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Digitalis

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D I G I T A L I S

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O M A H A

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INTRODUCTION

The first reference to digitalis was in the treatise of the Welsh physicians, A. D. 1250 (24). The first botanical description of the plant and its botanical name were furnished by Fuchsius in 1542 (130). Digitalis was later mentioned as an emetic and expectorant by Gerrarde in 1597 and Parkinson in 1640. William Salmon in 1707 recommended it for "obstruction of the liver and spleen," as an ingredient of ointments for wounds and scrofula, and as beneficial in epilepsy (107). Its specific action was not observed until Withering began using it in 1775. The story of his discovery of this needs no retelling. His famous book was published in 1785. The accuracy of his observations and the soundness of his therapeutic use of digitalis excite wonder when the incomplete knowledge of physiology and pathology of his time is considered. While he considered the drug as a diuretic, he recognized that it would not produce diuresis, in "encysted dropsies" (ovarian cysts) or in ascites associated with "visceral disease" (portal obstruction). He noted slowing of the pulse after digitalis is administered, but could not connect this with the diuresis. Withering's method of using the drug is classical, and, after frequently disregarding his rules for administration with unsatisfactory and often tragic results, the best

clinicians today use digitalis exactly as Withering used it. The only difference between the use of digitalis today and its use by Withering are due to means for studying the response of the patient which were not available to Withering.

Cullen, in 1789, attempted to associate the diuretic action of digitalis with "a general action on the system" which also involved the slowing of the pulse (24). Ferriar in 1799 spoke of its "sedative power" on the heart and its "proper action in retarding the velocity of the circulation."

In the first two decades of the nineteenth century digitalis was heralded as a specific for phthisis, by Beddoes and others. Beddoes noted that in some patients under digitalis the pulse rate was practically doubled when the patient sat up in bed. Currie and Bree found patients in whom the pulse rate was not slowed by digitalis. Magennis found that digitalis, in some cases, caused intermissions of the pulse at every third, fifth or seventh beat, and often the pulse became quite regular at forty. Vulpian in 1855 first used animal experimentation in an attempt to analyze the action of digitalis (24).

The high points in the literature on digitalis are marked by Withering's great report of 1785, Fothergill's essay in 1871, and the more recent publications

of Cushny, Christian and Luten. The writings of these five men have been freely used in the preparation of this paper.

The cardiac action of digitalis is not peculiar to this plant, but Digitalis purpurea is the best known of a large group of plants, the active principles of which vary only in potency and are known collectively as "the cardiac glucosides." All but digitalis and strophanthus have practically disappeared from use, and, for convenience, this paper shall consider these only.

It is not represented that the bibliography includes all the great mass of literature which has appeared on this subject. An attempt has been made, rather, to omit reports of all work which, however worthy, does not bear directly on the ability of digitalis to aid the patient with a damaged heart.

CHAPTER I

EVIDENCE OF CENTRAL ACTION

Since Traube in 1851 discovered that the slowing of the heart caused by digitalis could be removed by section of the vagi, authorities have differed widely over the question: "Does digitalis stimulate the vagal center of the brain, and if it does, of what importance is this action in the therapeutic use of the drug?" Fothergill in 1871 denied the theory of Traube (33). Haynes in 1906 (54) found little decrease in the heart rate in the atropinized heart perfused with digitalis and expressed a belief that stimulation of the vagal nerve endings is a large factor in the slowing of the heart in the climical use of digitalis. Mackenzie, who considered the therapeutic effect of the drug to be due largely to its effect in slowing the heart rate, thought that digitalis might act by stimulating the vagus nerve (74). In 1913, Robinson and Wilson studied the effect of digitalis on cats, with and without the vagi cut (102). With the vagi intact, they found that an inversion of the T wave of the electrocardiogram occurred when 25% of minimum lethal dose had been administered, prolongation of

conduction time at 50% of the m. l. d., idioventricular complexes began to appear with 70% of the m. l. d., and A-V. dissociation appeared with 80% of the m. l. d. When the vagi were cut, the inversion of the T wave was found after administration of 25% of the m. l. d., but A-V. conduction and the heart rate were almost unaffected by the total m. l. d.

Two years later Greene and Peller (46) reported an experiment in which a turtle brain-heart preparation was used, the heart being connected to the brain only by the fibers of the vagi. The brain was perfused with fluid containing digitalis bodies. The cardio-inhibitory center was stimulated, as shown by heart rate, and finally paralyzed, as shown by escape of the heart. Various degrees of inhibition were observed during subsequent perfusion with Ringer's solution. These authors report "not only is the rhythm inhibited but there is a blocking of the passage of the contraction wave from the vein and sinus to the ventricle by a decrease in conductivity."

Further evidence of vagal stimulation is taken from the blood picture. An eosinophilia frequently accompanies vagotonia (108). Smith and Benner (115) report that eosinophilia following digitalization was reduced by adrenaline and atropine, but not by pilocarpine. Romans and Geiger (104) report a case of

eosinophilia in a digitalized patient in whom there was a fall in the eosinophile count when digitalis was stopped, and a corresponding rise when digitalis was resumed.

It seems, then, that digitalis has a vagotonic effect. The importance of this action in the therapeutic use of the drug has been questioned by leading authorities, and will be considered again after the action of digitalis on cardiac muscle has been discussed.

CHAPTER II

EFFECT ON CONDUCTIVITY

It has long been known that digitalis produces characteristic effects on the rhythm of the heart. Cushny (24) summarizes the effect of the glucosides on the frog's heart as follows: when the heart is perfused with a minimum quantity of digitalis, there is first a period of delay, then the ventricle begins to beat at one-half its original rate. With continued perfusion the ventricular rate is halved again, to one-fourth original rate, the auricle's rhythm still being unchanged. This process may be repeated so that the ventricular rate is one-eighth that of the auricles, and finally the ventricle stops in complete diastole. This change in rhythm is independent of the extrinsic nerves, for it is not affected by atropine or curare.

Cushny credits Straub with being first to point that this slowing results from the failure of efficient stimuli to reach or act upon the ventricle. Similarly, he points out, the sinus may continue its rhythm while the auricle beats at one-half rhythm. There is also diminished conductivity within the ventricle. This may be exhibited by contraction of a part of the ventricle, or by lowering of the T wave. The halving of the rhythm is often preceded by alternation of large and small beats, the latter apparently being contractions of the base of the ventricle only.

There are two theories (24, 66, 69, 71, 127) by

means of which the explanation of this block-producing action has been attempted. These are (1) that the impulse fails to reach the ventricle, or (2) that, reaching the ventricle, it finds the ventricular muscle unresponsive. Evidence of reduced exciteability under digitalis is a reduction in efficiency of electrical stimuli after digitalis administration, as found by numerous investigators (Cushny, 24). Clinicians commonly assume that the block-producing action of digitalis is due to impaired A-V conductivity, a view which is not totally accepted by physiologists. Erlanger (290) believes that both lowered A-V conductivity and lowered ventricular exciteability must be considered important factors. In summary, "the question remains unsettled, but the balance of evidence supports Cushny's contention that digitalis acts at least partly on the conducting tissues (72)."

CHAPTER III

ACTION ON VENTRICULAR MUSCLE

The characteristic action of digitalis on cardiac muscle was first observed by Vulpian on the frog heart in 1855 (24), and was confirmed by several workers, including Fagge and Stevenson in 1865, and Fothergill. This same action was found to result from strophanthus by Fraser in 1873, when he studied this drug as an arrow poison used by natives of Africa. The action is so characteristic that it has since been used as a test for the presence of the cardiac glucosides. When a frog's heart is perfused with sufficient glucoside, it stops with the ventricle white and hard in a state of contracture, the auricles dark and distended with dammed-back blood (30, 34).

In 1887 Folleston reported that strophanthin causes a marked rise in intraventricular pressure (103). Cushny reported in 1897 that the shortening of the ventricular fibers in systole was increased by digitalis (24). An important observation was made in 1926 by Harrison and Leonard (51). These men found that digitalis definitely diminishes the output of the normal dog's heart. The following year Burwell and his associates (10) were able to report the same results in normal men. In 1929 Weiss and Blumgart (124),

working with vital capacity and arterial and venous pressure measurements, found the following results: (1) therapeutic doses of digitalis caused no appreciable change in the cardiac output of normal persons, and (2) of fourteen cardiac patients, seven showed increased heart output, four showed no change, and three showed decreased output. Bodo previously had stated that digitalis produces a tonic effect on the heart, enabling the heart to expel the same amount of blood with a smaller average heart volume (5). This may explain cases of heart failure in which clinical improvement without increased heart output was observed after digitalis administration. Weiss and Ellis reported four such patients in 1930 (125), and Friedman reported, of a group of twenty-two patients, eighteen who showed clinical improvement with no consistent alterations of cardiac output in proportion to oxygen consumption (35).

Cohn and Steelesummarize the effect of digitalis on the output of both dogs and men as follows (22):

"1. Digitalis decreases the volume output of the normal heart and decreases its size.

"2. The volume output of a failing heart is diminished and its size larger than when it is in a state of compensation.

"3. Digitalis increases the volume output of failing hearts and decreases their size."

"4. Digitalis, we think, has similar , perhaps identical, actions both in normal and in diseased hearts; it decreases cardiac size and increases the extent of ventricular contraction. The consequence of these actions is that the volume of the cardiac output which results,differs, depending on an initial difference in size of the ventricular cavities, in the two situations. In the one, the normal heart, it becomes too small; in the other, the diseased heart, it develops a suitable size."

The diuretic action of digitalis will here be discussed as a muscular effect. That diuresis is secondary to improved cardiac action was recognized by Fothergill (33) in his essay in 1871. Mackenzie later cast doubt on this theory because of his fallacy of taking slowing of the heart rate as an index of the action of digitalis. He found cases which, under digitalis, showed diuresis before any slowing of the rate occurred, and other cases with heart block in which digitalis produced diuresis. Because he was unable to understand any cardiac action (74) of digitalis which did not result from slowing, Mackenzie attributed diuresis to an extracardiac action of digitalis. Kellum in 1932 found that (52) "Digitalis when given to the healthy human subject in therapeutic doses seems to exert slight, if any diuretic effect." Eggleston states (28) that digitalis

produces no diuresis in patients without congestive heart failure. Levy and Mackie (66) believed that diuresis was due to improved renal circulation rather than to direct action on the renal epithelium, an opinion which coincides with that of Herrmann, Stone, Schwab, and Bondurant. Cushing is of the opinion that "the removal of dropsy may causes diuresis, not vica versa." (54a).

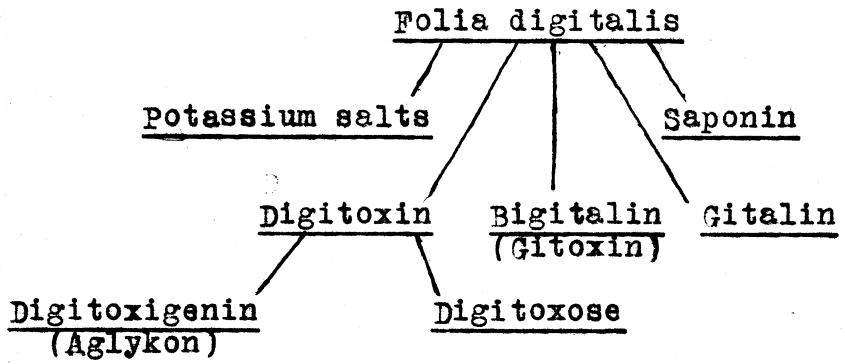
The question of whether or not cardiac hypertrophy constitutes a valid indication for digitalis has been discussed for many years. Eminent clinicians have held that a heart undergoing hypertrophy was responding naturally to changed demands upon it and did not require the stimulus of digitalis so long as symptoms of congestive heart failure were absent. Fothergill, quoted Niemeyer (33) "Digitalis in pure, uncomplicated hypertrophy is unsuitable. ... Its use is indicated in diseases in which the action of the heart is weakened, but never in cases where it is augmented." Fothergill agreed with this, but recognized that hypertrophy was not a contra-indication. Later cardiologists have largely held to this belief: that hypertrophy is a desirable process in a diseased heart, that as long as the heart can compensate for its deficiencies by increasing in mass, there is no need for medication. But now a new school has arisen,

a group of men who believe that hypertrophy of the heart is a bad thing per se (18), the beginning of a process which leads to dilatation and congestive heart failure, and that it should be avoided if possible. It has been suggested also that hypertrophy places a new obstacle in the path of a crippled heart by making more difficult the supply of blood to the heart wall. Cloetta (18) showed that the hearts of animals with experimental aortic insufficiency will undergo great hypertrophy, but that this hypertrophy may be largely prevented if digitalis is administered from the onset of the lesion. This immediately dispelled early beliefs that digitalisis a cause of hypertrophy, but the later results of the experiment were even more significant. The hearts treated with digitalis were found to be almost equal to normal hearts in absolute reserve energy, while the hypertrophied hearts which had not been treated with digitalis were quickly exhausted. Schwab and Herrmann (109) repeated Cloetta's experiment with a larger series of animals and also found that digitalis has a restraining effect on cardiac hypertrophy. Cloetta considers every heart with dilatation and hypertrophy as having diminished efficiency.

CHAPTER IV

BIOCHEMICAL ACTION ON HEART MUSCLE

The following is a schematic representation of the constituents of digitalis leaves (18):



The active principles of folia digitalis are the glucosides, of which the three mentioned above, digitoxin, bigitalin and gitalin, are the best known. Each of the glucosides contains a sugar component, digitoxose, the inert porttion, and a genin (aglykon), the active portion. Digitoxose is a common component of all the glucosides, which vary in potency according to their genin fraction. The genins alone are less cardio-active than the total glucosides.

After digitalis is administered to an animal or human subject, there is a latent period before its effects become noticeable. This latent period (14, 17, 18, 85) is shorter under intravenous administration than when the drug is given orally, but even

then is longer than could be required for simple diffusion through the circulating blood.

The glucosides have been shown to be crystalloids with the property of passing through membranes by dialysis. It has been shown (24) that the action of digitalis is reversible only in the very early stage. A short period exists during which the early action of the glucosides may be stopped by perfusion of a heart with Ringer's solution. This is called the membrane stage, and is believed by Cloetta to represent the period during which the glucoside passes through the cell membrane. After a few minutes, the action of the glucosides cannot be reversed by perfusion with Ringer's solution (18), and all efforts to recover them from the cells are fruitless. Fluid containing a fixed amount of a glucoside will affect each of a series of hearts less rapidly than the preceding heart, indicating that part of the active principle is taken out of the fluid by each successive heart (Straub's serial experiment). (24). It is believed that the glucoside has entered into combination with the heart muscle (has become "fixed") and that this fixation is chemical in nature. If this is a chemical union, the cumulative action of digitalis might be easily explained. After the crystalloid molecule has passed through the cell membrane and entered into chemical combination with the

intracellular material, it will lose its identity as a crystalloid and no longer exert osmotic pressure. Another molecule will then pass through the membrane and the process will be repeated. As evidence that this process is a chemical combination, Fischer (quoted by Cloetta) has shown that all of the cardiac effects of digitalis obeyed Vant Hoff's law: the effect is heightened in proportion to increase in temperature.

After fixation, the glucosides are slowly broken down into digitoxose and their genins (18). The genin is active and capable of continuing the digitalis action, but is less firmly fixed in the cell, so that they are gradually removed and their action ultimately disappears.

The process of fixation occurs in other tissues of the body, but is greater in heart muscle. If the amount of glucoside fixed in a given mass of heart muscle is taken as a unit, the amount fixed in other tissues will be as follows (14):

	Heart Muscle	Skeletal Muscle	Liver	Kidney
Digitoxin	1	1/14	1/4	1/2
Ouabain	1	1/10	1/5	1/2

While heart muscle fixes four and fourteen times as much digitoxin, weight for weight, as the liver and skeletal muscle, respectively, because of the difference in mass of these organs, the liver fixes approximately

the same amount of digitoxin as the heart, and skeletal muscle fixes more. For the same reason a hypertrophied heart absorbs a larger proportion of an equal sized dose of digitoxin than a heart of normal size, and thus receives more benefit from a given dose of digitalis than does a non-hypertrophied heart. Other factors affecting fixation are the rate of flow of the blood through the heart and the time the digitoxin is in the circulation, which is longer for glucosides administered orally and shorter for those administered intravenously.

The exact manner in which digitalis acts on heart muscle is not known, but curious similarities between its action and that of calcium have been found. Clark in 1919 stated that the increased force of contraction caused by digitalis was opposed by the presence of acid, or the absence of calcium from the perfusing fluid (16). Loewi (quoted, 24) thought that strophanthin did not act in Ringer's fluid which was free of calcium. Pietrowski (24), however, corrected the change in osmotic pressure by substituting sugar for calcium in the Ringer's solution and found that the strophanthin acted as normally. Ransom in 1920 arrested the movements of excised cat's uterus by placing it in Ringer's fluid containing no calcium, and found the movements restored and usually increased by the addition of strophanthus (92). He also found that a short exposure of uterine muscle to stro-

strophanthus made it extraordinarily responsive to calcium. Bower and Mengle (6)in 1936 found that previously digitalized dogs showed toxic effects from calcium in doses which were much smaller than were required when given without digitalis. They also reported two cases of sudden death from intravenous calcium administration of patients to whomdigalen had been administered previously without toxic effect.

Cloetta in 1929 stated that calcium and digitalis have different points of attact and that their actions cannot be identical (18). In 1936 Peters and Visscher (89) reported, "Calcium increases the oxygen consumption and efficiency of the heart muscle at constant external diastolic volume. Glucosides of the digitalis series have the same action as calcium, but the maximum effect is delayed."

Recently Cattell and Goodell (11) reported that the digitalis glucosides cause the frog sartorius muscle cell to lose potassium. Simultaneously with this, Nahum and Hoff announced electrocardiographic evidence (81) that the actions of calcium and digitalis on the hearts of normal rabbits are not additive. At the present time the exact mechanism of the cardiac action is not known, but evidence seems to point to some connection with the calcium - potassium ratio in the heart muscle cell.

CHAPTER V

EFFECT ON CORONARY CIRCULATION

The possibility of inducing attacks of angina pectoris in certain patients by the use of digitalis has justifiably stimulated a certain amount of study. Gilbert and Fenn reported a tendency for attacks of anginal pain (31) to be more frequent under digitalis and subsequently cited evidence which appeared to show that digitalis might have a vasoconstrictor action on the coronary vessels of dogs (36). Bodo (5), using small amounts, obtained an increase in flow through the coronary vessels. Gold (37) found that "a heart that has been in ventricular fibrillation from coronary occlusion and has recovered temporarily also shows no diminished tolerance to the toxic action of digitalis." He found that varying degrees of coronary obstruction did not "alter the average fatal dose of digitalis for seventeen animals. Gold and his associates have recently reported a series of 120 patients with arteriosclerotic heart disease who were given digitalis alternated with a placebo. As a result of their observations, they reported, "Digitalis in large doses rarely, if ever produces effective constriction of the coronary arteries in man." (43).

These conclusions confirm the observations made by Fothergill over half a century previously. Fothergill pointed out that the coronary vessels are filled by the "arterial systole": by the pressure of blood in the aorta during cardiac diastole, and that digitalis, by its action on the cardiac muscle, increases the filling of the aorta by ventricular contractions, and thus increases coronary circulation (33). Regardless of what experimental evidence points to coronary constriction by digitalis, this powerful and opposing action must not be lost sight of.

CHAPTER VI

THE THERAPEUTIC ACTION OF DIGITALIS

With a drug that affects the heart by several different methods at the same time, that produces varying effects with varying dosages, and that seems to act differently on normal hearts than upon abnormal hearts, it is not difficult to understand that a degree of confusion has long existed so far as the therapeutic action of digitalis is concerned. For this reason a discussion of the therapeutic use of the drug has been largely deferred until its several actions on the heart have been examined. It is now proposed to consider of those actions in the light of its importance in the treatment of the failing heart.

It has been rather well established that digitalis is a vagus stimulant and is capable of slowing the heart by its vagal action. It has also been established that digitalis slows the heart in certain cases of heart failure. The natural but unfortunate assumption that the beneficial effect of digitalis is the result of vagal slowing has confused the picture and resulted in a great deal of improper use of the drug. Mackenzie thought that heart failure was benefited by digitalis by a primary slowing effect which he thought might be due to

vagus action. But Mackenzie thought of the effect of digitalis only in changes of heart rate. He could not explain cases in which clinical improvement followed digitalis administration before slowing occurred, nor could he explain the improvement of patients with normal rhythm in whom no slowing was obtained. The appearence of diuresis before slowing in patients with congestive heart failure was believed by him to indicate that diuresis was an extracardiac effect of the drug.

Parkinson in 1917 found that digitalis produced no slowing in soldiers with "irritable heart" and a fast pulse (87). Since then ample evidence has accumulated that digitalis produces little or no slowing in normal rhythm cases or in the normal heart, in therapeutic doses. It has been shown that digitalis produces clinical improvement in congestive heart failure cases without tachycardia as well as those with tachycardia. Lutem believes that tachycardia in heart failure is a reflex phenomenon, a physiological adjustment which is compensatory to impairment of cardiac output (71, 128). He concludes that the abatement of tachycardia is not the cause of the improvement, but the result of it, and that the direct sinus slowing of the heart is of little or no significance so far as beneficial results are concerned. The most recent authoritative opinion is, then, that slowing of the heart under the thera-

peutic use of digitalis is due to "action on the muscle - an action whereby the heightened irritability of the muscle is reduced (71)."

Action on the A-V tissues an an important therapeutic effect of digitalis cannot be dismissed so easily. This theory has been firmly established in the minds of cardiologists largely through the writings of Mackenzie and Lewis (67, 73, 75). These men considered auricular fibrillation to be the prime indication for digitalis therapy, and slowing of the heart rate to be its only beneficial result. There is an abundance of experimental evidence to show that digitalis does have an inhibitory effect on the conduction tissues of the heart. When Broadbent (7) in 1917, dared to state that increased strength of contraction and not depression of conduction produced the beneficial results of digitalis treatment, he was immediately the target of bitter attack by Lewis (68). Broadbent pointed to cases of heart failure without auricular fibrillation in which clinical improvement was obtained by digitalis, and to cases of auricular fibrillation not due to heart failure in which no change in rhythm was obtained by digitalis. Lewis challenged Broadbent to produce a series of cases to support his belief. During the next twenty years these cases (13, 71. 88, 119) have been furnished in

abundance, and, moreover, Mackenzie's own cases have been critically analyzed to show the error of their conclusions. That depression of A-V conduction plays a part in restoring normal rhythm to some cases of auricular fibrillation with heart failure cannot be denied. Luten's recent book contains an analysis of Mackenzie's cases. It is shown that in cases where great clinical improvement was noted, but without change in rate, Mackenzie said "Digitalis had no effect on the heart." (74). While he agrees that digitalis does have an effect on A-V conduction which in some cases is sufficient to slow the heart, especially in auricular fibrillation or auricular flutter, Luten (71) concludes that the "special effect on the A-V tissues... has been assigned a prominence altogether out of proportion to its importance when compared to the indication for obtaining muscular effect."

CHAPTER VII

INDICATIONS AND CONTRAINDICATIONS

It has been established in preceding paragraphs that the major therapeutic effect of the digitalis glucosides results from their action in increasing the contraction of cardiac muscle. This section will be based on that premise and its logical conclusion: that the prime indication for the use of digitalis is myocardial insufficiency. Following Mackenzie's noteworthy observation that digitalis slows the heart rate only in auricular fibrillation, and the subsequent emphasis of this observation by Lewis there was a period of some twenty years during which auricular fibrillation was considered the principal indication for digitalis. Almost at the same time that Lewis was teaching this, however, Wenkebach was saying that "digitalis is indicated in all cases of heart failure ... irrespective of the cause of the heart failure itself." (123). Since then a large number of men, mostly Americans, have compiled series after series of cases to show that digitalis will benefit auricular fibrillation only when the fibrillation is due to heart failure, and that it will produce clinical improvement regularly in cases of heart failure without auricular fibrillation (1, 24, 50, 71. 76a, 119). In other words, the leading clinicians

have returned to the principles of Withering and Fothergill.

So firmly established is the specific action of digitalis in congestive heart failure that clinicians are almost willing to define congestive heart failure as a disease which is benefited by digitalis. This has led to two new and interesting uses for the drug: its use in potential heart failure and its use as a diagnostic procedure in certain puzzling cases in which early heart failure is suspected. Digitalis has commonly been used to prevent the repetition of attacks of heart failure (39). This application has now been extended to include the use of digitalis in preventing or postponing initial attacks of heart failure in patients with known or suspected heart damage. This use of digitalis has been advocated chiefly by Christian (15). He finds this "tonic" and especially effective in older patients with hypertrophy or other evidence of arteriosclerotic heart disease. This use of digitalis is strongly supported by the experimental proof, presented by Cloetta (18, 109), that digitalis definitely prevents cardiac hypertrophy after experimental valve lesions, and conserves cardiac reserve. Christian points out that the effects of digitalis in these cases of "occult" or "potential" heart failure, while less dramatic than its effect in

arresting auricular fibrillation, are a beautiful demonstration of the great flexibility of digitalis dosage. It has been shown elsewhere in this paper that a hypertrophied heart absorbs more of a given dose of digitalis, and that when the rate of blood flow through the heart is slow, the heart absorbs more digitalis than when the rate of flow is fast. In the tonic use of digitalis, as the heart begins to undergo hypertrophy and the circulation becomes sluggish, more digitalis is absorbed by the heart. In other words, when the heart needs more digitalis, it absorbs more; when it needs less, it absorbs less; and the physician need not change his dosage in either case (15). Luten (71) warns that the tonic use of digitalis should not be attempted in young patients who may still harbor active infection.

The use of digitalis in diagnosis and prognosis is less common. Luten points out that auricular fibrillation may be an early sign of congestive heart failure in older patients, and that abatement of this by digitalis would be of diagnostic value. He states also that this may be done in certain cases presenting such symptoms as enlargement of the liver, in which the diagnosis is not quite clear. Goldring and Grunbaum state that the degree of response to digitalis is an indication of the extent of myocardial damage and the amount of cardiac

reserve, and as such is of prognostic value.

The etiological classification of heart disease has often been considered in relation to the use of digitalis. Corrigan in 1832 announced that aortic insufficiency contraindicated digitalis, a belief that persisted for many years (23). Corrigan's statement was based on the supposition that digitalis increased aortic regurgitation by lengthening ventricular diastole, and upon one case which showed increased symptoms after the treatment was discontinued and the patient "allowed to live a normal life." Investigation shows the treatment included frequent cupping, bleeding, and starvation among its several benefits. It is difficult to judge how much of the patient's improvement resulted from the discontinuance of digitalis and how much from being "allowed to live a normal life." Balfour (2) in 1899 denied this lesion as a contraindication, stating that digitalis diminished the area of the base of the arterial column by contracting the heart. It is recognized that digitalis is of less benefit in aortic insufficiency than in other valvular lesions. This probably depends on the severity of the lesion. But many cases respond rather favorably, and certainly a greater need for digitalis is not a contra-indication to it. Marvin (76a) found that digitalis resulted inconsistent improvement only in arterio-sclerotic heart disease, and almost devoid of

effect in rheumatic heart disease. This does not coincide with the general clinical opinion, and Marvin explains that his failure to obtain good results in cases of rheumatic heart disease by saying that the "signs and symptoms of heart failure represent a later stage of failure in the rheumatic group." (76a).

The effect of digitalis on the coronary artefies has been discussed. It has been explained that digitalis in therapeutic doses does not increase the frequency of anginal pains in failing hearts, but may reduce them. This, then, does not constitute a valid contraindication for digitalis, providing heart failure is present. In anginal pain without heart failure, the work of Stewart and Cohn in showing that an increase of pain may result from the established effect of digitalis in decreasing the output of the normal heart must be considered (118a). As it stands now, angina pectoris without heart failure is not an indication for digitalis. The same reasoning holds for the use of digitalis in coronary occlusion, except that recent work suggests that there may be a diminished tolerance to digitalis after coronary occlusion (71). For this reason, digitalis should be used cautiously in cases of coronary occlusion (37).

The use of digitalis in thyrotoxicosis has fallen into disrepute. The toxemia in this disease seems to

alter the toxic threshhold of the heart (32). Experience seems to indicate that auricular fibrillation in toxic thyroid disease is better controlled by removing the cause, while heart failure is an indication for digitalis (93, 80, 106).

In shock digitalis is of no value, either in prevention or treatment. Shock is probably a result of peripheral circulatory failure rather than cardiac failure, and no results would be expected from its use. It is therefore not indicated. (71, 121).

The use of digitalis routinely in pneumonia has been studied carefully. While there is some slight evidence that routine digitalis administration in pneumonia might be of value (64), the general principle that digitalis is of little value in acute febrile states (121) which probably involve peripheral circulatory failure has been supported by clinical evidence. Wykoff DuBois and Woodruff reported, in 1930, a series of cases in which alternate patients only were given digitalis. They found the following comparative mortality:

No Digitalis			Digitalis		
Total	Died	Mortality	Total	Died	Mortality
404	136	33.7%	338	140	41.4%

They conclude that digitalis is dangerous in lobar pneumonia (131).

The use of digitalis in diphtheria as a routine is discouraged because the diptheria toxin produces the same toxic effects on the heart as does digitalis (179), and only definite heart failure calls for digitalis (71). Active rheumatic fever is considered by some to be a contraindication for digitalis, and by others to call for care in dosage.

The practice of giving digitalis in circulatory failure due to toxemias, acute infections or other acute febrile states without direct indication but as a sort of "last resort" therapy in cases which do not yield to other therapy is generally condemned (122). Attention is called to the effect of temperature, in increasing the effect of temperature on the rapidity of action on digitalis (48) and to the report by Robinson that (quoted, 71) toxic effects are secured with lower dosages in febrile patients. This should call for exceptional watchfulness in the use of digitalis where patients with fever and true indications for digitalis are concerned.

The use of digitalis in heart block depends on the extent of the block. In partial heart block, the question of an increase of the block by the action of digitalis on the conduction system has been brought up. This has caused partial heart block to be a contraindication for digitalis. This opinion has changed. It is

considered that the beneficial effect of digitalis when indicated might outweigh any block producing effect. Warning is given that digitalis may precipitate Adams - Stokes attacks in the transition period between partial and complete block. This must be weighed against the possibility of lessening the attacks by improvement of heart action, or the elimination of the attacks by converting of partial block to complete block (28). Complete heart block is no contraindication for digitalis, for the block cannot be increased (110) (94) Bundle branch block has sometimes been regarded as a contraindication to digitalis, but clinical results have disproved this (52).

The use of digitalis in cases showing extra systoles is not well understood. The fact that digitalis may produce extra systoles is well known (55, 71, 114, 90). On the other hand, cases of extra systoles abolished by digitalis are frequent. The same is true for paroxysmal tachycardia, auricular fibbrillation and alternation. These all may result as toxic effects of digitalis, but when due to heart failure, may be abolished by digitalis. It follows that the appearance of one of these arrhythmias during the administration of digitalis should require the stopping of the drug, but that otherwise they are not contraindications (3, 4, 26, 112, 95, 96).

The use of digitalis with ephedrine (60), calcium or barium is to be accompanied with caution because of the possible additive effect of the drugs in producing

toxic symptoms.

Experimental evidence that digitalis causes constriction of the arterioles (9, 24, 25) has brought up the question of its use in hypertensive patients. There is little evidence that digitalis in therapeutic doses causes vasoconstriction in man. The commonest finding is a transient and slight rise in systolic pressure. If increased cardiac output induced by digitalis in heart failure patients results in increased arterial pressure, as it certainly must in some cases, there must be an accompanying vasodilation or other compensatory reflex adjustment. Hypertension is not considered a contraindication to digitalis.

The routine preoperative use of digitalis is condemned as being not indicated (77). If indication exists, digitalis should be given pre-operatively in effective doses.

CHAPTER VIII

TOXIC EFFECTS

Nausea and vomiting as caused by digitalis have been known almost as long as the drug itself, for one of its earliest uses was as an emetic. But Withering was first to recognize them as toxic effects rather than as therapeutic effects (130). It was originally believed that this was a result of gastric irritation, later that it was due to the action of digitalis on the vomiting center of the medulla. Hatcher and Weiss (53) showed that vomiting could not be produced in animals by perfusing the brain with the glucosides, but that it could be prevented by cutting the nervous connections of the heart. Nausea and vomiting are, therefore, the result of a reflex originating in the heart. This was confirmed in man by Eggleston and Wyckoff (29). The importance of this is in showing the futility of attempts to continue digitalis by rectal administration after the onset of vomiting due to digitalis. Usually there is a prodromal period of anorexia. The vomiting reflex is a protective mechanism which may, in some cases of overdosage, remove the unabsorbed excess of digitalis from the gastro-intestinal tract. This is of theoretical interest only, for only time can remove the toxic dose which is fixed in the

heart muscle. The nausea and vomiting may appear in successive attacks, often over a period of several days, alternating with periods of freedom (130). Gold, Travell, and Kwit have observed that, after an initial period of vomiting, there may be a depression of the vomiting center so that death may ensue without a recurrence of vomiting. This is clearly of clinical importance (44).

Cerebral symptoms are of importance and may be the earliest toxic manifestations. Headache is most common. Disturbances of vision, particularly color perception, are of importance (130, 117).

The greatest variety of toxic effects is referred to the heart. A toxic degree of A-V conduction is a well known symptom, even to the extent of complete block. Since a certain amount of A-V block probably occurs in the therapeutic range of digitalis administration, the degree of impairment of conduction must be evaluated in interpreting this action as a toxic effect. The same may be said for extra-systoles and sinus arrhythmia. Auricular fibrillation (59), auricular and ventricular tachycardia, A-V dissociation, and ventricular fibrillation may be observed with higher degrees of toxicity. A special type of ventricular tachycardia which shows an alternate reversal in the direction of the Q R S complexes has been recorded many times, and usually

precedes ventricular fibrillation and death (78, 84, 116, 82).

Withering in his early use of digitalis used the appearence of toxic symptoms as an indication that the therapeutic zone of action had been reached, but later learned that by being aware of climical signs of improvement, he did not have to subject his patients to the discomfort of toxic effects. In this he was far ahead of many later users of the drug.

CHAPTER IX

ADMINISTRATION AND DOSAGE

There are several sources from which the digitalis glucosides are obtainable. These sources vary considerably in their absorbability, rapidity of action, rate of elimination, and potency (49). There is no essential difference between them, however, in the order of events observed electrocardiographically after the administration of successive fractions of lethal doses (42). The requirements of a satisfactory preparation are: (1) It must be of known potency. (2) It must be readily available. (3) It must be easily prepared. (4) It must be in such a form that the dosage can be easily controlled.

Digitalis purpurea fulfills these requirements better than the other plants, for oral or rectal use. Strophanthus has been shown to be more satisfactory for intravenous use. There is a larger fund of data available regarding the use of digitalis than the other plants of the group. The powdered whole leaf has been found superior to other preparations since the time of Withering. It is cheap, of highly constant potency, and, when properly prepared, its deterioration is negligible. The tincture deteriorates slightly, and the infusion much more so. Furthermore, correct dosage is more difficult when the fluid preparations are used; measurement by drops is completely unreliable and measurement by a graduate is inconvenient. The proprietary products and purified or

concentrated glucosides have no added virtue for general use, and are more expensive (65). Furthermore, the control of dosage, instead of being aided, is made more difficult by the pure substances, for as the potency of the preparation is increased, the mass of the dose is correspondingly decreased and the measurement and administration of fractional doses interfered with. Furthermore, the claims of pharmaceutical houses that their preparations will not cause nausea or other toxic symptoms are either admissions of lack of potency or deliberate misstatements of fact, for toxic symphtoms result from quantity, not quality.

The cardiac glucosides are standardized by biological assay. The cat method of Hatcher had been found to be the most reliable. The unit of potency under this method is the Cat Unit: the minimal lethal dose for cats per kilo of body weight. For crystallin g-strophanthin this is rather constantly 0.1 mg. per kilo. Digitalis leaves vary in potency, but the average is fairly constant at one cat unit per decigram (1½ grains) and the better preparations are adjusted to this strength by blending.

Oral administration is the most commonly used and most satisfactory method (101). In cases of nausea not due to digitalis intoxication, rectal administration may be employed, using diluted tincture, suppositories of whole leaves, or a suspension of the leaves in water or

starch paste. The rectal dose is the same as the oral dose (63). Rectal administration is usually preceded by a cleaning enema. In rare cases where a genuine need for quick action is present, parenteral administration may be justified (101, 85, 49). However, intravenous medication is dangerous and seldom justified, for the interval between administration and effect is not markedly reduced (17).

The full therapeutic effect of digitalis is not observed for several (eight to twenty-four) hours after a large dose. The earliest effects are seen in two to three hours, and some effects may persist for periods of two weeks or longer after full digitalization. This makes it obligatory for the physician to determine if a patient has been given digitalis within the previous three weeks before ordering a full therapeutic dose. If a possibility exists that a patient may have had digitalis within this period, or if the accurate information cannot be obtained, the physician must proceed very cautiously. Disastrous results have followed the giving of full therapeutic doses to patients already partially digitalized.

The persistence of action, the cumulation of effect of digitalis are such as to permit the most flexible and intelligent use of the drug in proper hands. While the exact mechanism of excretion or destruction of digitalis

is unknown, it has been established that the rate of disappearence from the body is not a fixed amount, but a quantity that varies with the amount of digitalis present in the body (40, 83). By taking advantage of the cumulative action and flexible rate of excretion, a cumulation of effect may be built up to a desired level of therapeutic action by repeated fractional doses, then the level maintained by a small daily dose (41). By reason of varying rate of disappearence, a patient may be fully digitalized by the daily administration of a small dose which may be continued as a maintainance dose. The therapeutic effect may be maintained at any desired level by adjustment of dosage. The optimum therapeutic level approaches the toxic zone of action more closely in cases of mild heart damage, and is very close to the toxic zone in children.

The effective dose is the quantity of the drug which becomes available to the heart in producing a certain level of effect. The average effective dose of digitalis has been determined by Eggleston to be 0. 146 cat unit per pound of body weight (29), usually given over a period of thirty-six hours. On this basis, the following formuli for estimating the probable effective dose have been arrived at (Christian):

(12a)

Single Dose Method

Av. total dose (oral) 0.15/lb. of body wt.

$\frac{C.\ U.\ X\ 0.15\ X\ W}{1000}$ = gm. powdered leaf.

$\frac{C.\ U.\ X\ 0.15\ X\ W}{100}$ = c.c. tincture.

$\frac{C.\ U.\ X\ 0.15\ X\ W}{10}$ = c.c. infusion.

Modified Large Dose Method

1/4 total dose given and repeated in 4 hrs. Remainder given in 0.1 or 0.2 gm. doses $\bar{q}$ 4 hrs. to end of 24 hrs., or

0.5 gm 1st dose, 0.5 gm in 4 hrs., then 0.1 or 0.2 gm $\bar{q}$ 4 hrs. if patient is awake until pulse begins to slow or diuresis or nausea appears.

Small Divided Dose Method

0.2 gm. or 0.1 gm. t. i. d. until signs of digitalis appear.

It must never be forgotten that "these represent quantities which, in the average, should be regarded rather as doses not to be exceeded than as doses to be administered; as top dosage rather than as optimum dosage." The effective dose varies from the average enough so that these are to be considered as guides to dosage rather than as fixed dosages to be administered

by rule to all patients. Serious results have followed the use of large doses based on the weight of edematous patients. There is no substitute for close clinical observation during digitalis administration. Digitalis should be administered in safe doses and stopped for several days if toxic symptoms appear.

The maintenance dose is the amount which must be supplied daily in order to maintain effect at the desired level.

The average maintenance dose is approximately one cat unit (1½ gr. powdered leaf) for the adult (86). Optimum maintenance does vary widely as does the therapeutic dose. Therefore it, too, must be arrived at by intelligent trials with the individual patient (8).

The use of digitalis in children varies somewhat from its use in adults. There is no qualitative difference between the action of the drug in children and in adults, but children require a therapeutic dose of about 50% more than adults when determined by the weight method, and the improvement seen in children is less striking than that seen in adults. Sinus slowing occurs early in children, but nausea and vomiting are late manifestations and cannot be used as criteria in estimating the optimum therapeutic dose. Digitalis is, of course, contraindicated in children with acute or chronic rheumatic disease (58, 79, 111, 113).

The electrocardiogram has been found to be an excellent quantative index of the amount of digitalis effective in the body. Since the time of Withering it has been necessary to administer digitalis until visible therapeutic or toxic effects were observed (33, 91, 130), and these were often noted too late to avoid unpleasant effects. The electrocardiogram will disclose that the therapeutic level of digitalization has been reached before more obvious evidences appear. The characteristic inversion of the T wave, or any other less characteristic change in the electrocardiogram which appears after digitalis has been administered may be taken as a signal that the therapeutic zone of action has been reached, and the maintenance dosage begun (8, 19, 20, 61).

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