The Clinical Use of Digitalis Preparations

By Calvin F. Kay, M.D.

I. The Various Digitalis Preparations
II. The Distribution and Fate of Digitalis
III. The Nature of the Action of Digitalis
   a. General Pharmacologic Properties
   b. Relation of Digitalis Action to Cations
IV. Quantitative Differences in Cardioactive Drugs
V. The Indications and Contraindications for Digitalis in
   a. Congestive Heart Failure
   b. Heart Disorders With Rapid Ventricular Rate
      1) Chronic atrial fibrillation
      2) Paroxysmal atrial fibrillation
      3) Atrial flutter
      4) Paroxysmal atrial tachycardia
      5) Paroxysmal ventricular tachycardia
   c. Heart Block
   d. Acute Myocardial Infarction and Angina Pectoris
   e. Disorders Not Primarily of Cardiac Origin
      1) Acute nephritis and toxemia of pregnancy
      2) Anemia
      3) Myxedema
      4) Beriberi
      5) Thyrotoxicosis
      6) Advanced pulmonary disease
   f. Potential heart failure
VI. The Administration of Digitalis
VII. The Manifestations of Digitalis Toxicity
VIII. The Management of Digitalis Toxicity
IX. References

The invariable result of functionally significant valvular disease), the degree of effectiveness of digitalis varies and is difficult to predict. Even when the fault lies entirely in the myocardium, digitalis may be ineffective, especially in acute inflammatory and degenerative diseases of the heart muscle (e.g., acute rheumatic fever, diphtheritic myocarditis, typhus). However, as a rule, if the heart is enlarged and congestive phenomena are present, digitalis should be used and will be beneficial.

Heart Disorders with Rapid Ventricular Rate

Digitalis is valuable in the management of most disorders of cardiac mechanism that are characterized by a rapid ventricular rate. When heart failure is present the results are more consistent than when it is not.

1) Chronic atrial fibrillation with rapid ventricular rate is a classic indication for

NOTE: In view of the length of this article, it is published in two issues. This issue will contain parts V through IX. The first part, I through IV was published in July, 1955. —ED.
digitalis. Atrioventricular transmission of impulses is depressed with resulting ventricular slowing. The ventricular rate serves as a useful guide to the adequacy of digitalis if the important limitations of this index are not overlooked. Inadequate digitalization may be associated with adequate slowing at rest. If the rate rises sharply with slight exertion, the drug effect is predominantly neurogenic, and further benefits may be expected with higher dosage. If the optimal level of digitalization has been exceeded, ventricular slowing may be excessive, or the rate may again rise. The latter important manifestation of toxicity may be caused by ventricular premature beats, or by a regularization of the ventricular response with progressive tachycardia.\textsuperscript{16}

When heart failure occurs in the presence of chronic atrial fibrillation at a slow ventricular rate, digitalization rarely results in dangerous depression of the rate at dosage levels that are effective in relief of the heart failure. The drug should be given cautiously and the effects followed closely.

(2) \textit{Paroxysmal atrial fibrillation} is also an indication for digitalis therapy, but results are much less consistent than in chronic atrial fibrillation. When atrial fibrillation with rapid ventricular rate develops under stress (e.g., postoperatively, with acute febrile illness, and with pneumothorax) in an individual with little or no antecedent heart disease, digitalis in any form may be entirely ineffective, even at toxic levels. In a reported series,\textsuperscript{63} neither reversion nor appreciable ventricular slowing followed intravenous preparations in 26 of 27 cases, or followed oral digoxin in 17 of 18 cases. The experience of many others has been much more favorable. Although negative results of digitalis therapy have often been observed, conversion to normal sinus rhythm has occurred many times, and an appreciable slowing of ventricular rate has been a frequent if not a consistent occurrence.

Continuous digitalization of a patient with recurring bouts of paroxysmal atrial fibrillation is not notably successful. The hope that attacks, when they occur, will be relatively asymptomatic, with a slow ventricular rate, is not realized in many individuals in whom paroxysms occur as frequently as before, and as severely. Since, in other patients, either the frequency or severity of the attacks is reduced, a trial of digitalis is warranted if other measures fail. The therapeutic limitations of digitalis in atrial fibrillation, acute or chronic, that is associated with thyrotoxicosis will be discussed.

(3) \textit{In atrial flutter}, digitalis is usually of value. A rapid ventricular rate may be reduced by decreasing the ratio of ventricular to atrial beats, or the flutter may be converted to atrial fibrillation with a more readily controlled ventricular rate. To achieve either of these results, unusually large doses of digitalis are often required.\textsuperscript{68} Sometimes fibrillation reverts to normal rhythm after the digitalis has been discontinued, especially with the assistance of quinidine. At other times sustained digitalis therapy is indicated.

(4) \textit{Paroxysmal atrial tachycardia} usually responds to simple measures and rarely requires digitalis. If the attack is protracted, especially if a serious form of heart disease is present, or if the signs of heart failure are developing, digitalis is the drug of choice. Abrupt reversion to sinus rhythm frequently results. Avoid, of course, the serious mistake of giving digitalis to a patient with paroxysmal atrial tachycardia induced by digitalis toxicity.

(5) \textit{Paroxysmal ventricular tachycardia} should always suggest the possibility of digitalis intoxication. Even when this can be excluded with certainty, other measures should be exhaustively tried before digitalis is used.

(6) \textit{Ventricular premature beats}, unless caused by digitalis toxicity, are not a contraindication to its use. This form of arrhythmia may be a manifestation of stress in a failing heart. Relief of the failure with the help of digitalis may result in the disappearance of the premature beats.

(7) \textit{Sinus tachycardia} is neither an indication nor a contraindication to digitalis therapy. A slight slowing of heart rate often accompanies restoration of compensation but it is not a useful guide to the adequacy of digitalization.
When sinus tachycardia is caused by anything other than heart failure, the heart rate will be little influenced by digitalis unless toxic doses are used and then it may be increased.

Heart Block

In persistent complete heart block with failure, digitalis is indicated. The hazard of digitalis administration to a patient with partial or intermittent heart block has been overemphasized, but cannot be ignored. Divergent opinions are cited by Blumgart and Altschule who demonstrated, in 19 such patients with arteriosclerotic and rheumatic heart disease, that the effects of drug and disease upon atrioventricular conduction were not additive. The pre-existing abnormal conduction was not appreciably disturbed by therapeutically effective doses of digitalis. However, attempts to convert intermittent atrioventricular block with syncopal seizures to permanent complete heart block have been occasionally successful. Digitalis is likely to increase the frequency of syncopal seizures associated with carotid sinus sensitivity.

Acute Myocardial Infarction and Angina Pectoris

Opinions differ concerning the use of digitalis after acute myocardial infarction. Some believe that it should be used almost routinely; others recommend it only as a last resort in advanced failure, fearing the drug induction of a fatal arrhythmia or cardiac rupture. Evidence from coronary occlusion experiments upon animals indicates a hazard in its use. In a controlled human study, no evidence of hazard was demonstrated. Most patients with acute infarction do not need digitalis when other measures are appropriately used to prevent the development of congestive failure. If, despite these, progressive failure is evident, cautious digitalis administration is indicated. Rapid digitalization or dosages approaching a toxic level should be avoided. The symptoms of angina pectoris are not significantly influenced by digitalis. It is neither an indication for the drug, nor a contraindication if heart failure is present.

Disorders Not Primarily of Cardiac Origin

A variety of disorders may cause symptoms and findings similar in one or many ways to those caused by heart disease. Dyspnea and palpitation are the outstanding symptoms of one group of these disorders, which include anemia, thyrotoxicosis, arteriovenous fistula, beri beri, Paget's disease, neurocirculatory asthenia, pregnancy, and advanced pulmonary disease. In these conditions the cardiac output is characteristically high. Edema is the outstanding feature of another group, which includes hypoproteinemic states, myxedema, acute glomerulonephritis, and toxemia of pregnancy. Most of these disorders increase the work of the heart. An intrinsically diseased heart, capable of adequate function for normal demands, may fail under the added stress. For example, if a patient with well compensated mitral stenosis becomes pregnant, congestive heart failure may develop, and a need for digitalis is created. Some of these disorders, if sufficiently severe or protracted, may be the direct cause of intrinsic heart disease.

In general, in the disorders not primarily of cardiac origin, digitalis will not help unless the heart muscle is failing. Specifically, the indications for and against, and the effects of, digitalis may be considered:

1. In acute nephritis and in toxemia of pregnancy, cardiac dilatation occurs under the stress of the associated hypervolemia, hypertension and capillary vascular disturbances in the myocardium. When hypertension, elevated venous pressure, and cardiac enlargement are all present, digitalis is often useful.

2. In anemia, some cardiac enlargement may be expected with hemoglobin levels at or below 40 per cent of normal. With sustained very severe anemias, the pathogenic sequence is dilatation, hypertrophy, myocardial atrophy, and lipoid replacement. Even if frank manifestations of congestive failure occur, digitalis preparations are rarely helpful in anemic heart disease.

3. In myxedema, the cardiac silhouette may be greatly enlarged, often from pericardial effusion, and many of the physical
findings usually associated with congestive failure may be present. If digitalis is effective, it is in meeting the demands of associated intrinsic heart disease of other etiology, for digitalis is not useful in uncomplicated myxedema.

(4) In beri beri, specific vitamin and general nutritional therapy is ordinarily highly effective. Digitalis may later be of some help if cardiac enlargement and elevated venous pressure persist, as occasionally they do.

(5) Thyrotoxicosis is especially prone to exaggerate the effects of coincident heart disease of other etiology. Although thyrotoxicosis produces no specific pathologic lesions, it alters cardiac metabolism. Atrial fibrillation frequently develops, and when it does, the ventricular rate is usually rapid. When heart failure occurs, all measures usually effective, including digitalis, should be employed. However, the results may be disappointing until the thyrotoxicity is controlled. With atrial fibrillation, large doses of digitalis are usually required to produce an appreciable slowing of ventricular rate. No attempt should be made to reduce the rate below that which would be present if the patient were in normal sinus rhythm.

(6) Advanced pulmonary disease may be associated with a variety of physiologic and anatomic abnormalities of the heart and general circulation.\textsuperscript{70} Digoxin\textsuperscript{70} or lanatoside C\textsuperscript{71} may result in an acute rise in cardiac output, even when it had been above normal before medication. Oxygen saturation may concurrently fall. In a longer term study, digitalis appeared to be a factor in clinical improvement, associated with a fall in pulmonary arterial pressure and in cardiac output.\textsuperscript{70} Digitalization has been suspected as a cause of sudden death in these individuals,\textsuperscript{71} but a cautious trial of the drug is indicated in patients with severe dyspnea, cyanosis, appreciable cardiac enlargement, or peripheral evidences of congestive failure. The results may be good, bad, or indifferent.

**Potential Heart Failure**

Also, opinions differ concerning the value of giving digitalis to the patient with a large heart, but in whom failure has never appeared. In these individuals, as in normal people, resting cardiac output is either little changed or reduced by digitalis administration.\textsuperscript{84} The concept of "prophylactic digitalization" was recommended by Christian\textsuperscript{72} a generation ago. It is supported by some evidence in man\textsuperscript{73} and in animals,\textsuperscript{71} but has never gained wide acceptance. Szent-Gyorgyi,\textsuperscript{71} impressed with the validity of the concept, concludes: "Why give the heart rope to hang itself?" This important problem warrants further attention. It may be that a patient with progressive cardiac enlargement deserves digitalis whether failure is present or not.

**VI. The Administration of Digitalis**

When it has been decided that a digitalis preparation should be given, the usual plan calls for selection of a suitable drug and its administration in amounts sufficient to produce a minimum effective level of digitalization within a reasonable time. The dosage is then adjusted to reach an optimum level, and finally readjusted to maintain the optimum level for a long period of time. Since any plan of therapy requires a considered guess at the amount of drug required to produce a desired effect, it is the first responsibility of the physician to recognize, as well as possible, those patients in whom major toxicity may result from doses that would ordinarily be safe. Cautious administration is necessary in the aged or debilitated, in patients with myxedema, electrolyte disturbances, advanced pulmonary disease, recent myocardial infarction or active myocarditis, and it is particularly necessary in those who have already received digitalis in any form.

Responsibility for establishing with certainty whether or not the patient is already digitalized is too often neglected, especially when a patient is transferred to a hospital or to the care of a new doctor at home. This is a major cause of digitalis poisoning. The fallacies of clinical judgment and of the patient's memory are better avoided by means of a telephone than an electrocardiograph. If there is any uncertainty, large single doses are almost never justified. If the preparation, dosage and
times of previous administration can be established, a rough estimate of additional requirements can usually be made. Further doses should be on the conservative side of this estimate.

The exact dose of any digitalis preparation necessary for the optimal therapeutic effect in any patient can be determined only by a clinical assay of the drug in that particular patient. However, the dose that will produce a definitely beneficial effect in most patients and yet produce only minor toxicity in a few has been reasonably well established. A single oral dose of 1.2 mg. of digitoxin to each of 512 cardiac patients produced gastrointestinal symptoms in only 15 (2.8 per cent). A comparable single dose of digitalis leaf produced nausea or vomiting in 20 per cent, and a single dose of 2.0 mg. of digitoxin to 98 patients produced similar symptoms in 32 per cent. Dangerous manifestations of toxicity did not develop in any of these patients.\(^{24}\) These and other studies indicate that, for digitoxin at least, an effective level of digitalization can be induced within less than 12 hours with a wide margin of safety. Nevertheless, this is rarely a necessary or a wise procedure. Although previous digitalis medication may be denied, sometimes mistakes are made. If vomiting does occur, an unknown amount of the drug may be lost, and even gastrointestinal symptoms are undesirable at best. If the series is large enough, sooner or later rapid "complete digitalization" will result in disaster. It has also been shown\(^{24}\) that a daily dose of 0.2 mg. of digitoxin will effectively digitalize within a period of two or three weeks. For the patient who has developed mild congestive failure over a long period of time, and who can be re-examined weekly, this is an entirely satisfactory treatment procedure. Usually, however, it is desirable to achieve a definitely beneficial effect within 24 to 48 hours, with a maximum of safety. For the patient under close observation, 0.4 mg. of digitoxin may be given every six to eight hours for three doses, noting the effects of each dose before the next is given. Thereafter, smaller doses are given at the same or longer intervals until an optimum effect is achieved, or evidences of early toxicity appear. Digitalis dosages, in grams, may be substituted for digitoxin dosages, in milligrams, for either of these therapy techniques.

The principal guide to the optimum level of digitalization is rarely clearly defined. It consists of a clinical judgment of the relief of the manifestations of the congestive failure. In the presence of atrial fibrillation, the apical pulse rate is a useful index, with limitations noted above. Manifestations of toxicity (except local gastrointestinal effects which appear within two hours after drug administration) usually indicate that the point of maximum benefit has been reached or passed. In some patients, particularly those who are severely ill, the toxic and therapeutic ranges may overlap, and maximum benefits are achieved in the presence of minor toxicity. In most patients, digitalis is helpful at doses well below the toxic range. Considered over a period of time, the slight benefits of higher dosage do not justify the discomforts and hazards that may develop. It is sometimes wise, however, to approach the toxic level at least once, as a trial, because the therapeutic dividend may be surprising.

Prolonged maintenance of optimum levels of digitalization, like initial digitalization, is an experiment in each individual. A reasonable estimate of dosage requirements is made; then, as subsequent developments dictate, it is revised. An occasional patient will be helped by, and will tolerate no more than, 0.05 mg. of digitoxin daily. Equally rarely, as much as 0.3 mg. is required and tolerated. In the majority of patients, 0.15 mg. daily is a satisfactory dose, and is usually recommended as a starting level. The guides to optimum maintenance are the same as those for initial digitalization. Several weeks may be needed for an error in dosage in either direction to be apparent. About one patient in three will require subsequent revision, more often downward than upward. The dosage for satisfactory maintenance, once established, does not ordinarily fluctuate widely unless there is a change in the physical state of the patient.

Digitalis, U.S.P., and digitoxin, U.S.P. are by far the most widely used of the several
preparations available for initial and maintenance therapy. They are the most slowly effective of the group. This is rarely a disadvantage, for in the vast majority of instances, a few hours is not a significant delay. Their effects are also the most persistent. This is a distinct advantage insofar as it results in stability of the level of digitalization, once achieved. It is a disadvantage in that toxicity once it develops, lasts longer. Digitalis produces more local gastrointestinal irritation than digitoxin, and is probably not quite so uniform in potency from lot to lot. It may be more likely to produce noncardiac systemic manifestations of toxicity before cardiotoxicity appears. If so, this has been considered an advantage by some, who believe that the cardiotoxicity appears more frequently without warning when digitoxin is used. Conversely, the maximum therapeutic benefits may be denied by troublesome nausea and vomiting with digitalis. Nevertheless, either of these preparations is highly satisfactory for most digitalization needs.

Some physicians prefer other preparations derived from digitalis for initial digitalization and prolonged maintenance. The basis for this preference must rest upon a very few proven differences between the drugs. Eight criteria of acceptability of a digitalis preparation are listed by Goodman and Gilman. Two of these, ease of administration and drug stability, are equally well met by all preparations. A third, adequate intestinal absorption, is probably met by all. Since the absorption of the other preparations, with the exception of lanatoside C, fall within the range between digitalis (20 per cent) and digitoxin (100 per cent), it is not reasonable to claim superiority over both. A fourth factor is cost. A year's supply of any of these preparations costs the average patient less than 10 dollars. A fifth factor is uniformity of potency. The purified glycosides are probably more uniform than the whole leaf preparation, but the differences are of borderline clinical significance. A sixth criterion is effective myocardial action. No convincing evidence has been presented in animals or in man that any one of these preparations differs appreciably from any other in this regard. A seventh criterion pertains to the margin of safety between effective therapeutic dose and toxicity. A mass of convincing data conclusively shows that all digitalis preparations have approximately the same margin of safety. 

Recently, an exception to this generalization has been reported by Buttermann, DeGraff and Rose. From their studies they reached the conclusion that the difference between therapeutic and toxic doses is greater with gitalin (amorphous) than with any other digitalis preparation. Hejtmancik and Hermanni did not confirm this observation, but they were impressed by the value of gitalin in the management of several patients who responded poorly to other preparations. It is of interest that when toxicity did occur, nausea, vomiting, or other extracardiac manifestations preceded evidences of cardiotoxicity in only 12 of 29 cases; the reverse was observed in nine, and in eight they appeared concurrently. Asymptomatic cardiotoxicity from gitalin has also been noted elsewhere. Other recent reports have been favorable, but investigators in the past have been unimpressed. In animal preparations, comparing therapeutic and irritability doses with lethal doses, gitalin was not found to be unique. If further studies convincingly demonstrate a superiority of gitalin (amorphous) with respect to toxicity, it should eventually displace other preparations currently in use. The evidence does not justify such a conclusion at this time. Controlled investigation of comparative toxicity and therapeutic effects, in which neither the patient nor the evaluating physician know the drug or its dosage, should be helpful in the clarification of this important point.

The eighth and final criterion is the rates of accumulation and elimination which permit digitalization at varying speeds and the maintenance of optimum cardiac effects over long periods. Special merits, if any, must be based chiefly upon this criterion. Each of the other preparations listed affect the heart more rapidly than does digitalis or digitoxin. Since the effects of each succeeding dose develop more quickly, they may be more clearly defined and more quickly used to judge the next dose. Also, the danger line may be approached with greater safety, because if toxicity
develops, it soon abates, which is a factor of considerable importance if toxicity is severe. These arguments have some merit as they pertain to the management of a patient who is very ill and must be carried on the borderline of serious toxicity in order to obtain maximum benefits of the drug; nevertheless, the advantages over the slower acting preparations are small, at best. Few patients get or need the constancy of attention required to take advantage of these supposed superiorities. Rapid action and short persistence may occasionally be used to advantage in a severely ill patient in whom it is suspected that the maintenance dosage of digitalis or digitoxin is inadequate. One or two small doses of digoxin, added to the regular maintenance schedule, may provide the basis for a rapid answer with a minimum of hazard. These properties are also of some advantage in the management of paroxysmal atrial tachycardia, fibrillation or flutter in which maintenance is a small problem once a satisfactory initial effect has been achieved.

Oral dosages of several preparations for initial digitalization and for maintenance are shown in table 1. The average figures, given in divided doses and spaced over 24 to 48 hours, will produce definite therapeutic effects in most patients, with a wide margin of safety in all, with the important exceptions noted above. The dosages indicated are somewhat lower than those found in many tables, which list the average optimum dose. The general plan for initial digitalization with any of these preparations is the same as that described for digitoxin and digitalis: slow administration if the patient is to be re-examined at long intervals, administration of the average figure in divided doses over 24 to 48 hours for a patient under careful observation, or in less than 24 hours if the demand is urgent. If further dosage is then needed for optimum effect, the amount listed under average maintenance dose may be given every six to eight hours, carefully observing the effects of each dose.

In a patient who is unable to take or retain oral medication, digitalis preparations may be used intravenously with but little added risk, provided that small doses are injected slowly, with an adequate interval for observation between doses. If digitoxin is used, the doses are the same by the intravenous as by the oral route. With all other preparations, the intravenous dose is appreciably smaller than the oral dose, as shown in table 1. For maximum safety, effective digitalization should not be attempted in less than 48 hours, with an additional period for establishing optimum levels.

Burrell and Coggins describe the lethal consequences of an intravenous injection of acetyl strophanthidin. Ventricular fibrillation developed suddenly, with none of the usual prefibrillatory warnings. Catastrophes of this sort are rare, but they have been reported from

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**TABLE 1.—Approximate Doses of Various Cardioactive Preparations for Oral and Intravenous Use (See Text)**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Initial Digitalization</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>I V.</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Digitalis U.S.P.</td>
<td>1.2</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Digitoxin U.S.P.</td>
<td>1.2</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>Acetyl Digitoxin N.N.R.</td>
<td>2.0</td>
<td>1.5-2.5</td>
</tr>
<tr>
<td>Gitalin (amorphous) N.N.R.</td>
<td>5.0</td>
<td>4.0-8.0</td>
</tr>
<tr>
<td>Digoxin U.S.P.</td>
<td>2.0</td>
<td>1.0-4.0</td>
</tr>
<tr>
<td>Lanatoside C U.S.P.</td>
<td>6.0</td>
<td>5.0-10.0</td>
</tr>
<tr>
<td>Ouabain U.S.P.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acetyl Strophanthidin</td>
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</tbody>
</table>

* Maximum dose for a single injection, to be diluted and administered in not less than five minutes. The average total dose for full digitalization is approximately 1.2 mg.
the rapid, especially from the intravenous, administration of many drugs, even when the total dose is not excessive. With digitalis preparations, it is always possible to err in predicting the size of a dose. Rapid intravenous digitalization should be avoided unless the demands for speed are extremely clear. Unless the situation is so critically urgent that a few hours cannot be allowed to pass for oral drug effects, the dangers of intravenous digitalization should not be accepted.

When demands are extreme, as in severe pulmonary edema associated with rapid atrial fibrillation or flutter or paroxysmal atrial tachycardia, intravenous digitalization may be lifesaving. In such an emergency, intravenous lanatoside C, or digoxin are effective within a few minutes. When it is certain that a digitalis preparation has not already been used, one half the average intravenous digitalizing dose may be given in one dose, injected in a five-minute period, followed if necessary, by half as much in each of two hourly doses. Thereafter, further administration must be deferred for six hours for the full effects to develop. Some prefer ouabain, which is even more rapid. An initial dose of 0.5 mg. is followed each half hour by 0.1 mg. for two doses, then hourly by 0.1 mg. for a maximum of three doses. These are the absolute maximum rates and amounts of administration. When these or any other of the intravenous preparations are used, the patient must be most carefully observed. When the emergency phase has passed, further digitalization, if necessary, should proceed at a slower rate, and orally. After ouabain, especially, transition to a more stable preparation, without toxicity or loss of therapeutic effects, may be difficult.

Occasionally, the most astute clinician is unable to be sure whether a desperately ill patient would be benefitted by more digitalis, or conversely, whether toxicity is already present. In such a dilemma, the choice lies between stopping further drug administration and waiting until toxic effects, if present, may have abated, or administering a small dose of a rapidly acting preparation (digoxin, lanatoside C, or ouabain) in the hope that if improvement does not result, the aggravation of the toxicity will be rapidly apparent, and also rapid in its disappearance. Either course may be hazardous. Lown and Levine have suggested that potassium first be administered. Improvement would then confirm the suspicion of toxicity; but if there is no improvement, acetyl strophanthinid may be used as a trial drug. The procedures to be followed and the interpretation of the results are described. Acetyl strophanthinid should be used with full recognition of its potentially lethal hazards. Administered intravenously, it is extremely rapid in action with peak effects in less than 20 minutes, and complete disappearance of effect in four hours at most.

VII. The Manifestations of Digitalis Toxicity

Severe toxicity is certainly more common than it was only a few years ago, although, in the opinion of this writer, it is neither so ubiquitous, so persistent, nor so regularly disastrous as some recent reports might indicate. The principal reason for increased incidence of toxicity is plain. More patients are now receiving digitalis preparations in larger doses, more rapidly administered. The standard maintenance dose of 0.1 Gm. of leaf has declined in popularity, and the days of 15 drops daily of tincture (equivalent to about six minims or 0.04 Gm. of leaf) are gone. Daily doses equivalent in potency to 0.15 or 0.2 Gm. of leaf are now widely used. Whereas the benefits of the digitalis preparations have been more widely realized, the ill effects are understandably more frequent. Minor manifestations of toxicity are, to a degree, useful, marking the sometimes overlapping boundaries of therapeutic effectiveness and the danger zone. Major toxicity is usually the result of obviously excessive dosage or careless inattention to warnings.

Unusual individual variations in tolerance to digitalis preparations account for occasional, but important toxicity. The causes of these variations are often obscure. In some instances they are predictable or at least understandable. Advanced hepatic or renal disease may sufficiently reduce degradation and excretion to reduce digitalis requirements slightly. The thyrotoxic patient will usually require a
reduction in digitalis dosage as thyrotoxicity is controlled. Similarly, after I\textsuperscript{11} therapy in an euthyroid patient, digitalis requirements may be considerably diminished. The digitalis tolerance and needs of the patient in severe cardiac failure are generally considered to be above average, but some of these patients are unusually sensitive, especially if body potassium has been depleted, spontaneously or with the help of various therapeutic measures. The hazard of calcium administration to a digitalized patient has also been discussed above. Finally, it may be that differences do exist between the essential toxic potentialities of different digitalis preparations, and that minor toxicity warnings are more evident with one than with another. If so, these would account for only an occasional example of the major toxicity that is seen in clinical practice.

The manifestations of toxicity may be obvious, or they may be so similar to those of the underlying disease that differentiation between the two is both difficult and important. The appearance of any toxic symptom or sign (excluding local gastrointestinal irritation effects) is a forewarning that serious toxicity, either cardiac or extracardiac, may ensue with any increase in dose.

Extracardiac Manifestations of Toxicity. These serve as useful warnings, provided they do not of themselves seriously impair the well being of the patient at drug levels below those required for full cardiotherapeutic benefits.

(1) The gastrointestinal manifestations of toxicity are the most frequent: anorexia, nausea, vomiting, or occasionally diarrhea. Abdominal fulness and discomfort from toxicity are easily confused with those caused by the visceral engorgement of cardiac failure itself. When any of these symptoms appear within one or two hours after an oral dose, they are usually caused by local gastrointestinal irritation and need not be confused with true toxicity. Otherwise they are usually of central origin, and, therefore, of greater significance. Digitalis causes both local and systemic symptoms more frequently and at smaller doses than most of the other preparations.

(2) Visual disturbances, “snow” or yellow vision, are not often mentioned voluntarily by the patient, but are elicited in response to questioning. Yellow vision occurs most frequently, but not exclusively, with whole leaf digitalis preparations.

(3) Neurologic symptoms are occasionally observed, especially headache or neuralgias of the face and upper extremities. Withdrawal of digitalis may result in a surprising relief of these symptoms.

(4) A variety of vague symptoms may take the place of more specific toxicity manifestations. General weakness and lassitude, insomnia, and irritability, for example, are especially likely to occur in the aged or debilitated. The vagueness of this “wilting” may obscure both its specific cause and its considerable therapeutic importance.

(5) True idiosyncrasy to digitalis preparations is very rare; thrombocytopenic purpura has been described. The statement by a patient that he cannot tolerate any digitalis preparation, even in the smallest doses, must be accepted with reservation.

Cardiotoxicity from Digitalis Preparations. Serious effects of digitalis on the heart may become manifest in a progression of cardiac failure. This may not be attended by other, more specific indications of toxicity; but when other manifestations have reached major proportions, especially those associated with arrhythmias, the benefits of therapy are customarily lost. The end-all of cardiotoxicity is ventricular fibrillation, but digitalis may produce almost any form of disturbance of rhythm.

(1) Sinus bradycardia may occur, but it is a poor guide to the adequacy of therapy. Sinus arrest or sinoatrial block may or may not be preceded by bradycardia.

(2) Atrial premature beats are less frequent than ventricular premature beats. Occasionally an established ectopic atrial rhythm develops at a rate only slightly faster than the previous sinus rhythm; it is easily mistaken for sinus tachycardia. With increased toxicity, the rate increases. At atrial rates of about 150 to 170, atrioventricular block appears, sometimes with Wenkebach phenomena, sometimes with a regular 2:1 ratio, sometimes quite erratically. This form of toxicity, paroxysmal atrial tachycardia with or without block, is mistaken both clinically and electrocardiographically for
rapid fibrillation or "impure flutter." Such a mistaken diagnosis may lead to further digitalization, with lethal consequences. It is an important clinical syndrome, noted in earlier reports\textsuperscript{88-89} and described in detail by Lown and Levine.\textsuperscript{16}

(3) Atrioventricular conduction disturbances usually begin as a prolongation of the P-R interval and progress to complete A-V block. Ventricular slowing in atrial fibrillation is usually a valuable therapeutic index. With toxicity, the ventricular rate may become excessively slow, or it may rise as the result of the activity of ectopic pacemakers, either ventricular or nodal.

(4) Ventricular premature beats precede classical bigeminy or trigeminy, multifocal ventricular ectopic beats, ventricular paroxysmal tachycardia, flutter, and finally fibrillation. One or several steps in this sequence may be skipped.

(5) A variety of other conduction disturbances and ectopic rhythms may occur, but it is noteworthy that bundle branch block is rarely a manifestation of digitalis toxicity.

Electrocardiographic changes, other than those specifically associated with the arrhythmias described above, characteristically occur with digitalis therapy. They may be transient after exertion, and thereby result in a false positive exercise tolerance test for angina.\textsuperscript{90} The magnitude of these electrocardiographic changes in any one individual may provide a guide to the relative level of digitalization in that individual, and has provided a criterion for biologic assay of digitalis preparations in humans.\textsuperscript{91} However, major cardiotoxic effects may occur in the absence of well developed "digitalis patterns," or the patterns may be very pronounced in an individual who has no associated evidence of toxicity.

VIII. The Management of Digitalis Toxicity

Slight anorexia or nausea, the pulse a little slow or an occasional premature beat have long been used as warnings and guides in digitalis therapy. Beyond this level, hazardous toxicity may be feared, and further benefits are not to be expected. These events indicate the need for a day or two of drug withdrawal, followed by resumption of maintenance at a slightly lower dosage level. When manifestations are somewhat more severe, withdrawal should be for a longer time and new maintenance levels should be set appreciably lower. Minor toxic signs and symptoms will usually abate or disappear within two to three days at most.

Hazardous toxicity is usually associated with rapid digitalization in excessive dosages, a major change in the physical status, or neglect of the warnings of minor toxicity. Severe vomiting or other extracardiac manifestations of toxicity may seriously complicate severe heart failure. Obviously, digitalis must at once be discontinued. Giving potassium may be of some specific benefit; it certainly reduces the danger of superadded cardiotoxicity if potassium is at all depleted, as it is likely to be in the presence of vomiting, diarrhea, or restricted dietary intake. Otherwise management of major extracardiac toxicity is entirely symptomatic. Major cardiotoxicity infrequently develops without warning, but once it is established an already deficient cardiac output may be so seriously reduced that the consequences are lethal, or ventricular fibrillation may occur. Since therapeutic measures are of themselves somewhat hazardous, the vigor of their application requires fine clinical judgment of the severity of toxicity and whether the level of digitalization is still on the upgrade or is declining. The duration of toxicity is related to the biologic persistency of the preparation employed, but even with severe toxicity from the most stable preparations, digitoxin or digitalis leaf, marked improvement or complete relief is the rule within three or four days at most. Exceptionally, toxicity may persist for a week or more. If improvement is slower, a cause other than digitalis toxicity should be suspected as the basis for the persistence of the symptoms.

Effective emergency treatment measures are available for the dangerous arrhythmias of digitalis poisoning. Constant professional attention is demanded, with the electrocardiograph continuously connected for records at frequent intervals. Oxygen should be given, and tourniquets, sedation and l-norepinephrine should be available for use as needed. Unless
there is reason to believe that hyperkalemia is present, potassium should be given either orally as chloride or citrate (4 Gm. in cold fruit juice, followed if necessary by 2 Gm. hourly for two hours) or, and this is preferable, given intravenously. The standard intravenous preparation contains potassium chloride, 3 Gm. (13 mEq. per Gm.) in 20 cc. of water. This solution should be diluted to 500 cc. in 5 per cent glucose solution. It may be given at a maximum rate of 5 cc. per minute until a total of 6.0 Gm. has been injected. The perfusion should stop if the arrhythmia is controlled. These rates of administration and total dosages may be increased in patients with frank potassium depletion, but otherwise should not be exceeded in the first six hours. Further potassium administration may be required to prevent return of the arrhythmia until the digitalis has been destroyed or excreted.

In ventricular paroxysmal tachycardia caused by digitalis poisoning, procaine amide is indicated if potassium is not immediately available, or if no effect has been achieved in three hours. Three standard capsules (750 mg.) of procaine amide may be given orally, followed if necessary by 250 mg. hourly for two additional doses. If the patient is unable to take or retain oral medication, 50 mg. every two minutes may be given in a continuous drip until 300 mg. have been given, then the rate is reduced to 50 mg. every four minutes to a maximum total of 1000 mg. in one hour. Procaine amide is available in 10 cc. vials containing 1000 mg. of the drug. Blood pressure should be taken every minute during intravenous administration. The infusion must be slowed if the pressure falls appreciably, or stopped entirely if the fall is alarming, as occasionally happens. If the pressure does not promptly return towards the preinjection figures, l-norepinephrine should be given.

**Conclusion**

Some of the most important aspects of the use of digitalis may be thus summarized. Any standard digitalis preparation, if used with reasonable care and skill, will produce excellent results in the majority of treatment problems. Proper use of the drug is more important than proper selection of the preparation, since, except for variation in accumulation and decline of effects, the drugs differ little. A growing tendency toward excessive use of rapidly acting intravenous preparations should be discouraged; it is unnecessary and dangerous. The value of these preparations, skillfully used when clearly indicated, has been offset by the harmful effects of indiscriminate use in inexperienced hands. Rapid improvement is better than slower improvement only when it is also safer.

Most instances of dangerous toxicity can be traced to mismanagement, though, even under the direction of the most competent physician, toxicity can occur. The importance of electrolyte disturbances in promoting digitalis poisoning deserves emphasis. Recognition of certain supraventricular tachycardias as manifestations of toxicity will prevent the hazardous consequences of further digitalis administration. From personal experience, toxicity from digitalis leaf or digitoxin is not so persistent nor so troublesome as some have stated, and stability of maintenance has been easier than with the more biologically labile preparations. Lanatoside C, digoxin, and gitalin (amorphous) have some advantages in the management of the severely ill patient who can be kept under close observation, and in the treatment of some of the arrhythmias. Acetyl digitoxin appears to be a compromise between the two groups.

No substitute for the digitalis drugs is on the horizon. They are of inestimable value in the every day life of millions of human beings. Perhaps, with more care and wisdom in the use of these drugs, many patients may be helped a little more and a few a great deal more.

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**References**


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CALVIN F. KAY

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