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Digitalis intoxication

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DIGITALIS INTOXICATION

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I. INTRODUCTION

Following the introduction of digitoxin into general usage within the past two decades, it was hoped that the problem of digitalis intoxication would be a decreasing one. Unfortunately, despite the introduction of this purified glycoside, the problem of digitalis intoxication has steadily increased since its introduction by William Withering in 1785.

Largely as a result of the medical advances within the past fifty years, more and more people are living to an age at which congestive heart failure is a common affliction. Concomitantly, the use of digitalis has increased.

Numerous investigators have commented upon the apparent increased incidence of digitalis intoxication, an increase apparently out of proportion to the increasing use of the cardiac glycosides. Statistical evidence supporting such a rise is of course difficult to obtain. One investigator (1), however, in studying the records of the metropolitan hospitals in one city, could find only two cases of digitalis intoxication in 1946, but found 28 such cases in 1956 without increased hospital admissions. Herrmann (2) also found a gradually increasing incidence, and using rough

statistics, found that by 1943 at his hospital, one in-patient in every fifteen on digitalis showed symptoms of moderate to severe intoxication. Flaxman (3) also feels there has been a disproportionate increase and attributes this largely to the introduction of digitoxin. He states that he did not see a case of severe cardiac arrhythmia due to digitalis until digitoxin entered into general usage in his region in approximately 1946-47. Of course, a number of factors distort the statistics concerning the incidence of digitalis intoxication -- two of the more important ones being the increased awareness of the manifestations of intoxications by members of the medical profession, and the second being the reluctance on the part of the physicians to make a written diagnosis of an iatrogenic disorder in their patients. It is interesting to note, however, that Withering's original report (4) shows that approximately 15 per cent of his patients on digitalis suffered from minor to major signs of intoxication.

Mortality: Diagnosis of digitalis intoxication as a cause of death is difficult for reasons which will be shown subsequently. For this reason, it is not difficult to understand why statistics concerning the mortality rate due to digitalis intoxication are not frequent in the literature. Shrager (5), however, in

a series of 40 cases of intoxication, attributed two of the deaths to toxicity. Crouch (6) felt that seven of 100 cases of intoxication which he reviewed died directly as a result of intoxication. Rodensky (7) reviewed 88 patients with intoxication, 25 of whom died. In 10 of the 25 deaths, intoxication was considered to be the immediate cause of death.

The difficulties involved in the use of this drug can be better understood when one realizes that in order to gain therapeutic effect, one must give approximately 60 per cent of the dose necessary to give toxic reactions, and that once toxic reactions occur, the patient has received approximately 40 per cent of the minimum lethal dose (8). Two case histories will further illustrate the difficulties involved in determining the size of dosage to be given a patient:

> Case 1: This patient entered the hospital for treatment of a prolonged episode of atrial flutter. He was given 2.5 gm. of digitalis leaf in order to reduce the rapid ventricular rate, this dose being given over the course of a few days. The rate was unaffected, however, and he was maintained thereafter on 0.2 gm. of leaf daily. In a further effort, 1.3 mg. of ouabain was given intravenously over a period of two and one-half hours, with the result that the ventricles finally were slowed. Despite this large amount of digitalis, the patient experienced no subjective evidence of intoxication and only a few extrasystoles, lasting for several minutes.

Case 2: A 66 year-old female with rheumatic heart disease became intoxicated with nausea and vomiting on 1.0 mg. digoxin, orally, in one day, in divided doses, although previously she had been able to tolerate 0.2 mg. of digitoxin. Attempts at maintenance with 0.25 mg. of digoxin every third day would produce bigeminy, and administration of only 0.15 mg. of acetyl strophanthidin would also produce bigeminy (10).

Case 3: This patient had atrial flutter with a 1:1 ventricular response and on three different occasions required massive doses of various digitalis preparations to control the ventricular rate. On one occasion, he needed 11.0 mg. digoxin plus 1.8 gm. leaf over 12 days, plus additional quinidine, to restore regular sinus rhythm. On one occasion, this patient with atrial flutter and a ventricular rate of 212 needed 3.3 mg. digitoxin intravenously over 60 hours, followed by an average of 0.6 mg. digitoxin daily as a maintenance dose to change the 1:1 ventricular response to the desired 1:2. (10).

These cases serve to illustrate the problem a clinician has in attempting to judge the required dose for an individual patient. On one hand, he is faced with the knowledge that inadequate digitalis in the patient will be of no value at all, and on the other hand, excessive digitalis may precipitate a fatal cardiac arrhythmia. A similar dilemma is faced by the physician with many other drugs; with few of the others must he contend with such a narrow therapeutic range.

Understanding the etiology, manifestations, and treatment of digitalis intoxication requires basic

knowledge of underlying mechanism of congestive heart failure and that of the action of digitalis. Consequently, a short review of the current knowledge in these areas is included.

II. PHYSIOLOGY OF THE MYOCARDIUM

A. Actomyosin and ATP

Cardiac muscle, like skeletal muscle, shows the characteristic markings of striated muscle. In both, the muscle fiber is composed essentially of sarcoplasm and thin cross-striated fibrils, myofibrils, which are present in large numbers parallel to one another within the sarcoplasm. Microscopic examination of the myofibrils reveals the familiar A, H, Z, I bands, delineating the sarcomere. The protein extracted from muscle, named "myosin" by Kuhn in 1868, has been regarded as the building block of the contractile structure. It was subsequently determined by Szent-Gyorgyi and his colleagues that myosin in fact consists of at least two proteins -- actin and myosin. This complex of two proteins was named actomyosin, and its principal components are now regarded as the working machinery of skeletal and cardiac muscle. The discovery that actomyosin could hydrolyze ATP suggested that the energy necessary for contraction of the sarco-

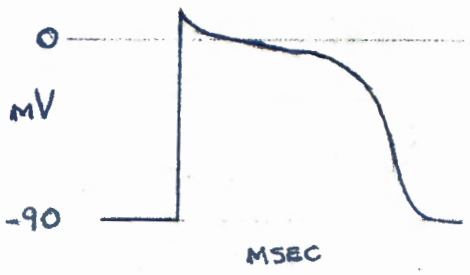
mere was supplied by interaction of the actomyosin with the ATP, with the energy released from hydrolysis of this molecule being transferred to the actomyosin, with resultant contraction.

Although the microscopic appearance of skeletal and cardiac muscle differ, it appears at present that the contraction process is essentially the same in both types of muscle.

B. The Action Potential

Activation of the ATP-actomyosin complex to cause "muscle contraction" is apparently accomplished indirectly or directly, by depolarization of the muscle fiber membrane. As do nerve cells, muscle fibers maintain a steady resting potential across their membrane, with the inside being negative with respect to the outside. The size of the resting potential generated by the sodium-potassium pump depends largely upon the relative permeability of the membrane to sodium and potassium; i.e., the more permeable to potassium and less to sodium the membrane is, the higher will be the resting potential across this membrane. The normal resting potential across muscle fibers is approximately -90mV. Muscle fiber membrane is relatively impermeable to the passage of sodium ions. It is apparent that the concentration of potassium ions within and without

the cell and the diffusion from the area of higher concentration to that of lower concentration is the chief determinant of the size of the resting potential. Any increase in the extracellular concentration of potassium ions would be expected to decrease the resting potential.



It is generally accepted that the sudden upswing of the resting potential is due to a sudden change in the membrane from being potassium permeable to being sodium permeable. With this change, there occurs a sudden net influx of sodium ions due to the negative potential within the cell and the gradient of sodium across the cell membrane. The upswing of the spike to electropositivity within the cell is apparently a result of the fact that the potential due to sodium exceeds that of potassium, with a net electropositivity within the cell being the result. Following the initial increased permeability to sodium, the membrane returns to its original state of increased permeability to

potassium and resistance to sodium, with the result that the membrane potential returns to its normal resting state.

It is well established that this sequence of depolarization is the direct or indirect initiator of contraction of the sarcomere. However, the events linking these two processes are not well understood (11), although recent evidence suggests that sodium, potassium, and magnesium in some way may activate the hydrolysis of ATP (34). Calcium is also thought to be a connecting link.

C. Cations and the Contraction of the Normal Myocardium

Ringer's classic work (12) showed that in order for a myocardial contraction to continue for more than a few minutes, sodium, potassium and calcium must be present in the perfusion medium. When the concentration of calcium in the medium is increased, the rate and force of systole increase. Conversely, when the concentration of potassium is increased, the rate and force decrease. In the intervening years, an enormous body of literature has accumulated on the relationships of these three cations to the contractility of the myocardium.

The precise role which calcium plays in muscle

contraction is as yet not well understood. This is in part due to the difficulty in measuring it, and the fact that it exists in both bound and free forms, neither of which can be measured separately. Calcium ion apparently is involved in maintaining the stability of the polarized cell membrane. The magnitude, rate, and direction of exchange of cations during polarization and repolarization depends upon the concentration of ionized calcium, but contradictory theories exist as to which ions are affected and in what manner (13, 14).

Contractility of the sarcomere is believed by investigators such as Szent-Gyorgyi (15) and Hajdu (16) to be directly related to the intracellular concentrations of various cations. Hajdu suggests that contractility is proportional to the ratio of:

$$\frac{[\text{Contractile Protein}]}{[K^+] + [Na^+]^+}$$

Thus, lowering of the intracellular levels of either of these cations should increase contractility. As will be discussed subsequently, most investigators found that digitalis in therapeutic doses causes a loss of potassium from the myocardium, thus supporting the above theory. However, Vick (17) subsequently demonstrated that glycosides which produce a negative inotropic effect also cause myocardial potassium loss.

This work is as yet unconfirmed. At the present time, therefore, the relationship between intracellular sodium and potassium and altered contractility is still in question.

Magnesium undoubtedly also plays a significant role. However, study of this ion has been hampered by difficulties in measuring its concentration. Like potassium, it is predominantly intracellular, and like calcium, it is partially bound to protein. Studies with radioactive magnesium have indicated that heart muscle exhibits a particular avidity for this cation (18).

In vitro work on isolated actomyosin bands and threads isolated and on other intracellular constituents of myocardial cells has enabled investigators to study the effects of various ions directly upon the contractile protein, with the discovery that magnesium, calcium, sodium, and potassium are directly involved in the ATP-actomyosin cycles (19, 20).

Although it is well established that depolarization of the membrane initiates contraction of the sarcomere, the events linking these two processes are not known. Evidence has been presented suggesting that one or more of the above cations may be the link. Thus, the entrance of sodium into the cell, the loss

of potassium, and the unknown movements of the other ions may in some way alter the stability of ATP so that hydrolysis occurs and energy is transferred to the contractile protein.

In summary, then, the myocardium consists of filaments of actin and myosin, bathed in an intracellular medium containing large concentrations of potassium and magnesium, along with lesser quantities of other cations. The components of the phosphate energy cycle are also present within the cell. These cells are covered by a membrane which is polarized at rest. Depolarization, with the sudden influx of sodium and outflow of potassium, in some way initiates the contraction of the actomyosin filaments. The recovery phase consists of repolarization of the membrane, of reformation of ATP, and of the return of the sarcomere to its resting length.

III. ALTERED PHYSIOLOGY IN CONGESTIVE HEART FAILURE

Myocardial failure may be defined as the progressive decrease in the ability of the heart to respond to a given degree of tension with the same contractile power. It is generally assumed that the dilatation of the heart is due to stretch of the sarcomere, per se, although unconfirmed recent work disputes

this theory (21).

Studies on isolated actomyosin bands or threads have shown conflicting results as to the presence or absence of differences between those from normal and those from failing hearts (22, 20). Final judgment on the significance of the various findings will have to be withheld until further work elucidates the connection these findings have with *in vivo* alteration of actomyosin and the validity of the techniques used. Furthermore, it must be understood that changes found in failing hearts are not necessarily those precipitating or causing the failure; rather, they may be the result of the failure.

Numerous studies have been undertaken to determine the concentration of various electrolytes in the intracellular and extracellular fluid spaces in congestive failure. The literature found on the subjects contain numerous contradictory reports due in large part to the inaccuracies of the techniques used at various times and the misinterpretation of the information gained by these various methods.

The studies with which we are chiefly concerned are those which differentiate between the intracellular compartment and the extracellular compartment. These spaces are normally measured by injection of a tracer

material which ideally is limited to the particular space in question, and the concentration of the substance after dilution indicates the volume of fluid in that space. Unfortunately, no ideal tracer has been found, although a number are in use. Inulin has frequently been employed as a means to measure the extracellular space. In a normal individual, this material gives a satisfactory result, but unfortunately in edematous individuals, the results are distorted because of the slow diffusion rate of this material and the long time necessary for equilibration to take place. This difficulty has not been widely appreciated, however, and inulin is commonly used to measure the extracellular space. Another difficulty attending this measurement is that this space is not homogenous and no substances diffuse evenly through it.

Direct measurement of the volume of the intracellular space has been impossible with techniques presently employed. The best methods available at the present time involve measurement of the total body water, usually employing deuterium or tritium isotopes of water, and then calculation of intracellular water by subtraction of the extracellular fluid volume. Determination of the volume and concentration of electrolytes and water within selective organs such as

the heart obviously becomes very difficult. Results in the literature often report a concentration of certain cations per gram of dried heart, with no attempt to differentiate between that which originated in the intracellular and extracellular spaces.

With these limitations in mind, the values and limitations of the reports to be presented can better be understood. These factors may account for contradictory results obtained by various investigators.

Most studies are in agreement that in congestive heart failure there is an increase in total body water and total body sodium, with the increase in sodium being relatively greater than that of water. Furthermore, both the intracellular and extracellular compartments share in this increase in volume (22). At the same time, total body exchangeable potassium is generally reduced, often markedly (22,-24).

Serum levels of these electrolytes, however, usually do not reflect the net body alterations. Hyponatremia is common, despite a net increase in body sodium, and is usually due to chronic dilution. Serum potassium levels, on the contrary, are usually within normal range, again despite the net loss of body potassium (25). Diuretics, of course, play a role in the determination of the serum level of these

electrolytes. However, the potassium levels normally are not altered in the usual course of such therapy. The sodium levels, however, may be markedly influenced by these drugs (25). The failure of the serum electrolyte level to reflect total body stores is of definite clinical significance and will be discussed subsequently.

Determination of the potassium and sodium content of the myocardium in congestive failure has generally not involved, as noted previously, attempts to differentiate between extracellular and intracellular compartments. It is generally agreed, however, that in congestive failure the myocardial content of potassium is decreased (26-28, 16).

IV. THE PHARMACOLOGY OF DIGITALIS

Digitalis is used clinically essentially for three purposes: to increase myocardial contractility in failure, to reduce atrio-ventricular conduction in atrial fibrillation or atrial flutter, and to prevent or control paroxysmal ectopic atrial or nodal arrhythmias.

A. Essential Cardiac Actions

The essential cardiac actions of digitalis are: 1) to increase the force of systolic contraction;

2) to decrease heart size; 3) to lengthen the refractory period and to slow conduction in the atrio-ventricular node and bundle of His; 4) to decrease the refractory periods of the atria and ventricles; and 5) although usually not apparent except at higher dosages, to increase the automaticity of the myocardium (29-31). The last three are the causative factors, apparently, of the cardiac manifestations of digitalis intoxication.

The lengthened refractory period and the slowed conduction in the A-V node and bundle of His are apparently due to two different effects of digitalis. The first is mediated through the vagus nerve, while the second is the result of direct action of digitalis upon this conduction mechanism. Stimulation of the vagus nerve has three pertinent effects on the heart; it: 1) decreases the rate of firing of the sino-atrial node; 2) decreases the rate of conduction of the depolarization waves through the atria and through the A-V bundle; and 3) increases the refractory period of the A-V bundle (32). The mechanism of increased vagal action is not yet clear. Gaffney (33) suggests that it is due to increased sensitization of the sino-atrial and atrio-ventricular nodes to acetylcholine. Earlier work, however, opposes this viewpoint and rather contends that the stimulation is central in origin due to

direct action of digitalis on vagal centers in the medulla. Other experimental and clinical findings support the belief that digitalis does have direct action on the central nervous system. Regardless of the mechanism, there is no doubt that vagal action plays a role, since atropine effectively blocks much of the action of digitalis on the atrio-ventricular tissue. That a direct action of digitalis upon the atrio-ventricular tissue exists is attested to by the fact that atropine even in extremely large doses fails to abolish the bradycardia induced by digitalis (35) or in patients with atrial fibrillation (36). A third mechanism involved in slowing the heart in cardiac failure when normal sinus rhythm is present is undoubtedly related to the positive inotropic action of digitalis producing improved cardiac output. Since the tachycardia of congestive failure, when a regular sinus mechanism is functioning, is considered to be a result of reflexes caused by the anoxia, correction of the failure would be expected to inhibit the sympathetic stimuli and promote vagal reflexes (30). In contrast to its effect via the vagus upon the A-V node and bundle of His, the refractory period of the atrial and ventricular tissue is shortened by digitalis, apparently by direct action. The shortened refractory

period allows more time for ectopic impulses to be generated and propagated. This alteration is considered to be essential to the increased automaticity of the myocardium with larger doses of digitalis and the predisposition of the myocardium in such cases to arrhythmias.

B. Effect of Digitalis upon the Electrolytes of the Myocardium

The literature is generally in agreement that in toxic doses, digitalis causes a loss of potassium from the myocardium (37-44). Much of this work suffered from inadequacies of the early techniques used in these studies and others from misinterpretation of the data gathered. The majority of the early studies were run in vitro, in which the electrolyte content of the heart was measured per gram of dried heart with no attempt to distinguish between intracellular and extracellular compartments, and no attempt to correct for this lack of distinction. Fortunately the errors introduced in this way were not significant in view of the apparently large degree of potassium loss and the normally low extracellular level of potassium.

In therapeutic doses, most authors agree that digitalis also leads to a loss of potassium, due to intracellular depletion.

Several authors, however, have disagreed with this viewpoint. Boyer (37), in 1940, suggested that, with therapeutic doses of digitalis, the potassium and water content of the myocardial cells increased. Hagen (44), in 1939, found a slight increase in myocardial potassium levels of isolated hearts, again not differentiating intracellular and extracellular levels. Friedman and Bine (39), in 1947, suggested that only toxic levels of digitalis would cause loss of potassium from the heart and that therapeutic levels did not essentially alter these levels. However, they based their results, not upon measurement of the potassium balance in their perfusion studies, but rather upon physiologic responses of the heart. This study was not well enough controlled to permit such conclusion from the observations made.

Clarke and Mosher (28), in 1952, analyzed human myocardial tissue from seven normal and eleven cardiac patients not on digitalis, and five cardiacs who were on digitalis. The sixteen cardiac patients all died with congestive heart failure. All specimens were obtained within an average of eight hours after death. The potassium levels were definitely decreased in the patients dying of congestive heart failure and not on digitalis, compared to the normal hearts, and were at

intermediate levels in those patients on digitalis. They further found that the sodium levels in the digitalized hearts were depressed toward the normal level. They suggest that these effects are due to direct action of the digitalis upon the myocardium, but do not rule out indirect action via the vagus. Staub (45), in 1959, added his support to the view that digitalis in therapeutic doses does not cause a further depression of myocardial potassium. His studies were based on analysis of the perfusion fluid bathing strips of myocardium.

It is impossible to say with certainty, however, that the changes found in Clarke's relatively small series of patients fairly indicate only the effects of digitalis. No indication is given as to other medications which the patients may have been taking, and it seems unlikely that patients who died with congestive heart failure but who were not on digitalis were not receiving some forms of medications -- possibly diuretics. The well-known effect of thiazides and mercurials to increase potassium excretion may have played a significant role here. These factors are of course difficult to evaluate and with such a study, controls are necessarily lacking. In vitro studies such as those performed by Staub introduced the

complication of asserting that the effects of certain medications in artificial situations adequately simulates actual in vivo events.

In summary, then, most authors agree that even in therapeutic doses digitalis does cause a loss of potassium from the myocardium (44, 38, 40, 27, 46, 16), and convincing proof to the contrary is lacking.

The effects of digitalis upon sodium and other cations have not been as extensively studied. As noted above, Clarke indicates that digitalis apparently causes an increase in myocardial sodium. This result, however, must be interpreted in the light of the objections already mentioned. Hajdu (16) states that digitalis does not appear to alter myocardial intracellular calcium levels.

C. Effects on Serum Cations

Lown (8, 47) has extensively studied the effects of digitalis upon the serum electrolytes. On the basis of 110 digitalizations of 40 dogs to an end-point of ventricular tachycardia, he found a statistically significant increase in serum potassium concentration of 0.64 mEq/L, and an average fall in sodium concentration of 3.1 mEq/L. He found no significant change in serum calcium in these experiments. An increase in potassium occurred in 93 per cent of the digitalizations;

in less than two per cent was a decrease present. A decrease in sodium occurred in 83 per cent of the 110 digitalizations and an increase in only eight per cent. He found that the earliest change in cation concentration was noted at the start of the digitalization and preceded any alteration in the electrocardiogram. When digitalization was carried out to an end-point of ventricular fibrillation, the rise in potassium and fall in sodium were even more marked -- averaging 1.8 mEq/L and 11.3 mEq/L, respectively.

The increase in serum potassium in these cases is too great to be accounted for simply by a loss of myocardial potassium. In Lown's studies, the increase in arterial blood potassium level in some animals was actually in excess of the total calculated potassium content of the heart muscle. His subsequent experiments indicated that two mechanisms evidently operate to cause this rise in serum potassium during digitalization. First, there is decreased uptake by the skeletal muscle of released potassium, and second, there is a generalized release of potassium from a number of tissues, with the liver playing the most significant role. This effect of decreased influx of potassium into cells will be discussed again in attempts to analyze the methods of digitalis action upon the myocardial cells.

On the other hand, the decrease in serum sodium is evidently due to increased uptake of this ion by liver cells exposed to digitalis.

The effects of digitalis upon magnesium levels in the serum is not yet well documented. Kim (48) found in experiments upon dogs that the serum magnesium level is lower during digitalis intoxication than after corrective therapy (not involving magnesium administration). He is uncertain as to the mechanism involved here, but suggests it may be due to decreased intake resulting from the anorexia associated with the intoxication, to shifts involving intracellular stores and bound forms, or to increased excretion. In view of the apparent involvement of magnesium with the contractile protein and the significant quantities of magnesium within the cells, it is apparent that further work is warranted on the interrelationships of digitalis and magnesium.

D. Intracellular Actions of Digitalis

As noted above, the contractile process can be thought of as two cyclic mechanisms. The first of these is the hydrolysis and resynthesis of ATP, while the second is the shortening and lengthening of the contractile protein, actomyosin. The first cycle is thought of as energy liberation, while the second is

considered energy utilization.

Two schools of thought exist concerning the mechanism of digitalis action upon the myocardium. The first school considers that the basic defect in congestive heart failure is that of defective energy liberation and that digitalis acts in some way to correct this defect. The second school believes that digitalis acts to rectify abnormal energy utilization.

The majority of studies on the mechanism of digitalis action attempt to compare its action upon the failing heart with that on the normal heart. The differences or lack of differences in the effect of digitalis in these two conditions must now be considered in light of the evidence that digitalis exerts a positive inotropic action even in the absence of heart failure (49). Thus it may be that we should expect merely a quantitative difference rather than the all-or-none difference which investigators have previously desired.

1. Digitalis and Energy Liberation:

Early evidence suggested that the high energy phosphate stores were reduced in experimental animals after spontaneous failure (53). Wollenberger (54-56) was unable, however, to demonstrate a depletion of these stores in his own experiment with spontaneous

failure in the dog heart-lung preparation.

Feinstein (57) recently undertook to reexamine this problem. Utilizing guinea pigs, he created artificial coarctation of the aorta by ligating the ascending portion of the aorta to 30-50 per cent of its original diameter. Control animals underwent the same operative procedure, except that no constriction of the aorta was created. Analysis of the ventricular tissue from these animals revealed a marked decrease in the concentrations of high energy phosphate compounds compared to the control animals.

In an attempt to determine whether cardiac glycosides exerted their action by elevating the concentration of high energy phosphate compounds within the myocardium, Feinstein then injected ouabain directly into the hearts of five of the animals who had artificial aortic coarctation. In these animals, a typical response to digitalis was observed. However, analysis of the tissue of these animals revealed no significant difference in the high energy phosphate compound levels compared to those animals which had not received digitalis but had also been forced into failure.

These results indicate that a positive inotropic response to the glycosides can occur without a return of the high energy phosphate stores. While these

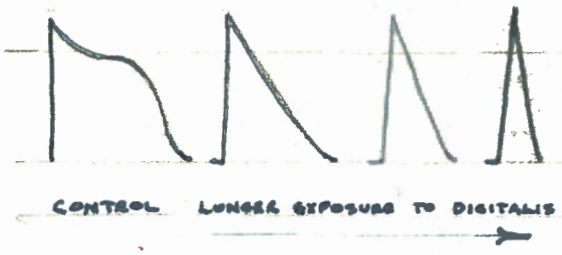
results would seem to indicate that the glycosides do not exert their effect through actions upon the high energy phosphates, i.e., on energy liberation, it must be kept in mind that these results do not reflect the turn-over rate of the phosphates. Changes in the rates of synthesis and utilization were not obtainable by these methods and these may in fact be more significant than the average level, at least early in digitalis therapy. However, at the present time, there is no evidence in this report to suggest that the glycosides act through the high energy phosphates, and little evidence overall to substantiate the belief that digitalis acts to improve energy liberation.

2. Digitalis and Energy Utilization:

At the present time, two major explanations have been advanced concerning the effect of digitalis upon energy utilization. The first of these is that digitalis exerts its effect upon the cell membrane. The second is that digitalis acts directly upon the contractile protein. These theories will be examined in that order.

a. Effects on the Cell Membrane and Action Potential: As explained above, the resting potential across the myocardial cell membrane is a result of the fact that the membrane is potassium permeable but impermeable to

sodium. The action potential is generated when the converse becomes true. The sudden influx of sodium creates the spike of the action potential; the down-slope of the action potential reflects the reversal of the membrane to its normal state of permeability and the return to resting potential levels. Since the resting potential is dependent upon the potassium and sodium gradients across the membrane, and upon the permeability to chiefly these ions, it would be expected that anything which would alter the permeability of this membrane would alter both the resting potential and the action potential. According to Hajdu (16), the chief effect of digitalis upon the action potential is to decrease its duration. This decrease is apparently entirely due to a shortened repolarization phase. In therapeutic doses, digitalis also sometimes increases the amplitude of the spike of the action potential. In experiments upon single ventricular fibers of the frog heart, Woodbury and Hecht (58) found the following alterations in the duration and shape of the action potential as digitalis was allowed to contact the fiber:



Both the rate of depolarization and the duration of repolarization were affected, suggesting effects on sodium and potassium permeability. Since it has been found that similar alterations in the duration of the action potential can be effected by increasing the extracellular potassium concentration (59), it does not seem unreasonable to inquire as to whether or not digitalis might act by increasing the potassium concentration at the outside surface of the cell membrane. This could be accomplished in two manners: first, by increasing the rate of efflux of potassium from the cell, or second, by decreasing the rate of influx. Support for the former viewpoint is found in the numerous reports indicating that digitalis causes a release of potassium from the myocardium. Blackmon (38), in his balance studies on the blood supply to the heart, found a rapid release of potassium from the myocardium after the administration of digitalis. Within

one hour after the digitalis had been administered, however, a positive potassium balance was again evident with return of the lost potassium stores to the myocardium.

Although these reports would seem to indicate that digitalis plays an active role in stimulating efflux of potassium from the cells, what in fact appears to be the case is that both the potassium which diffuses through the cell membrane to create the resting potential and the extracellular potassium normally present are prevented from entering the cell (60-62).

Conn (60), in radioisotope studies in dogs, found that digitalis apparently reduced the influx rate of potassium. In subsequent studies (62), he found a reduction in intracellular-interstitial potassium transfer rates using K^{42}, compatible with the theory that digitalis acts by inhibition of potassium influx into myocardial cells. Furthermore, digitalis alters not only the potassium influx in myocardial and skeletal muscles, but also alters the permeability of liver cells, red blood cells, and renal tubule cells to various cations. The diuretic action of digitalis, once thought to be due only to the improved vascular flow through the kidney, is now known to be at least

in part due to a direct action of the glycoside on the tubule cells.

Szent-Gyorgyi suggested in 1956 (63) that digitalis functionally replaces a substance which is normally present in the myocardium. He believes that both of these substances act not on the contractile protein but rather regulate ion exchange by action upon the cell membrane. Thus, he also supports the contention that digitalis acts primarily on the cell membrane.

The lowered concentration of potassium within the myocardial cells as a result of digitalis would, of course, be in accord with the theories of Hajdu (16), Dick (64) and Szent-Gyorgyi (15). As noted earlier, Szent-Gyorgyi believes that contractile force is proportional to the total intracellular quantities of sodium and potassium, and Hajdu suggests that contractility is inversely proportional to the combined concentrations of sodium and potassium within the cell. Vick's ingenious work (17), however, showed that negative inotropic glycosides also cause a potassium loss. Therefore, it appears that although the action of digitalis to increase contractility may depend on cellular potassium loss, another yet undiscovered mechanism is involved. This mechanism may still involve alterations at the cell membrane, perhaps

relating to exchange of other cations.

Thus, although digitalis does have effects at the cell membrane, the relationship of these effects to increased contractility is still unknown. It does appear, however, that these actions, especially those on potassium, are responsible for the shortened action potential and the consequent shortening of the refractory period and increased automaticity.

b. Effects on the Contractile Protein: Since the development of techniques for isolation of actomyosin bands and threads from animal hearts, a number of experiments have been done to test the effect of various ions and drugs upon this protein. The different techniques involved in isolating the protein, the variations in concentrations of ions in the perfusing fluid, and the concentrations of the drugs used all make interpretation of the various results difficult.

Miyahara (20) studied the effects of ouabain on actomyosin fibers extracted from normal and failing hearts of dogs and of skeletal muscle. In his studies on isometric tension development by the fibers, he found that in calcium-free medium, ouabain had no effect upon tension development. Although perfusion fluid containing calcium but no ouabain tended to inhibit tension development, addition of ouabain to

solutions of low calcium concentration tended to increase tension. When the concentration of calcium in the solution was increased, however, addition of ouabain would decrease tension development. Magnesium alone tended to increase tension development, but the presence of magnesium appeared to have no effect upon the action of ouabain upon the fibers. The effects of these ions and ouabain was essentially the same on cardiac muscle, both failing and normal, and upon skeletal muscle. Similarly, Bowen (65) found that digoxin increased the shortening rate of skeletal muscle myosin threads. The fact that ouabain exerted the same effect upon skeletal muscle as it did upon cardiac muscle would suggest that direct action of glycosides upon actomyosin fibers is not the normal mechanism of action, unless digitalis is prevented in some manner from exerting a demonstrable effect on the actomyosin of intact skeletal muscle fibers.

The results of Kako and Bing (22) disagree with those of Miyahara in that they found that calcium and digoxin separately had no effect upon actomyosin bands prepared from normal and failing hearts. When both calcium and digoxin were present, however, shortening of the bands was produced, with return of the bands from the failing hearts to normal contractility. At

the present time, no definite conclusions can be drawn from the various results with these techniques. The isolated band of actomyosin, of course, is quite different from actomyosin within the myocardial fiber. The danger in generalizing from the in vitro study to in vivo effects was well brought out in a well designed experiment of Wollenberger (262) which showed that certain effects of cardiac glycosides upon actomyosin could also be duplicated with glycosides which were totally inactive in vivo.* In other words, the inactive glycosides in the intact animal had no effect upon the failing heart, but in these in vitro studies, demonstrated the same capabilities of stimulating or not stimulating actomyosin as did the active glycosides. Another major objection to these experiments is the fact that it has never been definitely shown that the cardiac glycosides penetrate the cell membrane. Friedman (67), in 1953, apparently demonstrated this entrance, but other workers have questioned his results and techniques (16).

E. Catecholamine Theory

This additional proposed mechanism warrants brief mention at this time. Tanz (68) suggests that the glycosides may act via the catecholamines. He bases

* cf. work of Vick (17) mentioned earlier which showed that glycosides with no positive inotropic action do affect the cell membrane.

this theory upon the finding that the contractile effect of ouabain upon cat papillary muscle was blocked by dichloroisoproterenol, an adrenergic blocking agent. Thus far, however, this theory has had no substantive support. While catecholamines and digitalis have some similar actions, their mechanisms are probably independent although possible additive at times. This additive effect will be discussed subsequently.

Before summarizing the current theories on the cellular mechanism of digitalis, the interrelationships of calcium, magnesium, digitalis and the myocardium must be mentioned.

F. Calcium, Magnesium, and Digitalis

Since Ringer's original work, it has been well known that calcium is essential to myocardial contraction.

Supplementing Ringer's original work is a recent study by Feinberg (69) who demonstrated in in vivo studies on the dog that direct infusion of calcium into the coronary arteries via the aorta produces the following effects: increased heart rate, increased velocity of left ventricular pressure rise, decreased circumference of the left ventricle, and increased coronary blood flow. The question as to whether

digitalis and calcium act synergistically has been frequently discussed in the literature. This question took on major clinical significance after a report in 1936 by Bower and Mengle (70). They reported two cases in which digitalized patients died shortly after receiving doses of intravenous calcium. The first case was a 32 year-old female who was given digitalis to control tachycardia and extrasystoles. In an additional attempt to control the tachycardia, 10 cc. of 10% calcium gluconate was given intravenously. Two minutes later, the patient developed generalized convulsions and dilated pupils. The patient died shortly thereafter. The second case was that of a 55 year-old male who was given 10 cc. of 10% calcium chloride after a thyroidectomy, to counteract what was thought to be incipient tetany. The patient developed "cardiac collapse" and expired. Subsequent animal experiments apparently bore out the synergistic actions of digitalis and calcium in that when receiving calcium, less digitalis was needed to precipitate manifestations of digitalis intoxication.

Shrager (5) added reports of two additional cases. One was a patient who was rapidly digitalized with lantoside C over a 24 hour period, and who was given 10 cc. of 10% calcium gluconate to counteract tetany

which developed. The patient had a serum calcium of 6.7 mg.%. The patient suddenly died ten minutes later. Elliot and Blount (71) reported a case of a nine month old child with cardiorenal congenital anomalies who was mistakenly intoxicated with digitalis. Administration of EDTA in an attempt to control the intoxication prompted tetany, and administration of intravenous calcium apparently resulted in the development of ventricular fibrillation.

Numerous in vitro studies have appeared to substantiate this synergistic action (72-74). Baker (76) showed that if ouabain was infused with calcium into rabbits, the lethal dose of ouabain was diminished. If one per cent calcium chloride were given along with the ouabain, the lethal dose was decreased 17 per cent; with two per cent, it was diminished 36 per cent; and with three per cent, 54 per cent.

In vitro experiments in general indicate that cardiac muscle contraction will occur in the presence of calcium alone or in the presence of digitalis and calcium, but not with digitalis alone, and that the contraction produced for a given concentration of digitalis will be increased by the addition of calcium to the perfusing solution. It should be noted, however, that Hajdu (16) cites evidence that digitalis

can exert its effect in the absence of extracellular calcium, but that only when calcium is added does the true muscular "twitch" become evident. Prior to the addition of the calcium, only the increase in contractile force is apparent, but the complete contraction-release apparently does not occur.

The studies of Kako and Bing (22) previously mentioned indicated that contractility of actomyosin bands was dependent upon the presence of calcium and digitalis, with no contraction occurring unless both were present. As noted, however, these studies remain in dispute.

Disagreeing with the generally agreed concept of synergism between calcium and digitalis are two reports. Smith (77), in 1939, studied the effects of calcium and digitalis on dogs. In this study, the test animals were digitalized to the point of cardiovascular digitalis intoxication. Then both the control and test animals received intravenous calcium until death occurred. There was no evidence that the test animals were more susceptible to calcium than the controls since the amount of calcium necessary to produce death was not significantly different in the two groups. Furthermore, nine of the twelve animals used which received both digitalis and calcium died of

cardiac arrest rather than ventricular fibrillation.

Lown (8) noted that patients on digitalis are frequently given calcium gluconate to measure circulation time, apparently without adverse effects. In his studies on dogs, he could not demonstrate any sensitivity to calcium when the degree of digitalization varied from 0-90 per cent of toxicity. From this he concludes that synergism does not exist. However, it should be noted that when the animals had received at least 95 per cent of the toxic dose of digitalis, they were sensitive to intravenous calcium. Both of these studies further point out the fact that calcium per se can initiate cardiac arrhythmias.

Lown suggests that the difference between the results in his investigations and earlier ones may be due to the method of calcium administration. Variations in the rate of administration of calcium could, of course, alter the results of the experiment. Furthermore, as he mentions, the state of digitalization prior to administration in the earlier experiments was not accurately controlled.

However, that digitalis and calcium interact in some way is undoubtedly true. Lee (78) found that the action potential of a single myocardial fiber revealed the characteristic shortening of the action potential

within three hours after digitalization. Doubling the extracellular calcium concentration decreased the time required for this effect to one hour, and when the calcium was excluded from the perfusing solution, the typical digitalis effect upon the action potential did not develop. In a fully digitalized heart, withdrawal of calcium from the solution resulted in transformation of the typical digitalis action potential to a normal one within one minute.

From the foregoing information, it can be seen that calcium is essential for myocardial contraction and is intimately involved in the action of digitalis upon the myocardium. Sekul and Holland (79) suggest that calcium may be the link between depolarization of the myocardial fiber and the activation of the contractile protein. Other authors (13, 14) have suggested that calcium is chiefly involved in maintaining the stability of the cell membrane and that it may be a major factor determining the permeability of the membrane to various other cations. In this respect, of course, it may be similar in action to digitalis, and this may explain the similarities of action.

Although relatively little work has been done upon the relationships between digitalis and magnesium, Lown (8) states that magnesium deficiency sensitizes

the heart to digitalis. Honig (80) has reported that magnesium is involved indirectly in the hydrolysis of ATP.

G. Summary

It appears that digitalis exerts its effect at the level of energy utilization rather than energy liberation. Although it does have effects upon the exchange of potassium across the cell membrane, it is doubtful that the lowered intracellular level of this ion is the primary intermediate step to increased myocardial contractility following digitalization. The actions of the glycosides on the cell membrane's permeability to this and other cations have as yet not been shown to be essential to the inotropic activity of the drug.

Digitalis apparently does exhibit in vitro positive inotropic activity when combined with isolated actomyosin. However, the evidence is insufficient to conclude that, in vivo, the glycosides act directly upon the contractile protein. Further investigation may, however, demonstrate that this is, indeed, the actual mechanism.

The alteration in membrane permeability does have definite effects upon the duration and shape of the action potential. The resulting shortened refractory

period, perhaps in conjunction with altered myocardial concentrations of certain cations, is probably the cause of the increased automaticity of the myocardium.

The delayed conduction through the A-V node is in part due to vagal stimulation. However, the manner in which digitalis acts directly upon the node to retard conduction is not understood. If the action potential of the A-V nodal tissue is shortened as is that of ventricular and atrial tissue, faster conduction would be expected. Therefore, it may be that the cell membrane permeability of nodal tissue is affected differently, with a resulting prolonged action potential.

Calcium and digitalis probably act synergistically. Administration of calcium to a patient intoxicated with digitalis appears to be hazardous and may precipitate a fatal arrhythmia.

V. MANIFESTATIONS AND PATHOPHYSIOLOGY OF DIGITALIS INTOXICATION

A. Cardiac Manifestations

Digitalis is known to be capable of producing most, if not every, cardiac arrhythmia.

The frequency of these various arrhythmias precipitated by digitalis intoxication varies slightly in the reports in the literature. (1, 6, 2)

Arrhythmia	Per cent of Cases in which Present		
	Crouch (6) (100 cases)	Herrmann (2) (44 cases)	VonCappeller (1) (148 cases)
Frequent PVC's	65%	14%	73%
Bigeminy	34	27	33
Premature atrial contractions	16	--	5
Sinus tachycardia	16	--	8
Atrial fibrillation	19	23	18
A-V block	31	16	43
Ventricular tachycardia	13	--	11
PAT with block	7	45	10
Atrial flutter	4	2	2
A-V Dissociation	9	--	5
Ventricular fibrillation	3	5	0.7

The differences in the various reports no doubt reflect the criteria used to classify a case as one of digitalis intoxication. Furthermore, as reports appeared concerning the incidence of specific arrhythmias in intoxication, clinicians subsequently became aware of the possibility of digitalis intoxication when these arrhythmias were found. The ability of the cardiologist to interpret the various tracings also plays a role in determining the frequency of arrhythmias which he reports.

Premature ventricular contractions are generally agreed to be the most common arrhythmia found in intoxication. Although found in normal hearts and in diseased hearts not treated with digitalis, the cardiac

glycosides are the most common cause of these extrasystoles (81). When not due to digitalis, they are commonly unifocal in origin, while those due to digitalis are usually multifocal and often arise in the right ventricle (82). Bigeminy and trigeminy are often considered to be reliable signs of the action of digitalis upon the myocardium. The extrasystoles in these cases usually arise from the ventricle, although they may originate in supraventricular foci. However, according to Lown and Levine (9) and Sagall (82), digitalis is not the most frequent cause of bigeminy. In analysis of 183 instances, it was found that only fifty were definitely associated with digitalis (82). Administration of digitalis may actually abolish bigeminy not due to digitalis since the premature systoles may be a result of anoxia and secondary to poor coronary artery perfusion. Although often thought of as a relatively benign indication of digitalis intoxication, bigeminy may herald sudden death, probably through precipitation of ventricular tachycardia and then ventricular fibrillation (9, 82). Fortunately, it appears that neither a previous history of spontaneous premature ventricular contractions nor prolonged use of digitalis *per se* (at therapeutic levels) increases the susceptibility of a patient to

digitalis-induced bigeminy (83).

Although not as common as extrasystoles or partial atrial ventricular block, certain arrhythmias warrant discussion in light of their increased frequency or abnormal mode of expression in digitalis intoxication.

Paroxysmal atrial tachycardia with block: This arrhythmia has gained increasing recognition as a manifestation of digitalis intoxication since the work of Lown and Levine in the early 1950's (9). Earlier work by Herrmann (2) suggested that this arrhythmia might be a common indication of toxicity. He found, in a series of 44 cases of intoxication with arrhythmias, that 20 demonstrated PAT, while premature ventricular contractions were much less frequent. In a review of this subject in 1959, Lown (84) found 32 cases in one year at Peter Bent Brigham Hospital. Twenty-four of these 32 cases were the result of digitalis intoxication. Lown's criteria for a diagnosis of this arrhythmia are electrocardiographic evidence of 1) an atrial rate of 150 to 250, usually between 150 and 200; 2) demonstrable change in the P wave; 3) isoelectric baseline between consecutive complexes in all leads, and 4) the presence of A-V block, either spontaneous or induced by vagal stimulation. Lown (85) suggests that the not

infrequent difficulty in recognizing this arrhythmia by the electrocardiogram is one reason for variation in the reported incidence of this abnormality. He states that even experienced electrocardiographers often misdiagnose this arrhythmia when a 2:1 atrial to ventricular response is present and the blocked P waves are fused with the preceding T waves. In the presence of a 1:1 response and a rate under 150, the arrhythmia is commonly interpreted as sinus tachycardia and when faster, as atrial tachycardia. When the atrial rate is 250 or over, the pattern frequently cannot be differentiated from atrial flutter. He states that this rhythm has also frequently been confused with nodal tachycardia, atrial fibrillation, and ventricular tachycardia. Clinically, PAT with block may manifest itself in a number of ways. Usually the ventricular rate is rapid, due to the fact that the heart block is usually not constant and periods of 1:1 response are present. PAT with block is not uncommonly associated with increasing heart failure. Whether this is due to increased ventricular rate, or other effects of the digitalis upon the myocardium is not yet known. At other times, the patient may appear unchanged despite the development of this arrhythmia, and he may be completely unaware of his altered rhythm. However,

sometimes, Lown reports, there is an abrupt onset of dyspnea, palpitation, and apprehension, often occurring when the ventricular response increases due to diminished block. On physical examination in patients with a prior irregular rhythm due to atrial fibrillation, acceleration and regularization of the ventricular rate often was the initial clue to the development of PAT with block. This change in rhythm was commonly mistaken for return of regular sinus rhythm. Consequently, in patients who previously manifested atrial fibrillation, the sudden development of a regular rhythm with or without increased ventricular rate should suggest the possibility of digitalis intoxication. In patients with a previously regular rhythm, the initial manifestation may be irregularity of rhythm, due to the development of inconstant block. This alteration may be confused clinically with the development of atrial fibrillation. PAT with block should also be suspected if the ventricular rate increases in the face of increased doses of digitalis or after diuresis, for reasons which will be explained later.

Since PAT with block can occur without the prompting influence of digitalis, the recognition of the cause of the arrhythmia in patients on digitalis is important. In this connection, Lown states that

administration of potassium usually will alleviate PAT with block when caused by digitalis, but will not when unrelated to the glycoside. Of course, recognition of other manifestations of digitalis intoxication will help in the diagnosis. The frequency of these other symptoms and signs appears to be the same in this arrhythmia when caused by digitalis as in any other. Although original work by Lown suggested that this arrhythmia carried with it a poor prognosis, subsequent investigation on his part (84) has shown that the mortality rate is much lower than originally thought. Another report suggests, however, that the prognosis definitely is very poor if the arrhythmia is allowed to continue (86). In seven patients with PAT with block due to digitalis, the drug was continued because of lack of recognition of the evidence of intoxication. All seven of these patients died within a few days, with the arrhythmia persisting until death. In the same report, however, in 23 patients in whom the arrhythmia and its cause was recognized, the drug was stopped and only two of these 23 patients died.

Bidirectional ventricular tachycardia: Palmer (87), in 1927, reviewed the literature on this unusual arrhythmia and added two cases of his own to the eleven previously reported. Nine of these patients were

definitely receiving digitalis; one definitely was not. Sporadic cases have been reported in the literature since that time.

A number of mechanisms have been proposed to account for this unusual rhythm: 1) The alternating complexes originate from separate ventricular foci which alternate in their sequence of firing. 2) A ventricular circus movement first stimulates one side of the heart and then the other. 3) A single supraventricular focus alternates conduction paths down the right and left bundles to the ventricles. 4) Nodal impulses form a base line which are coupled with premature ventricular contractions to form regular bigeminy. At the present time, it is not known which of these proposed mechanisms is correct.

Ventricular tachycardia: (88, 89) This arrhythmia presumably occurs as an extension of the mechanism causing premature ventricular beats. Marked differences again exist in the reports of frequency of arrhythmia in intoxication. Even very small doses of digitalis have been known to precipitate ventricular tachycardia. Fremont (88) reports a case of a patient who had reportedly not received any digitalis for several weeks, but who developed ventricular tachycardia and vascular collapse one and one-half hours

after a single oral dose of 0.6 mg. of digitoxin. Because of the danger that this arrhythmia may precede ventricular fibrillation, it is important that it be recognized as soon as possible and proper treatment instigated.

Ventricular fibrillation: This apparently is a rare complication of digitalis administration, but cases have been reported in the literature. As Friedberg (89) points out, additional cases undoubtedly have occurred following intravenous injection of digitalis in which death occurred so rapidly that an electrocardiogram could not be obtained. Sufficiently rapid treatment is usually not possible in these cases.

Atrial flutter and fibrillation: Both of these arrhythmias are considered to be unusual manifestations of digitalis intoxication. It has been stated, however, that development of atrial fibrillation in a patient previously having normal sinus rhythm is an important sign of intoxication (90). Soffer (91) presented 24 cases of arrhythmias in digitalis intoxication. Only one of these had flutter, and two had fibrillation. Both of these abnormal atrial rhythms stopped when digitalis administration was halted. Coffman (92) reviewed the literature in 1959 and found only 15 cases of flutter apparently caused by digitalis.

He added one of his own. According to Friedberg (89), some of these cases of flutter may in fact represent misdiagnosed instances of PAT with block. Of course many patients with heart disease have both atrial flutter or fibrillation and also are receiving digitalis preparations. In the vast majority of cases, there is no cause and effect relationship, other than conversion of flutter to fibrillation. Alterations in the ventricular rate in atrial fibrillation may be an important sign of intoxication, however. Digitalis is commonly used in atrial fibrillation to reduce the ventricular rate. However, excessive slowing of the ventricles commonly represents excessive degrees of heart block and may in fact represent complete heart block with a nodal or ventricular pacemaker. On the other hand, it has been reported recently that an increasing ventricular rate may also represent intoxication in these instances. This question, of course, is of vital importance since a decreasing ventricular response is normally considered to be an indication of adequate digitalis therapy. In instances where the ventricular rate increases, commonly larger doses of digitalis are then administered. In a series of 100 cases of digitalis intoxication (6), atrial fibrillation with rapid ventricular rate was present in 10 per cent.

Another author (69) presents a case of a patient who received digitalis to change atrial flutter to atrial fibrillation. The patient received digitalis to the point of gastrointestinal symptoms of toxicity, but the ventricular rate remained rapid. Other authors (93) have also remarked upon this paradoxical situation.

Non-paroxysmal nodal tachycardia (atrio-ventricular dissociation): It has recently been stated that this arrhythmia is a more frequent and more valuable clue to the presence of digitalis intoxication than is PAT with block (94). The proposed mechanism (94) suggests that it is due to increased automaticity of the A-V node and is not secondary to atrio-ventricular block. These same authors also report that in those cases not caused by digitalis, digitalis may be necessary to convert this arrhythmia to a normal sinus mechanism. As in other instances where a question of increasing or decreasing digitalis exists, it is of vital importance to examine for the presence of other manifestations of intoxication in an attempt to determine the cause of the arrhythmia. Lown (8) states that in nodal rhythms due to digitalis, a regular response is usually present, and when irregular, "atrial capture" is usually evident. In further support of the viewpoint that the mechanism involved is one of increasing

automaticity of the node rather than a result of vagal action is the report of Stellar (96). He reports two cases of a nodal tachycardia following over-dosage of digitalis which were converted by carotid sinus pressure. If the nodal tachycardia were a result of escape secondary to increased heart block resulting from the digitalis, it would not be expected that increased vagal action would convert this abnormality. Rather, it should have no effect or accentuate the arrhythmia.

Atrio-ventricular dissociation, as used here, is considered synonymous with non-paroxysmal nodal tachycardia. This is in agreement with the viewpoint of Friedberg (89) and Soffer (97). In the broadest sense, atrio-ventricular dissociation indicates that the ventricles are responding to one pacemaker, and the atria to another. In this sense, complete heart block may be regarded as a form of atrio-ventricular dissociation, with the dissociation occurring because of lack of transmission of impulses from the atria to the ventricle and the resultant escape of an idioventricular or nodal pacemaker. In the view of these authors, however, it is preferable to restrict the term "atrio-ventricular dissociation" to cases in which increased automaticity of the A-V node allows it to gain control

of ventricular contraction. The additional distinguishing characteristic is that the nodal rate is above 70 per minute in the presence of a sinus rhythm or above 100 per minute in atrial fibrillation (94).

Atrio-ventricular block: This is a common disturbance in digitalis therapy and at mild levels is not considered to be an indication of digitalis intoxication. Thus, a first degree block is a not uncommon finding in patients on digitalis, and is not considered adequate reason for stopping therapy. It has been stated (89) by Friedberg that the Wenckebach phenomenon is probably a more common finding in digitalis intoxication than is generally recognized.

Other arrhythmias: Burwell (98) states that digitalis intoxication is the most common cause of sino-atrial block. Lown (8, 9) says that both sino-atrial and intra-atrial block or standstill are rare, but do occur. Sinus tachycardia can be a result of digitalis intoxication and is particularly prone to occur in the post-operative patient. He has also stated that intraventricular conduction disturbances are rarely, if ever, due to digitalis. Arvanis (99), however, recently described a case of paroxysmal atrial flutter and right bundle branch block in a patient following digitalization. The patient also manifested

other signs of apparent intoxication.

One last manifestation of digitalis intoxication upon the heart deserves mention again. It has been noted on occasion (5, 6, 100-102) that the only manifestation of intoxication may be increasing cardiac failure. The mechanism involved here is not well understood. However, this possibility should be kept in mind whenever a patient on digitalis presents with increasing myocardial decompensation. Rather than increasing the dose of digitalis, such patients may actually be benefited by anti-digitalis intoxication therapy. The so-called cases of refractory cardiac failure may on occasion be due to such intoxication (101).

Finally, mention should be made once again of the fact that all arrhythmias in patients on digitalis are not due to the glycoside. Cessation of therapy in such cases may indeed aggravate the situation if myocardial ischemia secondary to poor cardiac output is the inciting factor. The findings of bigeminy, PAT with block, or atrial ventricular dissociation should not lead one to conclude that the patient invariably is intoxicated with digitalis. Further, investigation is obviously needed before making such a determination.

B. Cardiac Pathophysiology

1. Physiological Alterations:

Although a great deal of experimentation has been done using digitalis in various concentrations, both in vivo and in vitro, relatively little information has been gained as to the actions of toxic, compared to therapeutic, doses of digitalis.

It has already been noted that numerous investigators have found that both the toxic and therapeutic doses of digitalis will result in a loss of potassium from the myocardium, although the work of Staub (45), Boyer (37), and Clarke (28) disagrees with this unified theory of action, asserting that only in toxic doses does digitalis produce a loss of potassium from the myocardium. These reports, however, suffer from the inadequacies previously discussed.

Blackmon (38) found that both toxic and non-toxic doses of digitalis caused a rapid release of potassium from the myocardium, and that this potassium returned to the myocardium within approximately one hour after the administration of the digitalis. He does not differentiate in his report between the time required for return of the potassium in the toxic and non-toxic states. It may be that a time differential would be found here, suggesting that less rapidly reversible

alterations in the permeability of the cell membrane result from toxic doses of digitalis. He suggests, however, that digitalis toxicity is related to the concentration of potassium in the intracellular fluid and the state of intracellular potassium, i.e., whether bound or free.

Woodbury (103) found that digitalis in toxic doses decreased the amplitude of the spike portion of the action potential rather than increasing it as therapeutic doses sometimes will do. Since the spike portion of the action potential is primarily a result of alteration of the cell membrane to one of sodium permeability, it may be that in toxic doses digitalis acts in one of two ways. First, it may allow less sodium movement than in therapeutic doses and, second, it may transform the membrane not to one permeable only to sodium, but rather one which allows movement also of potassium during the spike phase of the action potential. This would, in effect, reduce the amplitude of the spike.

The increased myocardial potassium loss with toxic doses may reduce potassium concentration below a critical level, and this may, at this level, impair contractility. This would be in accord with the clinical finding that digitalis toxicity can present

as increasing congestive failure; i.e., in toxic doses, digitalis may act to reduce the contractility of the myocardium (5, 100-102).

At the level of the contractile protein, evidence is incomplete as far as the action of the glycosides in therapeutic levels. Until it is known whether digitalis does act directly on this protein complex, it would be premature to correlate clinical manifestations of toxicity with the effects of toxic concentrations of digitalis upon isolated actomyosin.

2. Histological Alterations:

Pathological studies on tissues of patients dying of congestive heart failure with no digitalis or only therapeutic doses of digitalis, and in those dying of digitalis intoxication, generally have not revealed striking differences.

Bergy (104) reports a case of a 61 year-old patient who committed suicide by taking massive doses of digitoxin. After ingesting 7.5 mg. of digitoxin, the patient manifested signs of central nervous system and cardiovascular toxicity. Autopsy, however, revealed no definite cardiac damage.

Experimental work, however, has shown that digitalis in toxic doses can cause histologically evident alterations. Dearing (105) administered varying levels

of the lethal doses of digitalis to animals. Microscopic examination of the heart revealed that the earliest change was degeneration of myocardial fibers, often with hemorrhage. Following this evidence of fiber degeneration was invasion of the area by inflammatory cells. If digitalis was stopped, and the animal survived, the lesions healed by fibroplasia. No changes were found in skeletal or smooth muscles in these animals. He also found that older animals were much more prone to development of the lesions than were younger animals, and were much more prone to die of the intoxication. Sixty per cent of the minimum lethal (not toxic) dose administered as one dose was the smallest amount that could produce visible myocardial lesions. The frequency of the lesions thereafter rose with increasing dose. The lesions were focal in distribution and more common in papillary muscle and the left ventricular wall, and much less frequent in the right ventricular wall. The reason for this distribution is not known.

LaDue (106) found that prolonged oral administration of digitalis to dogs, even in levels ten times the therapeutic levels, produced no myocardial abnormalities. However, large doses intravenously would produce myocardial necrosis, fibrosis, and atrophy.

Travell (107) also found that parenteral but not oral administration of the glycosides would produce myocardial abnormalities in experimental animals. Other authors (108, 109) have also confirmed the toxic effect of massive doses of digitalis upon the myocardium of animals.

Buchner (109) suggested that the changes were secondary to disturbed blood supply and noted that the alterations were similar to those in patients dying of angina pectoris. LaDue (106) also thought that the lesions were secondary to localized spasm of arteries or arterioles with resultant ischemia. Manning (110) produced similar myocardial lesions by repeated vagal stimulation. These results led Kyser (110) to suggest that digitalis could cause these histologic alterations in one of three ways: The first of these would be direct action on the myocardium; the second, vasoconstriction secondary to vagal stimulation; and the third, vasoconstriction as a result of direct action of digitalis upon the coronary arteries. Both he and Manning found that administration of atropine markedly reduced the myocardial damage caused by excessive digitalis and by vagal stimulation, respectively. Kyser also found that one cardiac vasodilator, aminophylline, also reduced the myocardial damage due to toxic doses of

digitalis, but that another coronary vasodilator, papaverine, did not appear to protect the heart. He suggests that the difference in results here may have been due to inadequate doses of papaverine. It is interesting to note that Dearing (105) reported that administration of thyroid to his animals markedly increased the frequency of myocardial damage. An increased rate of metabolism would make the myocardial cells much more susceptible to ischemic damage.

It appears, consequently, that large parenteral doses of digitalis can cause myocardial damage secondary to vasoconstriction. This vasoconstriction is at least in large part a result of vagal stimulation. However, it appears doubtful that these severe alterations have any clinical bearing in view of the extremely large doses of digitalis required, and the absence of microscopic alterations in the hearts of patients dying of digitalis intoxication, even following massive doses. The fact that only parenteral doses were capable of producing lesions suggests that it is the sudden high concentration of the glycoside which directly or indirectly stimulates the critical degree of vasoconstriction. This, of course, recalls the clinical evidence that parenteral administration of digitalis is much more prone to result in intoxication than is oral

administration.

A possibility warranting further investigation is that a toxic dose of digitalis in humans produces its effect by ischemic changes which are significant enough to produce hypoxia at the cellular level, but not severe enough to produce microscopically visible alterations.

In his in vitro studies on human heart muscle, Trautwein (275) found that anoxic perfusion of the tissue resulted in an alteration of the action potential somewhat similar to that resulting from the administration of digitalis.

It must be remembered, of course, that experiments such as these do not allow one to make a cause and effect conclusion. Similar abnormal effects would be expected to occur in tissue under a variety of circumstances affecting basic metabolism, such as the poisoning of enzyme systems.

In conclusion, the histological alterations in the myocardium noted above have no known counterpart in clinical digitalis intoxication. It appears likely that these changes occur only at digitalis concentrations far above those ever encountered in practice. Nevertheless, it should be kept in mind that the diseased heart is more susceptible to hypoxia than is

the normal myocardium. Vasospastic changes may occur in digitalis intoxication sufficient to produce tissue hypoxia without microscopically visible alterations. This hypoxia may be adequate to alter the normal processes at the cell membrane or within the cell.

3. Mechanism of Arrhythmias in Toxicity:

The various arrhythmias generally are explained on the basis of alteration of the refractory period, automaticity, and A-V conduction of the heart.

Automaticity, or rhythmicity, refers to the property of portions of the heart to depolarize spontaneously, i.e., without the influence of external stimuli. The refractory period of the myocardium, or portions thereof, is the duration of time during and following depolarization when a stimulus cannot re-fire that tissue.

Even at therapeutic levels of digitalizations, these changes are present, although in lesser degree. The relationship between them and the cellular effects of therapeutic doses of glycosides -- i.e., changes in the cell membrane permeability, in the action potential, and in net myocardial cation balance -- was discussed earlier.

In essence, the altered membrane permeability to sodium and potassium decreases the duration of the

action potential and this in turn results in a shortened refractory period. The latter, possibly in conjunction with altered levels of certain cations within the myocardium, is probably the cause of the increased automaticity of the myocardium.

It is unclear whether toxic levels of digitalis simply extend these alterations past a critical point or whether other cellular changes occur which affect the refractory period and automaticity, as well as A-V conduction rate. As mentioned above, Woodbury (103) found that toxic doses of digitalis decreased the amplitude of the spike portion of the action potential, while therapeutic concentrations did not. Generally, however, most investigators believe that the cellular toxic effects of digitalis are simply an extension of those found at therapeutic concentrations.

Automaticity, excitability, and refractory period: Some authors fail to distinguish between such terms as "excitability" and "automaticity." The former is a reflection of the threshold stimulus needed to fire a particular portion of the myocardium, and may or may not be altered when automaticity of the tissue is changed. Although some authors (29, 112, 113) suggest that digitalis increases the irritability or excitability of the myocardium, most investigators now believe

that the reverse is actually true. Thus, Moe and Mendez (114, 115) found that while digitalis at lower dosage levels may increase excitability temporarily, larger doses definitely diminish this property of the tissue. Friedberg (89) also supports this viewpoint. All agree that automaticity is increased. This is probably a result, at least in part, of the altered atrial and ventricular refractory periods. Thus, Moe and Mendez found that the refractory period of the A-V node and bundle of His is lengthened by the action of digitalis, while that of atrial and ventricular tissue is decreased. Other factors are probably involved in increasing automaticity, since the automaticity of the A-V node is increased despite a longer refractory period.

Conduction time: Investigators (89, 112, 116) generally agree that conduction time through the A-V node is depressed by digitalis due to both a direct effect and an indirect effect mediated via the vagus nerve. Disagreement exists, however, as to which of these two mechanisms is the chief one operating in digitalis intoxication.

Since vagal stimulation is known to diminish the automaticity of the S-A node and to decrease the rate of conduction of the depolarization wave through the

atria, it has been suggested that the sino-atrial block, intra-atrial block and atrial standstill sometimes caused by digitalis intoxication may be a result of either vagal stimulation or hypersensitivity to vagal impulses (113).

Increased automaticity alone or coupled with a decreased refractory period probably accounts for most of the ectopic arrhythmias due to digitalis when severe conduction block is not present. These mechanisms would account for the premature ventricular contractions, ventricular tachycardia, and ventricular fibrillation found in digitalis intoxication. Although the reports disagree as to the alterations of the automaticity and excitability of the atria, this same mechanism probably is involved in ectopic atrial beats, as well as atrial tachycardias. Atrial ventricular dissociation is probably also a result of increased automaticity of the A-V node despite the prolonged refractory period (94). Atrial flutter and fibrillation are probably due to combined effects upon the automaticity and the refractory period of atrial tissue. Atrio-ventricular conduction blocks are a result of the direct and indirect actions of digitalis upon this tissue. The following table summarizes the general mechanisms involved in the production of the common

arrhythmias found in digitalis intoxication:

DUE TO VAGAL STIMULATION OR DIRECT DEPRESSANT ACTION	DUE TO ALTERATIONS IN AUTOMATICITY AND/OR REFRACTORY PERIOD
1) Sino-atrial block	1) Atrial flutter
2) Intra-atrial block	2) Atrial fibrillation
3) Atrial standstill	3) Atrial tachycardia
4) A-V nodal rhythm (escape)	4) Atrio-ventricular dissociation
5) Atrio-ventricular block	5) Premature ventricular contractions
	6) Ventricular tachycardia
	7) Ventricular fibrillation

Recent work has suggested the possibility that at least the ectopic beats may be due to release of catecholamines from the myocardium (68, 117, 118). Lucchesi (119) recently found that an adrenergic blocking agent would convert ouabain-induced arrhythmias in dogs to normal sinus rhythm. This work is as yet unconfirmed, but further investigation is certainly warranted.

C. Gastrointestinal Manifestations and Pathophysiology of Digitalis Toxicity:

Gastrointestinal disturbances are among the most frequent and often the earliest signs of toxicity. Withering (4) was aware of this fact and considered them reliable warning signals of toxicity. Anorexia,

nausea, vomiting and diarrhea are the usual signs and symptoms usually considered.

Especially in older people, anorexia may be the only indication of toxicity. It may manifest itself as a chronic slow loss of weight, rather than a specific complaint as to loss of appetite. On the other hand, this is commonly the first indication of toxicity, and loss of appetite in a patient should put the physician on guard.

Vomiting was originally believed to be entirely due to a local effect of digitalis upon the gastrointestinal tract. The early cardiac glycosides used were naturally impure and it was believed that, with the advent of the purified glycosides, gastrointestinal symptoms would vanish. However, this did not prove to be the case.

Borison and Wang (121) studied the mechanism of vomiting in digitalis intoxication. They dismissed earlier theories that it was due only to gastrointestinal irritation or to reflex vomiting as a result of stimulation of afferent fibers from the heart. It was shown that complete denervation of the heart did not prevent the emetic action of toxic doses of digitalis. Similarly, they showed that complete denervation (afferent) of all thoracic and abdominal organs,

including the entire gastrointestinal tract, also did not block the vomiting. Apparently, they refer to the diaphragmatic and abdominal wall muscle movements which are essential to the act of vomiting. Local gastrointestinal irritants ($CuSO_4$) would not produce vomiting here, however. From this, they concluded that the emetic action was in fact due to central stimulation. In animal experiments, they concluded that the central site is in the medulla and is not the same as the so-called "vomiting center." They agree, however, that local action of digitalis on the gastrointestinal tract is involved to some extent in the vomiting associated with oral administration. They did not, however, exclude the possibility that gastrointestinal irritation did play some role.

Gold (122), in 1952, studied the difference in emetic action when digitalis was given parenterally and orally. Using purified glycosides, they tested the amount necessary to produce vomiting via the parenteral and oral routes with a waiting period between the two trials on each patient. They used certain electrocardiographic changes as guide lines to indicate when the parenteral dose could be administered. Evidently they waited approximately seven days in each case after the oral digitalization before administering the

parenteral dose. They found that when the drug was given by the parenteral route, a degree of cardiac action as judged by the electrocardiogram was obtained without vomiting. Comparable cardiac effect was not possible without vomiting when the drug was given orally. This study suggests, of course, that gastrointestinal toxicity is at least partially a local response and that some patients who are on oral digitalis and showing signs of gastrointestinal reaction may yet be able to accept additional parenteral treatment without aggravation of the gastrointestinal disturbance and without precipitation of cardiotoxic effects.

In addition, it should be mentioned that continued digitalis administration after vomiting may result in tolerance development. The patient may develop more serious signs of toxicity without continued vomiting. The cessation of emesis may give the physician a false sense of security.

Diarrhea is an unusual manifestation of intoxication (29). Cole (123) presented a case of diarrhea and digitalis intoxication. It is uncertain, however, from reading his report whether the diarrhea in this case precipitated the toxicity or was the result of it (see below).

Rather than being an annoying side effect of the glycosides, the gastrointestinal manifestations have been an invaluable indicator in many cases of impending digitalis cardiotoxic activity. Their frequent occurrence prior to the onset of arrhythmias has enabled the physician to stop digitalis therapy before more serious signs of intoxication resulted. Investigators and clinicians now feel that the most desirable cardiac glycoside would be one which regularly showed gastrointestinal indications of over-digitalization before cardiac irregularities were evident.

In addition to the well-known gastrointestinal effects of digitalis, a recent report by Gazes (124) warrants mention. It reported the finding of acute hemorrhage and necrosis in the intestinal wall of ten patients, all on large doses of digitalis. Several of these patients apparently were intoxicated. Pathological investigation revealed patchy areas of marked venous engorgement with hemorrhage and edema of the intestinal wall. Congestive heart failure apparently was not the cause. The authors postulated that digitalis causes constriction of the hepatic vein or sinusoidal sphincter, resulting in portal congestion. The clinical diagnosis in these cases usually was

mesenteric thrombosis. They suggest that this abnormality of blood supply from the intestine be considered in any patient on digitalis who complains of abdominal pain. Other reports have not yet appeared in the literature confirming the authors' findings. However, it should be noted that vascular abnormalities have been noted in experimental studies with massive doses of digitalis (see above).

D. Central Nervous System Manifestations and Pathophysiology:

A common symptom of digitalis toxicity is a disturbance in vision. A number of authors have discussed this problem in the literature (125-128). One of Withering's (4) original patients complained of "green vision." The commonest abnormality seems to be a disturbance in color perception, so-called "yellow vision" being the commonest. The color abnormalities can be generalized or localized to specific areas in the visual field. Patients affected by generalized color abnormalities describe all objects they see as being either green or yellow. Other patients have described the objects in their visual fields as being red, blue, or covered with a "frost." Other complaints have been veiled, cloudy, or blurred vision. Others have complained of flickering of lights in front of

their eyes, of rapidly moving sparks, of diplopia, of black lines, glare, red and green spots, white and yellow snow, of inability to focus, and of burning and pain in the eyes. Objective examination has usually been negative in these patients, although some writers (126) suggest that conjunctivitis is sometimes present. It seems more likely, however, that the conjunctivitis is secondary to the patients' rubbing their eyes after the onset of the visual disturbances.

Of much less frequent occurrence is toxic retrobulbar neuritis. Wagener (128) presented a case in 1946 of a patient who had apparently taken excessive amounts of digitalis and presented with nausea, vomiting, weakness and blurred vision. On visual field examination, bilateral central scotomas were present. Electrocardiogram revealed an inconstant third degree heart block. After cessation of the digitalis therapy, the patient's vision gradually returned to normal; the blurred vision and scotomas disappeared within one month. Sykowski (129a, 130) presents several other cases. In one of these, digitalis apparently caused permanent bilateral central scotomas. Another patient presented with sudden onset of blurred vision two weeks after initiation of digitalis therapy. The patient denied any other complaints and examination was

negative except for ophthalmoscopic studies. Vision was 20/200 bilaterally. With reduced digitalis, plus the administration of thiamine chloride, vision rapidly returned to approximately 20/60 and 20/80. Funduscopic examination in these patients was generally uninformative. This, however, is characteristic of retrobulbar neuritis. Gelfand (131) presented another well-documented case in 1956. This was a 67 year-old patient who had developed, two years previously, visual abnormalities on 0.2 mg. of digitoxin. These symptoms were relieved by decreasing the dose to 0.1 mg. On admission to the hospital, the patient received 0.5 mg. of digoxin. The morning after a thoracentesis, the patient awoke totally blind. Digoxin was stopped and vision started to return within three weeks. On another occasion, after intravenous lantoside C, the blindness recurred. Within a week, vision slowly returned. This case is noteworthy in view of the long duration of the toxicity despite the digitalis preparations used in this patient.

A number of other neurologic complaints have also been recorded. Lown (9) states that patients may have pains in the lower one-third of their face, resembling typical trigeminal neuralgia, often associated with neuralgic shooting pains in the upper limbs, lower

lumbar areas and calves. Batterman (132) describes a case of a 33 year-old woman who on repeated occasions developed typical trigeminal neuralgia when digitalis was administered. When the medication was stopped, the pains gradually disappeared. She also had anorexia, nausea, vomiting, and visual disturbances. He states that neuralgias, paresthesias, and myalgias also occur, apparently not infrequently.

Generalized muscular weakness is also considered to be a manifestation of digitalis intoxication (133).

Convulsions have been stated to occur in reaction to excessive digitalis (112, 134). It may be, however, that these so-called convulsions were precipitated by Stokes-Adams episodes. Aita (135) in his neurological practice has seen no cases of convulsions which he considered to be caused by digitalis.

Dunst and Levy (136) recently presented a 3-1/2 month-old child who developed marked neurological reaction to digitalis administration. The child was diagnosed as having a patent ductus arteriosus, with recent congestive heart failure and was given digoxin. On the third day of therapy, after a total of 290 mg., the child developed fever, opisthotonos, conjugate deviation of the eyes, and asymmetrical movements of his extremities. Spinal fluid examination showed a

protein level of 64 mg.%, 1950 red blood cells, and no growth on culture. Nine lymphocytes were also present. Three days after the digitalis was stopped, the neurological signs disappeared. A challenge dose of digoxin was given and the opisthotonos and deviation of the eyes returned within ten hours and disappeared one day later. The authors consider that this was probably a case of allergy to digitalis with development of cerebral edema or vasculitis.

Duroziez (137), in 1874, first suggested that digitalis could cause bizarre mental symptoms. He reported a number of cases of patients on digitalis for a variety of reasons, including non-cardiac ones, who apparently showed psychic changes. The true etiology of this "digitalis delirium" was subsequently questioned by authors who pointed out that most of these patients were both elderly and gravely ill. They concluded that the psychic changes were in fact secondary to the generalized illness or to arteriosclerotic changes in the cerebral vessels.

Gold (138), in 1947, stated that digitalis in man can produce dizziness, drowsiness, depression, and psychoses. Lown (9) adds aphasia and stupor to this list. King (139) presented six cases which he considered to represent true digitalis delirium. One was

a 33 year-old woman apparently with subacute rheumatic myocarditis, who developed delirium and disorientation when placed on lantoside C. She also manifested nausea and vomiting. The periods of delirium in this patient appeared to correlate well with repeated administration and cessation of digitalis. The author could find no other factor in her history which could account for her delirium. He notes in this report that three of the six patients had aortic valvular lesions. Other authors have also mentioned the apparent increase in incidence of cerebral symptoms in patients with aortic lesions receiving digitalis.

Smith (134) commented that the diagnosis of digitalis delirium is usually made in a patient who is over fifty years old, who has advanced arteriosclerosis, and who has been receiving digitalis for a long time. Nevertheless, he does feel that digitalis does have a direct toxic effect upon the brain. Bergy (104) presented a case of a patient, previously cited, who attempted suicide by ingestion of 7.5 mg. of digitoxin. Along with the usual gastrointestinal and cardiac manifestations of intoxication, including PAT with block, the patient developed a "toxic delirium."

Other authors (140) have recently presented other cases supporting the contention that psychic

abnormalities can result from digitalis intoxication. It must be remembered, however, as noted, that most of these cases occur in patients who are chronically ill. It is a common finding in hospital wards to find elderly patients, whether on digitalis or not, to have periods of acute disorientation.

The mechanism of action of digitalis involving the nervous system is not understood. It is apparent from the work by Borison and Wang on location of the emetic center for digitalis, that the glycosides do exert an effect upon the central nervous system. It has been postulated (141) that the disturbance in the medullary centers may also spread to adjoining areas of the brain. The disturbances in color vision suggest that cortical areas may be involved, as do the reports of psychic abnormalities. Experiments on rats (138, 142) have shown that large doses of digitalis can produce convulsions, depression and disorientation. It is noteworthy, however, that rats are particularly resistant to the cardio-toxic effects of digitalis. Retrobulbar neuritis, on the other hand, is apparently the result of direct action of the glycoside upon the optic nerve.

It would be interesting to know if electroencephalographic abnormalities are present in digitalis

toxicity. However, apparently no work has been done studying the EEG in this disorder. Since digitalis exerts an effect upon cell membranes in many tissues throughout the body, it does not seem unreasonable to assume that digitalis may also exert an effect upon the neurons in a similar manner. One report (143) indicates that such an effect does take place.

Heuper (144) attempted to determine if digitalis could cause histologically evident alterations in the central nervous system. He found that the brains of animals killed with digitalis could show alterations even when the myocardium appeared normal. Microscopic examination of the brains revealed marked capillary engorgement and pericapillary edema, along with foci of vacuolated and disintegrating ganglion cells. Glial cell proliferation was also present. These changes occurred primarily in the cerebellum and basal ganglia, although he cites other work reporting that similar changes have been found in the cortex. He concludes that these changes were also due to hypertonic vascular disturbances, with resulting ischemia.

As is true with the myocardial vascular abnormalities in experimental intoxication, evidence is lacking which would suggest that such changes occur in clinical intoxication.

E. Other Adverse Effects of Digitalis Administration:

Digitalis has been reported to have several other effects detrimental to normal physiology. Although not properly classified as manifestations of digitalis intoxication, they will be summarized briefly.

Gynecomastia has long been known to be a side effect of prolonged digitalis administration (145). This action of digitalis administration supposedly is a result of estrogenic action by the glycosides. The similarity in structure between the glycosides and other steroids is well known.

Instances of apparent allergy to digitalis have also been reported (136, 146, 147). Other reports have suggested that digitalis alters blood coagulation in some manner. The earlier reports suggested that the apparent increase in thrombo-embolic episodes in patients on digitalis might be due to a direct action of digitalis on the clotting mechanism. Subsequent investigations have failed to confirm this effect, however, and it has been suggested that this increased incidence of embolism may in fact be a result of rapid diuretic treatment in patients with congestive heart failure. The rapid diuresis causes hemo-concentration with increased stasis and tendency toward thrombus formation (148-153). One author (154) reports a case

in which digitalis may have caused thrombocytopenia.

F. Summary

The incidence of the various manifestations of digitalis intoxication varies somewhat from report to report. Von Capeller (1) studied 148 cases of digitalis intoxication. The following shows the initial manifestations of toxicity in these 148 cases:

Initial Manifestation	No. of cases
Arrhythmias	44
Anorexia	42
Nausea	41
Increasing congestive heart failure	11
Vomiting	6
Diarrhea	1
Disturbed vision	1
Gynecomastia	1
Unknown	1

It is apparent from examination of this report that cardiac arrhythmias may frequently be the initial manifestation of toxicity. This conflicts somewhat with the general belief that gastrointestinal symptoms usually precede the arrhythmias. However, it must be taken into consideration that the frequency which certain investigators ascribe to certain manifestations is in part a reflection of their energy in determining if such signs or symptoms are present.

Church's work with deliberate digitalis intoxication (1) showed that, grouping all the glycosides

together, the initial manifestation was cardiac in 20 per cent, neurological in 20 per cent, and gastro-intestinal in 16 per cent. In the remainder, no single initial manifestation was noted.

Von Capeller further sub-divided his study to show the frequency of the various signs and symptoms in his 148 cases.

	Present in
Anorexia	61%
Nausea	61%
Vomiting	51%
Neuromuscular disorders	13%
Visual disturbances	12%
Increasing congestive failure	12%
Diarrhea	6%
Gynecomastia	1%

(Arrhythmias were not listed)

In Church's study, cardiotoxicity was present in 49 per cent of the trials. Shrager (5) found in his study that neurological manifestations were present in 48 per cent of his cases. Lown, on the other hand, states that 25 per cent of his patients demonstrated visual abnormalities or vertigo, with an additional 9 per cent manifesting more unusual types of neurological problems.

It can be seen from these scattered reports that no one sign or symptom can be expected to be present in every case of digitalis intoxication. The physician

is faced with the problem of studying the entire clinical picture. If he displays sufficient acumen, he will usually be able to elicit the early manifestations of intoxication, before more serious ones make their appearance.

VI. DIGITALIS INTOXICATION IN INFANTS AND CHILDREN

The subject of intoxication in children deserves special mention because of variations from the normal adult pattern. Joos and Johnson (102) report that congestive heart failure appears to be a more frequent sign of intoxication in children. They also note that atrial and atrio-ventricular conduction abnormalities are much more common than ventricular arrhythmias and suggest that prolongation of the PR interval may be a better indication of toxicity in children than it is in adults. Nadas (155) agrees that ventricular arrhythmias apparently are less frequent in children. Furthermore, he points out the frequent association of primary myocardial disease and digitalis intoxication in his series of eleven cases of intoxication.

VII. POTASSIUM AND THE PRECIPITATION OF DIGITALIS INTOXICATION

The intimate relationship between digitalis and potassium was stressed earlier. It was noted that on a cellular level, digitalis altered the rate of influx

of this cation into various cells of the body, including those of the myocardium, and that digitalis affects the net potassium balance of certain tissues. As will be shown subsequently, potassium is also involved in the therapy of digitalis intoxication.

Only recently has it been known, however, that potassium plays a significant role in the precipitation of digitalis intoxication.

It was frequently noted in the older literature that intoxication appeared to be prompted, on occasion, by diuresis, usually under the influence of mercurial diuretics. The mobilization of fluid from subcutaneous tissues and the pleural and abdominal cavities was thought to allow digitalis, dissolved in this fluid, to re-enter the circulation. The large levels of digitalis thought to be dissolved in this solution would elevate the circulating levels to the toxic range, thereupon precipitating intoxication.

This concept was supported by the finding of various authors that such fluid did contain digitalis (156-158). In 1937, Levine (156) tested the in vitro activity of edematous fluid from 18 patients on digitalis. In each case, they extracted the digitalis from 1000 - 5000 cc. and perfused a frog heart with a solution of this extract. In 13 of these 18 tests, the

specimen gave a positive result for the presence of digitalis. Eleven specimens from patients not on digitalis were all negative. Similarly, other authors (158) tested pleural fluid from a patient with digitalis intoxication and found that the solution gave a typical digitalis reaction with the frog heart.

No truly quantitative study of the digitalis content of edematous fluids was done, however, until 1953. At this time, St. George (159) determined digitalis levels by bioassay, using the embryo duck heart procedure. In eight patients, the level of digitalis was found to be negligible. The maximum concentration was found to be 20 micrograms/L -- an insignificant amount.

A typical case of diuretic-induced intoxication was presented by Goulay (158):

> A 58 year-old man was admitted to the hospital with congestive heart failure. He had been taking a diuretic and, unknown to the attending physician, digitalis. On admission, he was given additional digitalis for two days. On the third, the digitalis was stopped because of the presence of a normal sinus rhythm, with a ventricular rate of 60, accompanied by nausea and vomiting. He had also received one dose of a mercurial diuretic. Four days after cessation of the digitalis, the electrocardiogram showed a regular sinus rhythm with the only abnormality being ST changes.

> Within the next 15 days, the patient received four additional doses of mercurial diuretic. He received no additional digitalis after the second day of admission. The patient's course was one of increasing anorexia, mental disorder and cardiac deterioration as manifested on the electrocardiogram. Various arrhythmias appeared, along with central nervous system and gastrointestinal indications of digitalis intoxication, and the patient died 13 days after the last dose of digitalis.

In 1947, Friedman and Bine (39), in in vitro studies, noted that the absence of potassium in the perfusion solution enhanced the effect of lantoside C, that absence of potassium led to arrhythmias, and that potassium would decrease the A-V block caused by excessive digitalis. Four years later, investigators showed that potassium loss induced by mercurial diuretics or desoxycorticosterone acetate would apparently precipitate arrhythmias in patients given ouabain in a dose which previously had caused no toxicity. (160)

These and other experiments led investigators to conclude that loss of potassium would precipitate manifestations of digitalis intoxication at doses previously well tolerated. It has also been shown that administration of other diuretics, including the thiazides and acetazoleamide results in a loss of potassium (8).

Probably the most rewarding investigation in this field has involved use of the artificial kidney. This instrument has allowed selective alteration of the body levels of specific cations. By decreasing the concentration of specific ions in the dialyzing fluid below that of the plasma, those ions will be selectively extracted from the blood stream. In this manner, the effects of depletion of specific ions (or of elevation of certain ions) can be studied without having to consider the net body alterations in levels of other cations. Lown and Levine have carried out extensive work using this technique:

Dosages required to produce ventricular tachycardia in dogs in 178 digitalizations before and during hemodialysis

Period	Digitalizations	Average serum Potassium (mEq/L)	Acetyl Strophanthidin required for toxicity (mg.)
Before dialysis	82	4.1	0.74
During dialysis, with dialysis potassium concentration of 4.0 mEq/L	55	4.3	0.47
During dialysis, with dialysis potassium concentration of 0.1 mEq/L	19	2.1	0.19
During dialysis, with dialysis potassium concentration of 8.0 mEq/L	22	7.0	1.15

(Modified from Lown and Levine (9))

The four phases of this study were carried out at intervals of one to two weeks. During dialysis against the low concentration of potassium, 48 mEq were removed from each animal. During the phase of potassium extraction, prior to digitalization, minor electrocardiographic changes were noted, but no specific arrhythmias or conduction disturbances. As noted, however, the dose of the glycoside necessary to produce ventricular tachycardia was markedly reduced in the animals with lowered body levels of potassium. On the other hand, when body potassium was increased during dialysis, the animals apparently were protected against the toxic effect of digitalis and could tolerate much higher doses.. The authors also noted significant prolongation of the duration of toxicity in those animals who had lost potassium. Furthermore, multifocal premature beats, bigeminy, and bidirectional ventricular tachycardia were produced in the depleted animals, but not in the others. It appears that the lowered dose of glycoside necessary to produce ventricular tachycardia in the control dialysis period (0.47 mg.) compared to the control pre-dialysis period (0.74 mg.) was due to some basic stress mechanism inherent in the procedure.

In studies on patients undergoing dialysis for uremia, with potassium removal, the authors found

qualitatively similar results. Of 16 patients undergoing dialysis who were on digitalis, seven showed frank evidence of toxicity and an additional six showed electrocardiographic alteration characteristic of digitalis effect. Of 17 patients not on digitalis, one developed atrial fibrillation, while the remainder showed no change (9). Other authors have presented similar, although less convincing, evidence (161).

In a recent study by Lubash (162), electrocardiographic manifestations of digitalis intoxication or effect were found in nine patients (30 per cent of digitalized patients) undergoing hemodialysis. No similar changes were found in patients not on digitalis. In every instance, the patients were undergoing correction of electrolyte abnormalities, usually hyperkalemia. In these patients, it appears that the elevated body potassium levels secondary to renal disease enabled them to tolerate (or need) higher than normal doses of digitalis. On dialysis, however, with extraction of potassium, the excessive dosage became apparent.

It appears fairly well established, therefore, that loss of body potassium can precipitate the cardiac manifestations of digitalis intoxication. Reports as to the effect of potassium loss upon gastrointestinal

and central nervous system signs and symptoms are infrequent in the literature as such (163). However, review of most cases of intoxication originally attributed to excessive diuresis will, in most cases, reveal the other typical characteristics of toxicity (141, 158). It is interesting to note that one of the cases of amblyopia cited earlier was preceded by a thoracentesis of 1200 cc. In this case, the direct aspiration of the pleural fluid could have resulted in sufficient loss of potassium to precipitate the intoxication.

Once alteration in body level of potassium is implicated in the production of digitalis intoxication, other frequent methods of altering the body level of potassium must be kept in mind. Thus, vomiting, diarrhea, nasogastric suction, ileostomies, and enterocutaneous fistulas readily come to mind.

A common cause of potassium depletion is diminished intake. In the seriously ill patient maintained on intravenous solutions, not infrequently orders for glucose and saline are routine, while potassium addition is often forgotten. Over a short course of time, the body reserves of potassium are more than adequate to compensate for this decreased intake, but if prolonged, and associated with normal or above

normal urinary losses of potassium, depletion will result.

Hormonal abnormalities characterized by sodium retention and potassium loss in the urine could also be expected to decrease body stores of potassium. Primary or secondary hyperaldosteronism are two striking examples of this possibility. Congestive heart failure, per se, is thought to be associated, not uncommonly, with secondary hyperaldosteronism. Paradoxically, this is thought to occur because of decreased circulating plasma volume in the face of edema. Therefore, congestive heart failure in itself may promote, indirectly, potassium loss with the precipitation of digitalis intoxication. Thus, the disease in which digitalis is most commonly used may in itself result in hypersensitivity to this drug. In such patients, of course, it is important to measure the urinary output of potassium to determine whether potassium output is exceeding intake. While unlikely to occur in a patient taking nutrition orally, in a patient on parenteral feedings, potassium depletion may occur relatively rapidly.

Another cause of increased potassium loss may be rigid restriction of sodium chloride intake over a long period of time following diuretic therapy (164).

Potassium-related increased sensitivity to digitalis need not always be due to total body depletion of this ion. It appears that transfer of potassium from the extracellular compartment to the intracellular fluid, if done rapidly enough, may induce digitalis intoxication. Farber (165) and Flock (166) observed that parenteral administration of glucose resulted in a fall in plasma potassium levels, although Farber noted this change only in arterial blood. It is believed that entrance of glucose into cells requires that potassium accompany it, resulting in at least a temporary shift of this cation.

In 1955, Page (167) studied the effects of parenteral and oral glucose upon the electrocardiogram of digitalized patients. He administered 50 cc. of 50% glucose, or 200-400 cc. of 10% glucose at a rate in the latter instance of 15 cc./minute. Other patients received a high carbohydrate, low sodium meal. One patient, typical of the others, had a basal electrocardiogram revealing approximately two premature ventricular contractions per minute. Admission serum potassium was 5.3 mEq/L. Five minutes after receiving 100 gm. of carbohydrate orally, his T waves inverted. At 30 minutes, the premature ventricular contractions were occurring at the rate of eight/min. By 40

minutes, marked bradycardia was present, with classical changes of hypokalemia -- prolonged PR, inverted T, and prominent U waves -- and with 12 PVC/minute. In one patient, ventricular tachycardia occurred after administration of glucose.

Kunin (168, 169) has recently demonstrated the possible danger of administering glucose even if potassium is added, a common treatment for digitalis intoxication. In his experiments, despite the exogenous potassium, in 10 of 21 patients, the serum concentrations fell. However, no decrease occurred if mannitol was used in place of glucose. Apparently, the glucose requires more potassium accompaniment in traversing the cell membrane than is supplied by the infusion and lowered serum levels are produced. Although the myocardium may be the recipient of some of this potassium, its share would be small compared to that of, e.g., the mass of skeletal muscle. It thus gains little intracellular potassium while low extracellular levels further alter the membrane's stability. It is conceivable that other tissues preferentially receive the glucose (and therefore potassium), and that the myocardium actually loses potassium since the potassium given is inadequate to "cover" the glucose and, therefore, intracellular stores must be tapped.

This theory, although unsubstantiated by experimental evidence, would better account for the cardiac irregularities noted above. It would be interesting to determine whether the myocardium gains potassium when glucose is administered.

Since insulin promotes entrance of glucose into cells, it is not unexpected that investigators have found that addition of insulin to the infusion stimulates the movement of potassium. Parrish (170) found that intravenous administration of insulin alone would cause hypoglycemia and a fall in serum potassium. The administration of 40 to 80 units of regular insulin produced an average potassium fall of 1.89 mEq/L. In every patient except one, the blood sugar fell below 35 mg.%. The electrocardiogram at this time generally paralleled the fall in serum potassium by showing lowered T waves and a prolonged QT interval. Subsequently, the administration of glucose was found not to reverse these alterations. On the basis of our present knowledge that glucose alone will lower the serum potassium, these findings are not surprising.

The above work is embodied in one of our present methods of treating hyperkalemia, namely, intravenous infusion of glucose with insulin. The increased hazards of such a combination should be noted in the

digitalized patient.

A final cause of decreased serum potassium concentration is epinephrine administration. It has been suggested that the insulin-induced hypokalemia is mediated through epinephrine (171).

Potassium Distribution and Digitalis Intoxication

The preceding discussion has indicated that net loss of potassium from the body or alteration of the internal distribution of potassium can precipitate digitalis intoxication. It was initially believed that the increased susceptibility to the glycosides was directly related to lowered extracellular concentration of this cation. As further study was made of the relationship between body potassium and precipitation of digitalis intoxication, it became apparent that the serum levels did not consistently reflect this increased susceptibility. Thus, Lown, in studies concerning PAT with block in digitalis intoxication, found that the serum potassium level did not relate to either the onset or the end of the arrhythmia (172). Even when a cardiac arrhythmia has resulted from potassium loss, the serum levels do not consistently reflect this lowered level. Furthermore, the abolition of digitalis intoxication by administration of potassium is not related to any sustained rise in the serum potassium concentration.

In experimental studies on dogs, using the artificial kidney to selectively extract potassium, digitalis-potassium arrhythmias were not promptly reversed by restoration of the serum concentration of this ion to normal levels. On the contrary, the level of serum potassium at the time of reversion may actually be lower than the level present during the arrhythmia (8).

Numerous studies have substantiated the lack of correlation between serum potassium levels and the precipitation of digitalis intoxication and also the failure of the extracellular fluid to mirror changes in total body potassium (160, 23, 173-177). The lack of parallelism between extracellular and total body potassium levels is present regardless of whether digitalis is being administered.

Moore studied the total body exchangeable potassium in patients with a variety of chronic diseases. He could find no correlation between the total body and the serum levels (23). Schwartz (174) followed the electrolyte balance on a number of patients depleted of potassium by a variety of methods. Even with net losses up to 400 mEq/L, he could find no consistent reflection of these losses in these serum levels. Even in the face of a 25 per cent loss of total body exchangeable potassium, the serum level may be normal (175).

In hemodialysis experiments on dogs, with selective removal of potassium, Weller (173) found that he could demonstrate two phases in the serum potassium level reflection of the total body loss. In the initial phase, the serum levels reflected the loss of this ion, although more loss occurred than was indicated by the serum concentration. In the second phase, continued dialysis did not alter the extracellular fluid level. This plateau occurred at approximately 50 per cent of the control serum level. His experiments thus indicate that the intracellular space is the chief source of the extracted potassium, and that the body effectively acts to maintain the extracellular fluid level.

Thus, it is apparent that the body may suffer a sizable loss of potassium stores without this depletion being evident by the serum concentration, that digitalis intoxication induced by potassium loss may not be apparent from study of the serum levels, and that correction of this deficit by administration of potassium may not be apparent in the serum levels despite conversion of the precipitated arrhythmia.

The electrocardiogram, fortunately, has proven to be a valuable adjunct to serum levels in determining the body stores of potassium. Although it is recognized that the electrocardiogram is, <u>in general</u>, a

reliable guide to alteration in body potassium, it is not well understood which potassium alterations account for the electrocardiographic abnormalities. Thus, while numerous investigators have verified the relationship between certain changes in the ECG and hypokalemia (178-181), these and other investigators have commented upon the frequent occurrence of a normal pattern in the face of low serum potassium levels or the finding of a typical low-potassium electrocardiogram with normal serum levels (169, 182, 174). The lack of correlation between the ECG and the serum level is in part due to the fact that alterations in serum levels of both sodium and calcium can cause electrocardiographic alterations originally thought only to be due to changes in potassium levels (183).

Interpretation has further been clouded by the finding of Schwartz (174) that periods of positive total body potassium balance following total body depletion are not regularly reflected in the electrocardiogram, and the work of Blackmon (38, 40), which showed that the most serious electrocardiographic abnormalities occurred when the myocardium approached or attained normal total potassium stores after being depleted.

The preceding findings have suggested that both

the state and stores of intracellular and extracellular potassium are the determining factors in "potassium-effect" upon the electrocardiogram. Most investigators believe that the potassium gradient across the myocardial cell membrane is probably the critical factor (184, 60), although the mechanism is poorly understood. Another possibility is that the rate of flux of potassium across the membrane is involved.

Supporting the theory that the total intracellular level of potassium is the determining factor is the recent interesting work of Kanosky (185). He found that the electrocardiographic signs of potassium depletion are well correlated with low red blood cell potassium levels, regardless of whether the serum potassium was high, normal or low. In a study of five patients with cardiac disease who were receiving thiazides, he found that the serum potassium level fell during the first 5-8 days without alteration of the electrocardiogram or red cell potassium level. However, if the diuretic was continued, the latter two indicated potassium depletion, while the serum level rose.

Summary: Digitalis intoxication can be precipitated by depletion of body stores of potassium, chiefly intracellular, or by alteration of the potassium

gradient across the myocardial cell membrane. The serum level of this cation is frequently a poor guide to the implication of potassium alteration as a cause of digitalis intoxication. The electrocardiogram is a more valuable indicator of abnormalities of potassium stores or distribution. Potassium alteration sufficient to precipitate intoxication may, however, occur without being apparent on the electrocardiogram. Red blood cell levels of potassium may prove to be a valuable laboratory aid to the determination of myocardial potassium depletion. In general, contractility of the myocardium is increased despite or due to intracellular potassium loss, but at the expense of membrane stability, as reflected in altered refractory periods and myocardial automaticity. Sudden lowering of extracellular potassium levels by glucose, due to intracellular transfer of potassium, also upsets this stability. This may, however, also involve a covert myocardial potassium loss as a result of preferential utilization of the glucose by other tissues.

IX. INTOXICATION AND THE VARIOUS DIGITALIS PREPARATIONS

Numerous cardiac glycosides are available commercially. Drill (30) lists 13 preparations available, and the Physicians' Desk Reference of 1963 lists the five

most commonly used, under the various trade names. These preparations vary somewhat in preferred route of administration, in rapidity and duration of activity, and in rate of excretion. The various manufacturers make conflicting statements as to the relative toxicity of the different preparations. This confusion, however, is well supported in the literature.

General agreement exists that all the glycosides, if given in adequate doses, would produce equivalent therapeutic results. From the standpoint of toxicity, the most desirable preparation would be one whose early manifestations are relatively benign and whose duration of toxicity is short. Early nausea and vomiting in intoxication would appear to be the most desirable warning signals if they did not occur at dosage levels too far below those necessary for maximum therapeutic effect.

Digitalis leaf: Although still used by many clinicians, this glycoside has lost popularity since the advent of the purified preparations. In part, this was due to the inconstant rate of absorption and the consequent belief that it was more difficult to predict the amount of glycoside which would enter the systemic circulation. Furthermore, it was felt that the incidence of gastrointestinal toxicity was greater than

after the administration of purified glycosides. Some authors, however (30, 186), have stated that it is this very "disadvantage" which makes this preparation less likely to cause arrhythmias without first exhibiting anorexia or vomiting. The excretion rate of digitalis has not been accurately determined, but it is believed that the duration of toxicity is slightly less than that of digitoxin.

Digitoxin and Digoxin: A number of authors have commented that digitoxin is probably more dangerous than digitalis, digoxin, or gitalin, as far as intoxication is concerned. Thus, Shrager (5) concluded that digitoxin more frequently resulted in severe intoxication with less marked subjective manifestations. Similarly, Flaxman states that cardiac abnormalities were often the earliest indication of toxicity (3), and Levine (187) has the "clinical impression" that the onset of intoxication due to digitoxin is more insidious.

Digitoxin is apparently more prone to produce prolonged intoxication. Apparently this is the result of delayed excretion. Okita (188) found that unchanged digitoxin can still be shown to be present in the body 40 days after injection of a single dose, and Modell (112) states that it takes two weeks for complete elimination of a single digitalizing dose. Experiments

with the heart-lung machine have shown that a longer time is required to wash digitoxin out of the body than faster-acting preparations (189). Other authors have stated that the half-life of digitoxin in the body is over twice that of digoxin (186), and studies on the urine of patients on glycosides have demonstrated that the excretion rate of digitoxin is much slower than that of digoxin (190, 191). It is not surprising, consequently, that most investigators have found intoxication due to digitoxin is often longer than that due to other glycosides. Shrager, for example, found that in his series of 40 cases of intoxication, despite treatment with oral KCl, toxicity lasted an average of nine days with digitoxin, compared to 2-3 days with digoxin. Not uncommonly, cases are reported in which the toxicity due to digitoxin lasts 1-2 weeks or longer.

Further supporting the contention that digoxin is the preferable glycoside from the toxicity standpoint is the experience of Soloff and Zatuchni (192), who found that nausea was almost always the initial manifestation of digoxin toxicity. In only four of 40 cases of intoxication did cardiotoxicity precede nausea, and the abnormality present in these four cases was premature ventricular contractions.

Gold found that a single dose of 1.2 mg. of

digoxin would produce nausea and vomiting in approximately one of three patients, while the same amount of digitoxin would produce these effects in only one of 50 despite similar therapeutic effects upon the heart (193). Wax and Kirshner (194), in their study, also found that digoxin produced gastrointestinal symptoms more frequently than did digitoxin and that cardiac or central nervous system abnormalities did not occur alone with digoxin. On the other hand, they found that digitoxin did produce such isolated manifestations and was also the most common cause of cardiotoxicity. Their study consisted of administration of these glycosides to patients until toxicity was noted and then recording the manifestations present (194).

Gitalin: This glycoside gained popularity because of reports that it possesses a wider margin of safety than the other preparations. Batterman (195, 196), in 1951, studied the relationship between the therapeutic and toxic doses of digitoxin, digitalis leaf and gitalin. In one study, he determined the therapeutic and minimum toxic doses by digitalizing his patients first to the point of adequate cardiac effect (therapeutic dose) and then administering additional glycoside to the point of initial intoxication (toxic dose). Although the report does not make the procedure entirely

clear, apparently the patients were previously not on digitalis for a period of time and were then given the various preparations via the oral route over approximately a one to two day period. The therapeutic: toxic ratios for leaf, digitoxin and digoxin were approximately 60 per cent. In studies with 24 patients with gitalin, the ratio was 37 per cent, with an average digitalizing dose of 5.7 mg., and an average dose to produce toxicity of 14.0 mg.

In a second study, they compared these glycoside preparations in another manner. They determined the number of patients who would become toxic if their maintenance dose of their respective glycosides was doubled. With digoxin, digitoxin, and lanatoside C, approximately 60 per cent became toxic, while with gitalin, only 41 per cent became toxic. Twenty-seven patients were using gitalin in this study.

Other authors have also been impressed with the apparent safety margin of gitalin (197, 198). These authors, however, present only their clinical impressions.

A number of authors have also noted that gitalin is apparently effective in cases of cardiac failure which did not respond to glycoside therapy prior to the appearance of toxic manifestations (197-199). Such

findings, of course, further support the contention that gitalin possesses a wider therapeutic range. These authors cite a number of cases in which patients were unable to tolerate a wide range of dosages of the commonly used glycosides, but could tolerate the generally accepted equivalent doses of gitalin.

These investigators are generally in agreement, however, that the duration of toxicity and the manifestations of toxicity with gitalin do not differ appreciably from those with the other long acting glycosides.

Most of the opposition to the claim of a greater safety margin for gitalin has stemmed from an article in 1952 by Hejtmancik and Herrmann (199). In their study on a much larger series of patients (200), they found that the digitalizing dose of gitalin was approximately 60 per cent of the dose necessary to produce intoxication. This, of course, is the ratio which Batterman found to exist for the other glycosides. Although these authors (199) state that they use the method of digitalization with gitalin suggested by Batterman (195), examination of their protocol reveals that they did not do this. After the initial dose of 2.5 mg., Batterman suggested using 0.75 mg. every six hours until digitalization was complete clinically.

Hejtmancik and Herrmann, on the other hand, followed their initial 2.5 mg. dose with 1.5 mg. every six hours. Thus the rate of digitalization was much faster in the latter study, a rate which would be expected to produce intoxication at a lowered total dosage.

Consequently, although it would initially appear that the later study (199) is more significant in view of the larger series of patients, re-evaluation is in order in view of the different dosage schedules utilized. Unfortunately, this report was used as a basis to conclude that the therapeutic range of gitalin was no greater than that of the other glycosides. Since no subsequent study has been reported in which this conflict could be resolved, the question of margin of safety is as yet unanswered. The evidence thus far available, however, certainly does not warrant the conclusion that gitalin definitely does not possess a greater therapeutic range than the other commonly used glycosides.

Despite the claims for the various preparations, many investigators feel that essentially no difference exists in terms of toxicity between the various glycosides. Accurate comparison of glycosides by control study is difficult since no agreement exists as to equivalent dosages among the various digitalis

preparations. Some investigators take the initial manifestation of toxicity as being the end-point, while others administer the glycoside until cardiac abnormalities appear. Others compare the dose necessary to produce toxicity by administration of elevated maintenance doses, while others determine the amount of glycoside that can be given within a relatively short period of time before producing toxicity. Subjective interpretations on the part of the physician, based on his clinical experience, rather than a control study are, of course, difficult to evaluate. Unequal experience with the various preparations and the relatively small number of cases of intoxication seen with each glycoside make generalizations by clinicians somewhat hazardous.

In a retrospective study, Levine (187) could find no significant difference in the frequency of toxicity in patients on digitalis leaf or on digitoxin. Gold (122), in a controlled experimental study, found a marked variation from patient to patient in duration of toxicity with digoxin and digitoxin, with the range approximately the same for both preparations. Other authors have also supported the contention that no significant differences exist between the glycosides concerning manifestations and duration of toxicity

(201-203).

As noted above, it has been claimed that certain preparations are more likely to be manifested by cardiotoxicity initially, while others more commonly present with gastrointestinal symptoms. Thus, digitoxin has been accused of causing cardiotoxicity without warning and digoxin has been stated to be safer than digitoxin because of more frequent occurrence of warning gastrointestinal symptoms.

Church (204) recently sought to examine this problem in a controlled study. In this study, 39 patients with heart disease were digitalized to the point of toxicity with digoxin, digitoxin, and/or gitalin. The preparations were given orally at a slow rate of administration. A suitable interval was allowed after each experiment to allow for dissipation of the effect of the previous glycoside. Thus, most patients were digitalized first with digoxin, then with gitalin, and finally with digitoxin. The earliest manifestations (often multiple) of toxicity were recorded. Examination of the various cases presented reveals the following frequency distribution with the various digitalis preparations:

Initial Manifestation	Digitoxin	Digoxin	Gitalin
Cardiac alone	18%	25%	14%
GI alone	36%	17%	10%
CNS alone	14%	11%	19%
Cardiac total	32%	64%	43%
GI total	64%	58%	62%
CNS total	41%	47%	68%
Number of trials with each preparation	22	36	21

(adapted from Church et al (204))

The above rearrangement of the authors' data reveals rather interesting findings. Thus, digoxin was the commonest cause of cardiotoxicity as the sole presenting manifestation of intoxication. On the other hand, digitoxin was the most frequent preparation with gastrointestinal symptoms as the single early manifestation. In many of the cases, according to the authors' data, the patients presented with cardiac, gastrointestinal and/or central nervous system manifestations of toxicity at the same time. In all probability, a closer watch on the patients would have revealed one type of manifestation presenting earlier than the others. Regardless of this fact, when the information is tabulated as the authors have presented it, it is found that digoxin caused cardiotoxicity as the only, or as one of the manifestations of toxicity twice as often as did digitoxin (64% vs. 32%). The total

frequency of gastrointestinal symptoms was roughly the same for all three preparations. Central nervous system manifestations, however, were more common with gitalin.

This investigation further revealed that a patient was as likely to develop the same as different manifestations of intoxication when treated with the various preparations. Some patients developed the same manifestations regardless of the preparation, while others developed different signs and symptoms. A particularly interesting facet of the investigation was the finding that repeated digitalizations of the same patient with the same preparation could as frequently produce the same as different manifestations. Thus, one patient, on the first trial with digoxin developed ventricular premature beats and ventricular escape; on the second, anorexia, nausea, A-V block, and ventricular escape; on the third, the same; and on the fourth, ventricular premature beats. Another, treated with digitoxin, developed central nervous system abnormalities on the first trial and gastrointestinal manifestations on the second.

Investigations such as these are prone to the many difficulties which have been mentioned previously. Study of the previous table might indicate that gitalin

would be the drug of choice since it is the most infrequent cause of isolated cardiotoxicity. Hajtmancik and Herrmann's earlier work (199), on the basis of 30 cases, suggests somewhat different information:

Manifestations	Frequency (gitalin)
Cardiac only	33%
GI only	40%
Cardiac total	57%
GI total	67%

This second study would suggest a much more frequent occurrence of cardiotoxicity as the sole manifestation of digitalis intoxication.

Conclusion: Present evidence suggests that gitalin may possess a wider therapeutic margin than the other glycosides. However, this awaits further corroboration. Conflicting evidence also exists concerning the duration of toxicity with the various preparations. However, the bulk of information suggests that persistence of toxicity is related to speed of onset of excretion, with digoxin having the shortest and digitoxin and digitalis leaf the longest periods of intoxication. Frequency of specific manifestations of toxicity with the various preparations depends somewhat upon the route of administration. Thus, oral administration is most likely to produce

gastrointestinal symptoms, with digitalis leaf, because of its local irritant effect, being the most frequent causative preparation. It appears unlikely that with the same route of administration and equivalent doses, that any difference in frequency of gastrointestinal symptomatology really does exist among the various preparations. Similarly, cardiotoxicity has been associated with all of the preparations available, and it appears probable that none of those discussed is more likely to produce cardiotoxicity, either alone or in conjunction with other manifestations of intoxication than another. The differences in the various reports apparently are due to varying methods of procedure, and probably more importantly, varying degrees of scrutiny of the patient for indications of toxicity. No one preparation is more likely to produce serious cardiotoxicity than is another.

X. INSUFFICIENT AND EXCESSIVE DIGITALIZATION

It is often difficult to decide whether a congestive failure patient's lack of response to digitalis is due to over or under digitalization. It has previously been noted that one of the manifestations of digitalis intoxication can be increasing congestive heart failure. On the other hand, arrhythmias frequently associated with intoxication can also be

produced by myocardial hypoxia, secondary to poor cardiac output. In this latter case, more, rather than less, digitalis is needed.

In general, it is accepted that the initial manifestation of intoxication, whatever the type, is indication to diminish or stop the administration of digitalis, depending upon the severity of the toxicity. However, investigators have found that a level of digitalization sufficient to produce gastrointestinal toxicity may be sub-optimal as far as cardiac effect is concerned (205). Herrmann (2) and other authors (30) do not consider anorexia or nausea, per se, as indication of overdosage.

Digitalis levels just below those necessary to produce cardiotoxic effects apparently are adequate for maximum therapeutic effect (206), although Gold (83) did find clinical improvement at dosages which would produce bigeminy. The presence of "digitalis effect" on the electrocardiogram is no indication as to the presence or absence of digitalis intoxication. Such alterations may be absent when a patient is intoxicated and may persist long after the level of digitalis has fallen below useful concentrations (5, 9).

In some patients with an abnormally narrow therapeutic range, it may be necessary to digitalize to the

point of initial toxicity in order to gain maximum therapeutic effect. Normally, however, clinicians stop short of this level. In patients with atrial fibrillation and congestive heart failure, the ventricular rate serves as an accurate guide to adequate digitalization. The absence of a pulse deficit and a ventricular rate under 80/minute, which does not accelerate to over 100/minute on mild exertion, is a commonly used guide (8). When the patient has a normal sinus rhythm, the ventricular rate is not as accurate an index, and clinical evaluation such as clearing of dyspnea, orthopnea and decreasing hepatomegaly must suffice.

The serious problems arise in those situations in which it is difficult to determine whether the patient's increasing congestive heart failure or arrhythmia is due to too little or too much digitalis.

It has been suggested that administration of antagonists to digitalis intoxication might be helpful in differentiation. Thus, if the patient improves following the administration of potassium or EDTA, this might suggest that intoxication was present. This method will no doubt prove useful in some cases, but it must be remembered that arrhythmias not due to toxicity are commonly abolished or suppressed with

A. Calcium-Digitalis Tolerance Test

Nalbandian (207, 208) suggested using the possible synergism between calcium and digitalis to determine the level of digitalization. His "Calcium-Digitalis Tolerance Test" involves administration of 10% $CaCl_2$ intravenously to the patients until the electrocardiogram shows signs of arrhythmia, other than solitary premature systoles. The authors have devised a formula which theoretically indicates the level of digitalization by the amount of $CaCl_2$ required to produce the arrhythmia. The most common end-points found were short runs of premature systoles or bigeminy. The authors report utilizing this test with satisfactory results in 24 patients in congestive heart failure and on digitalis.

Recently, however, Reaume (209) reported unsatisfactory results with this test in animal experimentation. Three animals actually required more calcium to produce the electrocardiographic end-point desired after being digitalized than before the digitalis. Lown (84) has also not been impressed with the test in his experience with it.

Even if this test should prove to be a reliable indicator of the level of toxicity, there remains the danger of cardiotoxicity due to the possible synergism

between calcium and digitalis, as discussed earlier. In view of the absence of further clinical support for this test and the possible dangers inherent in it, general clinical use of the calcium-digitalis tolerance test does not appear warranted.

Administration of small doses of rapid-acting glycosides has also been suggested as a means of determining the efficacy of additional digitalis:

B. Acetyl Strophanthidin Tolerance Test

This agent is a synthetic ester of the cardiac alycone strophanthidin. Following intravenous administration, its earliest effect appears at 1-5 minutes, compared to 5-20 minutes for ouabain. Its peak action and persistence of effect are twelve minutes and two hours, respectively, compared to 60-120 minutes and 1-5 days for ouabain.

Lown and Levine (9) utilized this drug in an attempt to determine the level of digitalization of 20 patients, all acutely ill. The method used was the following:

> A patient suspected of being in digitalis intoxication was given initial and second doses of 0.15 - 0.3 mg. of acetyl strophanthidin (diluted to 0.06 mg./cc). Subsequent doses consisted of 0.3 mg. The time interval between all doses was 5-10 minutes.
>
> Interpretation of the test was based upon

> the amount of the drug required to produce cardiotoxicity. If toxicity developed after a total of 0.3 mg. or less was given, intoxication was presumed to be present. Toxicity following 0.6 mg. without evidence of additional therapeutic effect was thought to indicate adequate digitalization. If the patient showed a therapeutic improvement with 0.6 mg. or required more of the drug to produce toxicity, under-digitalization was believed to be present. If 1.2 mg. or more was required, full digitalization was believed to be necessary.

In all but two of the twenty trials, the test correctly evaluated the state of digitalization, as evidenced by subsequent treatment. Clinical judgment was frequently contradicted by the test, but in each of these cases, the test was correct. The results were uncertain in one case, and in the final one, death resulted from ventricular fibrillation, apparently due to the test.

Gilbert and Lyons (210), in 1956, re-evaluated this test, using the same method noted above. In 21 trials, the results were excellent, with the test correctly contradicting clinical judgment in nine. However, one fatality also occurred in this investigation, apparently as a result of the test.

The danger to the heart of the administration of acetyl strophanthidin has also been recorded by other authors (211). It appears, therefore, that this test

should be reserved for those situations in which a decision as to digitalis therapy is needed immediately. The accuracy of the test must be weighed against the five per cent mortality rate thus far reported.

Crouch (6), however, has stated that if differentiation between intoxication and under-digitalization is difficult, and the status of the patient warrants it, it is safe to give lanatoside C, 0.4 mg., or digoxin, 0.5 mg., I.M. or I.V., every four to six hours to test for therapeutic effect. Unfortunately, no control studies of this method are available. Since these glycosides have a longer duration of action than does acetyl strophanthidin, it would be expected that should increased toxicity result, the deleterious effect would be present for a relatively long period of time. It would appear, consequently, that the test as devised by Lown and Levine would be the safer of the two.

X. PREVENTION OF DIGITALIS INTOXICATION

The narrow therapeutic range of the glycosides makes intoxication an inherent problem in their use. The addition of the purified glycosides has decreased the local irritation of the gastrointestinal tract, thus allowing, at times, more absorption of glycoside

before systemic effects occur than was the case with digitalis leaf.

Intoxication can be insidious in onset and the physician must, consequently, be on guard for the initial signs of toxicity. He must be aware that tolerance to a dose of digitalis changes as the health of the patient changes, and a dose earlier taken without incident may subsequently provoke intoxication.

Treatment of congestive heart failure is now multi-faceted. Administration of diuretics is standard procedure in the treatment of this disorder. As discussed in detail earlier, administration of mercurials, thiazides, or even purely osmotic diuretics can result in considerable alteration in the distribution and total body levels of electrolytes, especially potassium.

Prophylactic Administration of Potassium: The present understanding that congestive heart failure is accompanied by myocardial and total body loss of potassium, and the finding that lowering of the myocardial or serum potassium can precipitate digitalis intoxication suggests the concomitant use of potassium in digitalis therapy.

A number of investigators have shown that experimental digitalis intoxication can be prevented or

mollified by prior administration of potassium (38, 120, 40, 212). Since it is known that digitalis decreases the rate of influx of this cation into the myocardial cells, elevation of the serum potassium level may so increase the gradient across the cell membrane that more potassium is able to enter the cell, thus counteracting the effects of the digitalis. Lown (213), for example, found that in hemodialysis studies, elevating the serum potassium allowed the experimental animals to tolerate a much higher dose of digitalis before suffering intoxication.

Furthermore, potassium administration does not interfere with the therapeutic actions of digitalis (8, 214).

The use of potassium salts is certainly not a new method of treatment of congestive heart failure. For many years, they were used primarily for their diuretic activity, in doses of 5-10 gm., causing a loss of body sodium and water (215, 175). Generally speaking, administration of potassium to patients in congestive heart failure, in doses ranging up to 10 gm. per day, for short periods of time, or smaller doses over a long therapeutic course, will cause no difficulty (176, 216). Of course, if the patients are receiving diuretic therapy, potassium replacement is standard

therapy.

It is commonly stated that such prophylactic therapy cannot hope to alter the potassium balance of the body since such administration does not correct the basic physiological derangement. In other words, whether chronic disease, congestive heart failure, per se, or digitalis therapy is at fault, the body's capacity to maintain normal potassium balance has been altered. Unfortunately, few studies are available to support the contention that potassium administration in these cases is not beneficial. Cort and Matthews (176), however, present a patient in congestive failure and receiving digitalis who, during a base line study of 30 days, continually lost potassium and retained sodium and water, despite bed rest, diet and continued digitalis. Daily administration of 65-200 mEq/day of potassium, however, resulted in a positive potassium, a negative sodium, and a negative water balance, with return of the previously low serum sodium levels to normal. Muscle biopsy before and after potassium therapy revealed that the markedly low intracellular potassium levels had returned to normal. During therapy, the patient's net retention of potassium was between 800 and 900 mEq.

Most of the present day fear of potassium

administration in large amounts stems from the well known dangers of hyperkalemia. Obviously, patients with known renal insufficiency cannot tolerate large loads of potassium. It is also known that patients with congestive heart failure cannot excrete potassium loads as well as normal individuals. In most cases, this is apparently due to diminished renal perfusion and/or secondary hyperaldosteronism.

Brown (217) studied the effects of oral administration of 200 mEq of potassium to normal patients, and to patients with compensated and uncompensated congestive heart failure. Serum potassium rise in each case was 26 per cent, 43 per cent and 67 per cent, respectively. Thus, even with administration of a large dose, the compensated cardiacs showed evidence of being able to tolerate the load much better than the uncompensated patients. These studies would appear to indicate that maintenance administration of potassium to compensated cardiacs receiving digitalis is warranted, barring other factors diminishing the patient's ability to tolerate potassium. A supplementary daily divided dose of 25-75 mEq. taken between meals would appear to have little chance of elevating the serum potassium levels to the toxic range. At the present time, however, no study definitely proves or

disproves the value of such therapy in preventing digitalis intoxication.

XI. INCREASED SUSCEPTIBILITY TO DIGITALIS INTOXICATION

Regardless of the health of the patient, digitalizing and maintenance doses must be suited to that particular patient. The literature contains numerous references to disease states which apparently increase the patient's susceptibility to digitalis intoxication. In general, these involve alterations in the state of the myocardium, the adequacy of renal function, or of electrolyte imbalance. The latter has been detailed above. Few control studies exist concerning this supposed increased susceptibility. For the most part, clinical impression forms the basis of the following list:

Diseases and Medications Associated with Increased Digitalis Sensitivity

Myocardial and pulmonary disorders

- Acute myocardial infarction (7, 10, 160, 186, 218, 219)
- Primary myocardial disease (10, 7, 155, 220-222)
- Cor pulmonale (10, 90, 223, 224)
- Ventricular tachycardia (98)
- A-V block
  - Partial (225)
  - Complete (226, 89)
- Intraventricular block (98)
- Chronic lung disease (7, 219)
- Traumatic heart disease (227)

Renal insufficiency (7, 10, 191)
General anesthesia and surgery (8)
Cerebral vascular accident (7, 219)
Acute infection (160)
Reserpine administration (117, 118, 186, 228, 229, 230)
Old age (10, 231)

Certain of the above warrant elaboration:

Acute myocardial infarction: As noted above, most authors have felt that the injured myocardium is more susceptible to the influence of digitalis. However, most now believe that the infarcted heart can usually be digitalized without ill effect, providing caution is taken. Askey (232) studied fifty patients with proved myocardial infarction who received digitalis and fifty with infarction who did not receive any glycoside. He found no difference in the frequency of arrhythmias in the two groups.

Cor pulmonale: Although many investigators believe that digitalis may do more harm than good in this disorder, it is also believed that while rapid digitalization may be harmful, slower administration of these glycosides may be beneficial.(90).

Ventricular tachycardia: This arrhythmia has generally been regarded as a definite contraindication to the administration of digitalis. It has been reported, however, that in some cases of ventricular tachycardia due to myocardial damage, digitalis has

been beneficial (233). In some cases, digitalis may have to be utilized for persistent ventricular tachycardia not due to intoxication, providing other methods of treatment have proved inadequate (89).

A-V block: Since digitalis is known to increase the refractory period of the A-V node, and to decrease the rate of conduction through this node, it is not difficult to understand why many investigators have felt that digitalis could only aggravate a pre-existing partial block. This contraindication, however, is not generally accepted (89, 224). If digitalis is definitely needed to counteract congestive failure, digitalization may be carried out provided careful observation is made for the appearance of complete block. The possibility of inducing Adams-Stokes syncope or complete ventricular standstill must be kept in mind, but the likelihood of such events appears to be more theoretical than actual.

It is difficult to understand why complete block has been regarded as a contraindication to the use of digitalis since the drug obviously cannot aggravate the pre-existing block. By decreasing the refractory period of the ventricle, the possibility of serious idioventricular arrhythmias should be noted when digitalis is administered. However, in the face of

congestive failure and complete block, digitalis is not contraindicated (90, 205, 234-236).

General anesthesia and surgery: Alteration of body physiology by these two mechanisms may either increase susceptibility to digitalis or increase the requirement. Apparently, these changes are due to electrolyte disturbances involved in anesthesia and surgical procedures.

Reserpine administration: Reserpine is known to deplete the myocardium of catecholamines, and some investigators believe that the glycosides act via the catecholamines (228). It is believed that the liberation of these amines at the same time that digitalis is administered increases the likelihood of arrhythmias, in view of the known ability of both types of drugs to induce cardiac abnormalities. Di Palma (237) found that administration of reserpine or digitalis alone to dogs, at certain dosage levels, would not produce arrhythmias, but when both were given at the same time, arrhythmias were produced. Schreader (238) found premature ventricular contractions occurred twice as frequently in patients on both drugs as those on rauwolfia alone. Lown (230) measured the amount of acetyl strophanthidin necessary to produce arrhythmias before and after reserpine administration. He found

that the cardiotoxic dose was lower after reserpine therapy. However, Yelnowsky (239) could find no difference in the frequency of premature ventricular contractions between dogs receiving both drugs and those receiving only digitalis.

Since both these drugs are commonly used in patients with hypertensive congestive heart failure, it is of definite clinical importance to know whether an additive effect exists. If arrhythmias occur at a low level of digitalization, maximum therapeutic effect will be impossible.

In addition to the above, it should again be noted that any manipulation of electrolytes or administration of certain drugs such as intravenous glucose with or without insulin, calcium, epinephrine, or isoproterenol should be done with caution (231, 161, 12). These drugs are often used in conjunction with digitalis, normally without deleterious effects. However, the dangers inherent in their use should be kept in mind.

Summary: The prevention of digitalis intoxication is primarily dependent upon the awareness by the physician of the many subtle factors involved in its precipitation. Dosage must be individualized to the patient's needs, taking into account any compromising illnesses or medications. Electrolyte manipulation

must be done with caution, and administration of diuretics should be accompanied by potassium therapy. Intravenous digitalis should be avoided whenever possible. The physician must be aware that intoxication may occur long after complete digitalization has taken place, and after the patient has tolerated a maintenance dose without difficulty for a long period of time. Finally, the insidious and often confusing initial manifestations of toxicity must be kept in mind so that serious effects of overdosage do not result.

XII. TREATMENT OF DIGITALIS INTOXICATION

> Let it be continued until it either acts on the kidneys, the stomach, the pulse, or the bowels; let it be stopped upon the first appearance of any of these effects, and I will maintain that the patient will not suffer from its exhibition, nor the practitioner be disappointed in any reasonable expectations (4).

Withering's adage, of course, is the cornerstone of treatment of intoxication. Administration of the glycoside should be halted. In selected cases, when toxicity is mild, diminishing the dose or dividing the same total dose may be sufficient, but in general, the drug should not be given until the clinician can be reasonably certain it will not further endanger the patient's cardiac status. Often, simple cessation of digitalis therapy and limitation of diuretics is

completely adequate and no additional treatment is necessary.

Most physicians believe, however, that unless the toxicity is mild, consisting chiefly of gastrointestinal manifestations, other therapy is indicated. Usually, this consists of potassium administration and, if necessary, specific anti-arrhythmic agents. Other methods of treatment such as magnesium administration and calcium chelation, using EDTA have also been utilized.

A. Potassium Therapy

Use of this cation to counteract digitalis intoxication was made as early as 1917 (66). Although utilized generally to counteract cardiotoxicity, neurological abnormalities have also apparently been corrected by potassium administration (163). It has been found effective against arrhythmias due to digitalis, regardless of the presence of hypokalemia or total body potassium loss. It has been found similarly effective in arrhythmias not due to digitalis intoxication.

Mechanism of Action:

At the present time, it is not understood whether potassium acts to counteract digitalis-induced arrhythmias by elevating the intracellular concentrations

of potassium or by a hyperkalemic effect, per se. Generally, no correlation has been found between the effectiveness of this therapy and alteration in the serum potassium levels. Lown (8) has specifically stated that the effectiveness of the potassium is proportional not to the rate of administration, but to the total amount given. However, other investigators have found that suppression of ectopic beats is directly related to the rate of infusion (240, 241). Vassalle (242) concluded that potassium specifically acts to depress the automaticity of the ventricular Purkinje fibers and the sinus pacemaker. The rapid onset of action of potassium infusion in counteracting ventricular premature beats would suggest that elevated extracellular concentration of this cation, even if only transient, is at least partially responsible for its action. Subsequently, the altered potassium gradient across the cell membrane may partially counteract the effect of the action of digitalis to reduce the influx rate of this cation into the cell, thus allowing replenishment of diminished intracellular stores.

Hazards:

As has been discussed previously, the cardiac patient is less able to tolerate loads of potassium.

Renal insufficiency unrelated to the cardiac status may further hamper potassium excretion. With the body less able to excrete potassium, and with digitalis reducing the rate of influx into cells, serious hyperkalemia may result, with the well-known depressant effects upon the heart and the danger particularly of cardiac standstill.

In certain instances, potassium administration may actually aggravate an arrhythmia. It has been found that elevation of the serum potassium can decrease the rate of conduction through the A-V node. Rather than counteracting the effect of digitalis, in this case, potassium potentiates it. Enselberg (243), whose work prompted the present day use of potassium in digitalis intoxication, reported that, in general, conduction disturbances were worsened by potassium administration. Other authors have reported cases or experiments in which potassium produced complete A-V block, especially if the partial block was present beforehand (241, 244, 245). It has been reported, however, that in some cases of partial block, potassium administration has diminished the block (241, 39).

Dosage and route of administration:

Although most clinicians prefer the oral route of administration, some believe that the intravenous is

in fact safer (175, 205). Since the gastrointestinal tract has no known mucosal block to potassium absorption, slow, monitored intravenous administration would appear to be preferable. An oral dose, once given, cannot be retrieved, but an intravenous infusion can be halted once beneficial or detrimental effects appear.

Intravenous potassium is usually given in a concentration of 8 mEq/100 cc. of 5% glucose. Opinion varies as to the maximum hourly (24-40 mEq) and total daily (78-120 mEq) dose. If serum potassium levels are abnormal, infusion dosages should be adjusted accordingly. Lown (172) found that if 40 mEq was not sufficient to halt PAT with block, additional potassium was unlikely to revert the arrhythmia. Furthermore, the amount of potassium required apparently bears no relationship to the severity of the arrhythmia.

As discussed previously, Kunin (168, 169) has questioned the advisability of administering potassium in a glucose-containing solution. In studies on 21 potassium depleted patients, he found that infusion of potassium in glucose-containing solutions resulted in a significant fall in serum potassium levels in 10 of these patients. The fall was greatest when solutions containing high concentrations of glucose were

utilized. The hypokalemic effect of glucose infusion has been discussed previously, but this is the first report of such an effect when potassium was infused at the same time. Kunin suggests, on the basis of these studies, that if potassium is to be administered in glucose solution, a 5% solution containing 8 mEq/100 cc. should be utilized. Further work may suggest that mannitol should replace glucose in such infusions. The author utilized this sugar in five cases and found that the serum potassium level rose in each one. Since it appears that at least part of the effectiveness of potassium in digitalis intoxication is due to transient elevation of the extracellular level, the hypokalemic effect of potassium with glucose, if it occurs rapidly enough, would be expected to diminish this mode of action. Furthermore, under the influence of the infused glucose, other body cells would be expected to be the chief recipients in this transfer of potassium from the extracellular to the intracellular compartments. The net result is that while the myocardial cells may have participated to a slight extent in the intracellular rise in potassium, it is possible that they may actually lose potassium if other tissues preferentially utilize the glucose. In either case, the lowered serum potassium directly or indirectly

adversely affects the over-digitalized myocardium.

Oral administration of potassium is usually accomplished with the use of enteric-coated capsules to minimize gastrointestinal irritation. The usual dose is 5-7.5 gm. per day in divided doses (9).

Rate and duration of action:

Both oral and intravenous administration usually result in onset of activity within 30 minutes. The effect of the intravenous route may persist after the infusion is stopped, but often the arrhythmia resumes soon afterwards. Oral administration reaches a peak of activity at approximately two hours and is generally gone within eight hours (160, 246).

Potassium preparations:

Usually potassium is administered as the chloride salt, although acetate or citrate are sometimes used if acidosis is present.

Recently, Keyl (247-249) has suggested that potassium-(L)-glutamate is a more effective and safer means of administering this cation. In his experiments, he found that this preparation was capable of reversing digitalis intoxication in dogs where potassium chloride had failed. Furthermore, he found that administration of potassium as the glutamate salt produced a slower rise and a lower peak of serum

potassium level than did an equivalent amount of the chloride salt. Additionally, while both (D) and (L) glutamate had the same effect upon serum potassium, only the (L) form was effective in counteracting intoxication. This would strongly suggest that the anion plays an active role in this preparation.

In these experiments, Keyl added 100 cc. of 25% mono-potassium (L) glutamate in 900 cc. of 5% D/W. He infused this solution at approximately a rate of 10-30 mEq. potassium per hour, a rate comparable to those suggested above. The comparable rate of potassium administration and the diminished effect upon serum levels would suggest that potassium entered the body cells more rapidly when administered in the glutamate form. However, since only one isomer was found to be effective in counteracting intoxication, it is apparent that alteration in potassium distribution is not the sole mechanism of action of this compound. Furthermore, nothing is known as far as the effectiveness of glutamate in conjunction with other cations in this condition is concerned; neither is it known whether myocardial tissue exhibits a particular affinity for this anion.

In any event, it appears that this compound is a safer means of administering potassium since less

marked hyperkalemia is likely to result. Thus far, other investigators have neither disproved nor confirmed Keyl's work. Further work with this compound is certainly warranted.

Summary: Potassium is an effective means of counteracting digitalis intoxication. The mode of action of this cation is unclear, but it appears to be at least initially a result of an increase in its extracellular concentration, with subsequently elevated intracellular levels possibly also playing a role. Hyperkalemia and A-V block are the most serious hazards to its use. If the patient is hospitalized and adequate care is taken, the intravenous route appears preferable. Although potassium chloride is the preparation commonly used, work with the glutamate salt suggests that it may become the preparation of choice.

B. EDTA (ethylenediaminetetraacetic acid):

This chelating agent, as the sodium salt, has been introduced recently as a method of treating cardiac arrhythmias, including those caused by digitalis. Its mechanism of action in this case is apparently based upon its ability to bind ionized calcium. The probable synergistic actions of digitalis and calcium have been discussed previously. This agent has been used in a variety of illnesses and the dosage schedules utilized

have varied considerably. The following table lists the amount administered by various investigators:

Reference	Dose (gms)	Average rate (mg/min.)	Intoxicated patients treated
71	3.25 (1.25 - 4.0)	270 (max. of 570)	35
250	0.6	15 - 20	5
251	3.0	100	11
252	0.775	(?)	1
253	0.6 - 3.0	200	(?)
254	0.5 - 4.0	(?)	6 (?)
14	4.0	17	(?)

Results: Eliot and Blount (71) treated a total of 66 patients with EDTA, 35 of whom were intoxicated with digitalis. Their ages ranged from nine months to 90 years. Results were especially impressive in the treatment of A-V block. All nine patients with first or second degree block showed a definite decrease in the block, and five of seven with complete block converted to regular sinus rhythm or first degree block. The two remaining patients showed no change. Thus, 14 of 16 with block showed definite improvement. Furthermore, all five patients with A-V dissociation converted to sinus rhythm. In all patients treated, subjective symptoms were relieved, usually before the arrhythmia

was halted.

Jubner and Kallman (250) found that in their small series of cases, the chelating agent was effective against both ventricular and supraventricular arrhythmias. One case of PAT with block was converted after infusion of only 240 mg.

Jick and Karsh (251) had excellent results in their series of patients. The onset of action occurred usually within 10-30 minutes after the start of infusion, but usually lasted less than one hour, although one case of PAT with block and one case of bidirectional ventricular tachycardia were permanently suppressed.

Bernstein (252) reported a case of treatment with EDTA of attempted digoxin suicide. A 49 year-old woman ingested 25 mg. of digoxin and developed sinus standstill with irregular nodal escape, extrasystoles, and first degree A-V block. Conversion to normal sinus rhythm occurred with infusion, but the arrhythmias reappeared after the chelating agent was stopped. Although not representing a typical case of digitalis intoxication, this report demonstrates the effectiveness of EDTA in the face of severe overdosage.

Soffer (254) presents five cases of complete A-V block. In all five, administration of EDTA resulted in

an increased ventricular rate, due to increased nodal conduction in four.

Other authors (253, 14) have also reported favorable results using this agent.

In general, it appears that the effectiveness of EDTA is directly related to the rate of administration and the total amount given. This probably accounts for the lack of effectiveness in some cases. Eliot and Blount (71) believe that unless a patient has received approximately 3 gm. within 10 minutes, he cannot be classified as a therapeutic failure. On the other hand, because of the hazards discussed below, Soffer (254) concluded it is not safe to administer more than 2 gm. within 30 minutes, and Seven (253) states that the maximum rate should be only 15 mg. per minute.

Hazards: Even with rapid rates of infusion, as noted above, the effects of EDTA upon serum calcium levels have in general been minimal, with a decrease of 2 mg% being the normal maximum observed. Generally, the decrease in calcium levels is proportional to the rate of administration, as would be expected. However, occasional cases of tetany following EDTA administration have been reported (71, 254). In one of these cases (71), calcium was given intravenously to counteract the tetany, and ventricular fibrillation resulted.

The authors conclude that should signs of tetany develop in these cases, calcium definitely should not be administered. Other electrolytes are not significantly affected. In determining serum calcium levels in the presence of EDTA, it should be remembered that the standard oxalate method of determination will give erroneously low results (256).

Page and Real (212) suggested, on the basis of their animal experimentations, that administration of EDTA in the presence of an electrocardiogram suggesting hyperkalemia may be dangerous because fatal potassium intoxication may be precipitated. Administration of EDTA at 200 mg/min. to dogs showing ECG signs of moderate potassium intoxication produced hyperkalemic death. This work confirms that of Levine (183) who found that low serum calcium levels made electrocardiographic manifestations of hyperkalemia more striking. These results, of course, agree with those earlier mentioned, suggesting that calcium acts upon the cell membrane in some way to regulate potassium exchange.

Thus, although some authors have suggested that EDTA might be a useful agent in the treatment of digitalis intoxication in the presence of hyperkalemia, it would appear that the potassium abnormality would be enhanced by the chelating agent. These results must be

compared with other reports stating that EDTA had no effect upon the serum potassium, and further work must be done to clarify this question.

Nephrotoxicity due to EDTA has been reported in both human and animal investigations. In all of these cases, the pathological changes resulted only from massive doses of this agent, with histological alterations essentially consisting of tubular damage (257). Despite the fact that only extremely large doses of EDTA have produced renal damage, until further studies are complete, it would appear prudent not to give this agent to patients with moderate to marked renal insufficiency. Furthermore, when this agent is administered, the urine should be checked frequently and the drug halted if abnormalities appear.

Other side effects noted during or after infusion have been arm pain above the needle site, thrombophlebitis, malaise, fatigue, thirst, fever, myalgia, headache, paresthesias, anorexia, and transient leukopenia (253).

When administering this agent, it should be remembered that sodium is the normal cation, with each 5 gm. of EDTA containing 1 gm. of sodium. Potassium and magnesium salts have also been used, but the results are as yet inconclusive.

Conclusions: EDTA may prove to be a useful drug in the treatment of digitalis intoxication. Its generally rapid onset of action suggests that it may be used when rapid response is needed and when potassium cannot be used. Thus, in renal insufficiency, without hyperkalemia, EDTA may prove to be the drug of choice. Thus far, no detrimental results have been reported in the treatment of A-V block, whereas potassium has, on occasion, aggravated the cardiac status. Should these results be confirmed, EDTA may prove to be the long-sought drug needed to combat digitalis-induced A-V block, especially accompanied by multifocal premature ventricular contractions. The toxic and side effects of this drug have been essentially mild and transitory. If proper observation is maintained, overt tetany should not be a problem. Although the potassium salts would initially appear to be most desirable form, it probably offers no essential advantage since both the hypocalcemia and the administered potassium act apparently to at least transiently increase the intracellular potassium concentration. The recommended dose for patients without manifestations of hyperkalemia, renal insufficiency, or hypocalcemia is 3 gm. given within 10 minutes.

C. Quinidine and Procaine Amide:

These anti-arrhythmic drugs are often used in the treatment of digitalis arrhythmias in which more conventional methods have either failed or are contra-indicated. They act upon the heart to decrease automaticity, refractory period, and conductivity, and to increase the threshold of the myocardium. These actions are at least in part due to a decreased rate of depolarization, resulting from altered cell membrane permeability to sodium. This, in turn, may effect an increased intracellular potassium level as suggested by others (258).

The advisability of using these agents is not universally accepted. Lown and Levine believe that procaine amide has a definite use in the treatment of digitalis-induced arrhythmias (85, 9). Rose (90) has suggested using it prophylactically to suppress cardiotoxic manifestations of digitalis overdosage. On the other hand, Zapata-Diaz (259) concluded that it is a dangerous drug when used in association with digitalis. He treated 37 patients having cardiac arrhythmias. The only two to die were those intoxicated with digitalis; both died suddenly after having several oral doses of the procaine amide. Gold (260) has witnessed both beneficial and damaging results from the combined use

of digitalis and quinidine. He states that in cases of digitalis intoxication, use of quinidine may occasionally produce unexpected and disastrous results. As a result, he avoids their simultaneous use whenever possible.

Beneficial results following the use of these anti-arrhythmic agents have been reported in a number of arrhythmias (9, 221, 85, 261). The controversy has been chiefly focused on their use in digitalis-induced ventricular tachycardia and atrio-ventricular block. In cases of ventricular tachycardia without block, reports have appeared of ventricular fibrillation apparently induced by the administration of quinidine (263). Most investigators, however, believe that these agents are useful in the treatment of this arrhythmia (88, 235, 264-266).

The difficulty involved in treating arrhythmias associated with partial or complete A-V block is a result of the apparent dual actions of quinidine, and presumably procaine amide also, on the A-V node. On one hand, quinidine acts to slow conduction in the node by direct depression, and on the other, to accelerate conduction by blocking vagal function (260). The chief danger, therefore, lies in the possibility of inducing ventricular standstill when treating ventricular

premature beats or ventricular tachycardia associated with A-V block. Despite the experiments of Gold (267), indicating that the block may be reduced by the action of quinidine, most authors agree that these two anti-arrhythmic agents are contraindicated in the presence of A-V block (101, 263, 226, 254).

These drugs should be administered orally whenever possible and intravenously only in emergencies. The intramuscular route offers an intermediate route of administration (268) and may prove to be as effective as the intravenous method.

D. Other Methods of Treatment of Digitalis Cardiotoxicity:

Magnesium has been used with good effect in the treatment of arrhythmias due to digitalis, both clinically and experimentally (48, 269-272). Unfortunately, its effect is only transient (20). It may increase the cardiac irregularity (81, 273) and it appears to be contraindicated in the presence of A-V block (200, 271).

DCI (dichloroisoproterenol), an adrenergic blocking agent, has been used experimentally to revert ouabain-induced arrhythmias (119). Rationale for its use may be founded in the work suggesting that the cardiac glycosides act via the catechol amines (68).

This line of investigation awaits amplification and confirmation.

Sympathomimetic amines, especially isoproterenol (Isuprel®), are frequently used in the treatment of atrio-ventricular block (226, 235). Unfortunately, little work has been done studying the effects of these agents in treating block due to digitalis. It is well known that these agents tend to increase the irritability of the myocardium, although isoproterenol is less likely to do this than the others. If other measures fail or are contraindicated, a trial of isoproterenol appears warranted as long as close observation of the electrocardiogram is maintained.

Grinnell (274) found that a large number of synthetic estrogens and estrogen-similar compounds protected dogs against digoxin-induced cardiotoxicity. This work has as yet not been confirmed. However, it would be interesting to know whether large doses of these compounds would be effective in treating digitalis intoxication. As mentioned earlier, digitalis is a steroid, and it appears possible that these estrogen preparations act by competitive inhibition.

E. Conclusions

Mild cases of toxicity may be treated by reduction in dosage or withdrawal of the glycoside for a short

period of time. More severe cases warrant definite therapy. Potassium therapy remains the cornerstone of such active treatment and generally gives excellent results. A-V block may be aggravated by potassium administration, however, and other treatment should be considered in such cases although potassium may be given a therapeutic trial in small doses providing electrocardiographic studies are made often enough to detect aggravation of the block. EDTA may prove to be the safest and most effective therapy for digitalis-induced A-V block and certainly merits use in those cases of first degree block worsened by potassium or those with second or third degree block.

The anti-arrhythmic agents should be reserved for those cases resistant to potassium or EDTA and to those in which these agents are contraindicated, remembering, of course, the danger of giving all of these drugs other than EDTA in A-V block.

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