart precludes any fine molecular combination in the muscle.

Digitoxin does not cause a greater vasoconstriction in the splanchnic area than in the periphery, and it appears to be capable of restoring the rhythm of the heart to an extraordinary degree when this is disturbed by pathologic conditions, apparently by virtue of its lessening the susceptibility to abnormal stimulants.

It will be noticed that the principal objections to digitoxin are connected with its insolubility, and Cloetta has succeeded in preparing a soluble, amorphous digitoxin, which may be injected subcutaneously.

I have not been able to find an account of the process of manufacture, but his original article is usually quoted to the effect that it is prepared by a very complicated process, evolved after five years of effort. This preparation, called digalen, is marketed by the firm of Hoffmann, LaRoche & Co., which, so Cloetta states, despite the trouble and expense amounting to 11,000 marks per kg., has happily undertaken the preparation, selling it at but 2 marks (48 cents) for a small vial so that it may be universally used.

Quite a bit of philanthropy, it would appear, but when we reflect that a kg. costing 11,000 marks contains 3,000,000 doses and sells for 440,000 marks (\$105,600), the philanthropy becomes less obvious.

While clinical evidence seems to show that digalen is an effective substitute for infusion of digitalis, Karl Reitter, in Schrötter's clinic in Vienna, was unable to obtain the therapeutic effect with less than 6 c.c. (6 mg. daily), and finds it no better than the leaf and more expensive.

This preparation presents the anomaly of requiring a much larger dose when injected intravenously, presumably because of its rapid elimination by the kidney, and it will be interesting to know what the effect will be on that organ of the continued administration of so irritant a substance.

#### STROPHANTHIN.

Loeb found that strophanthin had much less constrictor effect on the coronary circulation than digitoxin has. This is of much importance, as it has been shown that the heart tension, or strength, is dependent on blood supply to an extraordinary degree. If an agent causes general vasoconstriction it means that the heart must contract against an increased resistance, and if the constriction of the coronary vessels is pronounced, the blood supply of the heart may be diminished despite high aortic pressure.

P. Maas has shown dilator and constrictor nerve fibers for the coronary vessels, but we can not study blood supply of the heart when the vessels are under central control in the mammal.

Strophanthin possesses the typical digitalis action; it can be prepared in constant and stable form, it is not expensive, it can be given for long periods without inducing cumulative effects (Fränkel having given it to a cat in just submaximal doses for ninety-two days). The effective dose lies much further from that which causes cumulative effects than in the case of digitoxin. It is quite soluble in water, hence much quicker to act. This occurred in three hours as against forty-eight hours for digitoxin. It is much more active and less irritant than digitoxin.

Sollmann has suggested that it probably deserves the preference over digitalis, and it has been used with satisfaction in France, Holland and Belgium, but for some reason many species of seed, many of them inert, have been brought into Germany and the United States, and some tinctures were found to be but one-sixteenth as strong as others. This has caused the crude drug, its preparations and its pure principle to fall into disrepute.

#### ANTIARIN.

This substance is of such extraordinary power that 1-10,000 of a milligram causes slowing of the frog's heart and 1-1,000 mg. causes systolic stand-still, being apparently 250 times as active as digitoxin.

Hedbom studied its action and that of antiarigenin—which he found but slightly toxic to the mammalian heart, though differing from antiarin only in the loss of a molecule of glucose. The extraordinary difference in the activity of these principles suggest that they possess an active nucleus so combined that it enters into more effective combination with the sensitive apparatus of the heart in some cases than in others, and it seems probable that further research may discover means of modifying some of the many more active principles of this type.

#### OBSTACLES TO USE OF DIGITALIS.

The greatest obstacle to the use of digitalis and its preparations arises from their variability, due to differences in methods of collection and preservation.

It has been shown that leaves gathered in the proper season quickly dried, cut up, dried thoroughly in a vacuum and hermetically sealed, will undergo but little change in a year. We should, therefore, demand leaves which have been thus preserved and physiologically tested on the frog's heart, with the date of the test stamped on the package, as is done with sera.

Kobert tested leaves which had thus been dried and made into tablets with sugar of milk and starch, finding them effective.

This may appear as too complicated for practice, but there is no reason why such leaves should not be sold very much cheaper than the nostrums which are being so much lauded as possessing all the virtues and none of the objectionable features of digitalis.

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### PHARMACOLOGY OF VERATRUM.\*

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I firmly believe that if pharmacologists, instead of spending their time investigating commercial synthetics would direct their energies to more careful study of pharmacopoeial remedies, the world would be greatly benefited. A splendid example of the general ignorance concerning drugs which we call "well-known" is found in the case of the veratrums. When the statement is made in standard works on pharmacology, that the active principle of *Veratrum viride* is veratrin, and that this plant is useful only as a local application, it becomes evident that there is room enough for more accurate knowledge even among those who devote their attention especially to the study of drugs.

Before considering the properties of *Veratrum viride* I would like to discuss for a moment the question of the identity of *Veratrum album* with this plant. The Eighth Revision of the U. S. Pharmacopeia has recognized *Veratrum album* as equivalent to *Veratrum viride*, making one title, veratrum, to refer to both plants. I shall not go into the discussion of the botanical relations of green and white hellebore, as this question seems at present impossible of final decision. It may be dismissed with the

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