UNIVERSITY OF TEXAS
HEALTH SCIENCE CENTER AT DALLAS
SOUTHWESTERN MEDICAL SCHOOL
MEDICAL GRAND ROUNDS

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DIGOXIN, 1977

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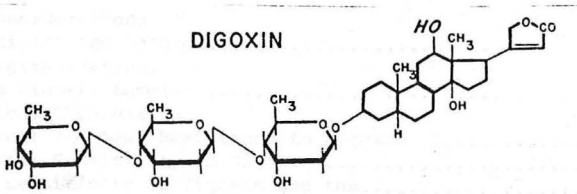

"I am more and more convinced, that the Digitalis, under a judicious management, is one of the mildest ... medicines we have, and one of the most efficacious .... it is not necessary to create a nausea, or any other disturbance in the system."

Withering, W.: Letter to Hall Jackson, 1786.

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HISTORICAL NOTE

From *An Account of the Foxglove and Some of its Medical Uses* by William Withering. Swinney, Birmingham, 1785.

"In the year 1775, my opinion was asked concerning a family receipt for the cure of the dropsy. I was told that it had long been kept secret by an old woman in Shropshire, who had sometimes made cures after the more regular practitioners had failed. I was informed also, that the effects produced were violent vomiting and purging; for the diuretic effects seemed to have been overlooked. This medicine was composed of twenty or more different herbs; but it was not very difficult for one conversant in these subjects, to perceive, that the active herb could be no other than the Foxglove.

My worthy predecessor in this place, the very humane and ingenious, Dr. Small, has made it a practice to give his advice to the poor during one hour in a day. This practice, which I continued until we had an Hospital opened for the reception of the sick poor, gave me an opportunity of putting my ideas into execution in a variety of cases; for the number of poor who thus applied for advice, amounted to between two and three thousand annually. I soon found the Foxglove to be a very powerful diuretic; but then, and for a considerable time afterwards, I gave it in doses very much too large, and urged its continuance too long ....

I had not, however, yet introduced it into the more regular mode of prescription; but a circumstance happened which accelerated that event. My truly valuable and respectable friend, Dr. Ash, informed me that Dr. Crawley, then principal of Brazen Nose College, Oxford, has been cured of a Hydrops Pectoris, by an empirical exhibition of the root of the Foxglove, after some of the first physicians of the age had declared they could do no more for him. I was now determined to pursue my former ideas more vigorously than before, but was too well aware of the uncertainty which must attend on the exhibition of the *root* of a *biennial* plant, and therefore continued to use the *leaves*. These I had found to vary much as to dose, at different seasons of the year; but I expected, if gathered always in one condition of the plant, viz., when it was in its flowering state, and carefully dried, that the dose might be ascertained as exactly as that of any other medicine; nor have I been disappointed in this expectation. The more I saw of the great powers of this plant, the more it seemed necessary to bring the doses of it to the greatest possible accuracy. I suspected that this degree of accuracy was not reconcilable with the use of a decoction, as it depended not only upon the care of those who had the preparation of it, but it was easy to conceive from the analogy of another plant of the same natural order, the tobacco, that its active properties might be impaired by long boiling. The decoction was therefore discarded, and the *infusion* substituted in its place. After this I began to use the leaves in *powder* ....

Further experience convinced me, that the *diuretic* effects of this medicine do not at all depend upon its exciting a nausea or vomiting; but on the contrary, that though the increased secretion of urine will frequently succeed to, or exist along with these circumstances, yet they are so far from being friendly or necessary, that I have often known the discharge of urine checked, when the doses have been imprudently urged so as to occasion sickness.

If the medicine purges, it is almost certain to fail in its desired effect; but this having been the case, I have seen it afterwards succeed when joined with small doses of opium, so as to restrain its action on the bowels."

GRAND ROUNDS: Digoxin, 1977

Introduction

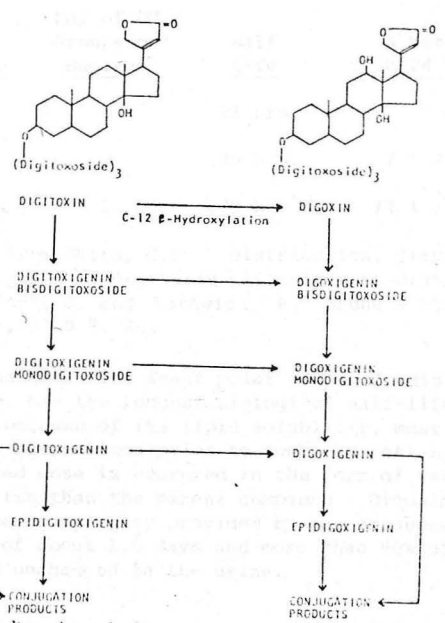
Digoxin was recently found to be the fourth most commonly prescribed drug in the United States. And, in 1972 some 600 papers were found under the heading "Digitalis" in the Index Medicus, epitomizing a recent information explosion. Digitalis drugs were used by the Egyptians 3500 years ago. Preparations containing digitalis continued to be used in folk medicine through the centuries, but it was William Withering who first placed its use on a scientific basis. Most of what he said is either still accepted or still argued about today. Because physicians often did not heed the cautions provided by Dr. Withering, the drug was held in disrepute through much of the 19th century. But digitalis regained its place in the physician's armamentarium in this century. The brilliant discovery of precise techniques for the easy measurement of this drug in serum and tissues has allowed the world's investigators to more completely describe its pharmacology. Because of the voluminous literature, I shall be selective rather than exhaustive in my subsequent remarks.

Basic Considerations:

A. Biochemical

The first figure shows the structure and metabolic degradation of digitoxin and digoxin (1). There are over 300 similar compounds

Figure 1



—Metabolic pathway for biotransformation of digitoxin and digoxin.

in the digitalis group. They all must contain a standard nucleus with a 5- or 6- membered alpha, beta unsaturated lactone ring, which characterizes the classes known as cardenolide or bufadienolide respectively, attached at the C-17 position. The double bond of the lactone ring appears to be necessary for cardiac action, and saturation results in near or complete loss of activity. A hydroxyl group in the beta configuration at C-14 and cis fusion of the C and E rings of the nucleus are necessary for cardiac activity. Thus, the structural requirements for activity are present in the aglycone rings, but the addition of one or more sugar residues at C-3 increases the potency and duration of action (2).

The steps in biotransformation are indicated by the arrows in the figure, and it should be particularly noted that digitoxin and various of its products can be converted to digoxin or the comparable digoxin metabolite by beta hydroxylation at the 12 position. Some of these conversions become exaggerated by drug interactions or occasionally in an individual who seems to develop an abundance of one of the necessary breakdown enzymes.

According to Okita, much of the disparate behavior of the several clinically important glycosides can be correlated with their polarity (1). Table 1 summarizes this information for ouabain, digoxin and digitoxin. It can be seen that the most water soluble of the three, ouabain with 5 OH groups, has the shortest biological half life and is excreted by

Table 1
Correlation of Polarity with Half-life and
Extent of Metabolic Transformation

Glycoside	No. of OH Groups on Nucleus	Half Life	% Metabolites in 24 hr. Urine
Ouabain	5	21 hrs.	0
Digoxin	2	36 hrs.	7 ± 2 (S.E.)
Digitoxin	1	120 hrs.	74 ± 3 (S.E.)

*Adapted from Okita, G.T.: Distribution, disposition and excretion of digitalis glycosides in Digitalis ed by Fisch, C. and Surawicz, B. Grune & Stratton, New York, 1969 P. 23.

the kidneys unchanged. The least polar compound, digitoxin with 1 hydroxyl group, has the longest biological half-life of approximately five days, and, because of its lipid solubility, must be largely broken down into metabolites prior to renal excretion. About 75% of an administered dose is excreted in the form of various more water soluble metabolites than the parent compound. Digoxin, with the relative increase in polarity provided by the presence of 2 OH groups, has a half-life of about 1.5 days and more than 90% of an administered dose is excreted unchanged in the urine.

B. Pharmacodynamics:

Figure 2 summarizes the important features of the pharmocokinetics of digoxin (3-6). When administered orally in an aqueous solution or in the form of an elixir, approximately 85% of digoxin is absorbed from the GI tract (7). Absorption is a passive, non-saturable transport process (8) occurring principally in the proximal small intestine (9,10). About half of an oral dose is absorbed by way of the portal vein (11). According to Doherty's data, approximately 6.8% of an administered dose is recycled through the enterohepatic circuit (7). More recent data would indicate that under some circumstances, for example in anephric patients, this amount may be significantly greater than 6.8% (12). The absorbed material, Figure 3, appears in the serum quickly and rises to a peak level approximately 1 hour after administration of the drug. This first rise and fall has a half-life of about 60 minutes and represents the plasma:tissue distribution phase which is then followed by the slow disappearance or excretion slope. This represents metabolism and excretion of the drug with a half-time of about 1 1/2 days or 36 hours. Three percent appears in the stool per day and 30% appears in urine per day equaling a total excretion of about 1/3 of the total body stores per day. As previously indicated 90% is in the form of digoxin and 10% approximately in the form of degradation products or metabolites. As one might suspect, the mode of administration may alter the time to peak serum level and the duration of plasma:tissue equilibration. When given intramuscularly, the first rise and fall requires some 10 to 12 hours and has a half-time of about 100 minutes, but then describes a similar slow excretion slope. Intravenous administration shortens this initial curve to a half-life of 30 minutes and declines to the excretion slope after about 3 to 4 hours (3,4).

The principal differences seen with the non-polar digitoxin are characterized in Figure 4. One notes the longer serum half-time, the 100% absorption figure, the larger proportion of an administered dose recycled in the enterohepatic circuit, the small daily percentage excretion with the major portion in the form of breakdown products (3,4,13).

Figure 5 describes the non-cardiac tissue distribution after intravenous administration to dogs, and demonstrates the large build-up in the organ of excretion, the kidney, in contrast to liver, pancreas, and diaphragm following an inotropic dose of .03 mg/kg (14). The myocardial distribution is noted in Figure 6, where several areas of left ventricle have equal and higher accumulations than the right ventricle. The atria were equal and accumulated about half the content observed in the left ventricle. Figure 7 shows the tissue:serum concentration ratios during the beginning of the slow excretion slope after an inotropic dose, dark bars, and it can be seen that throughout the left ventricle this ratio was approximately 30 to 1. It was Doherty who first noted the constancy of tissue:serum concentration ratios after plasma:tissue equilibration during slow excretion (15). This led him to predict that should a method become available for the measurement of digoxin in serum that it would have a predictable linear relationship to tissue content and therefore should be useful in clinical assessment of digoxin myocardial content.

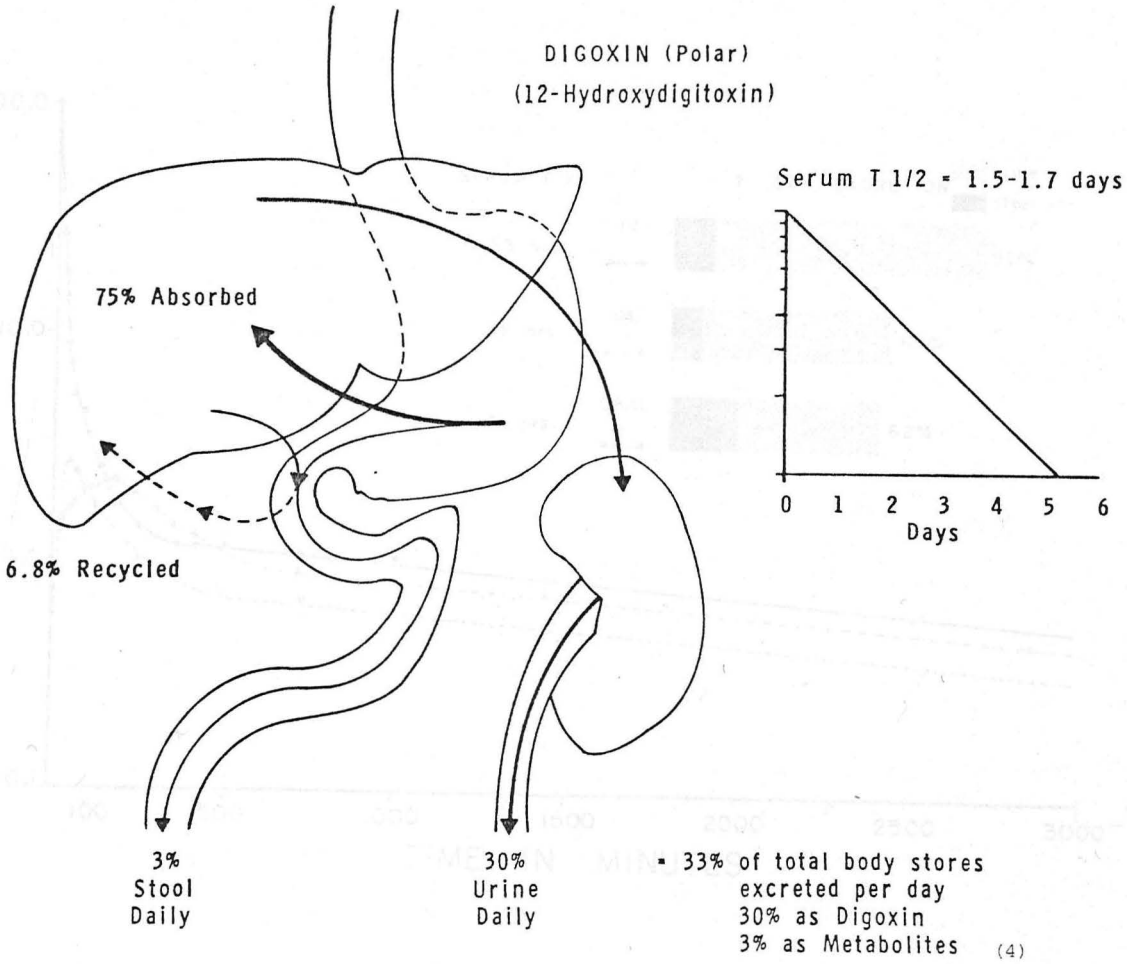
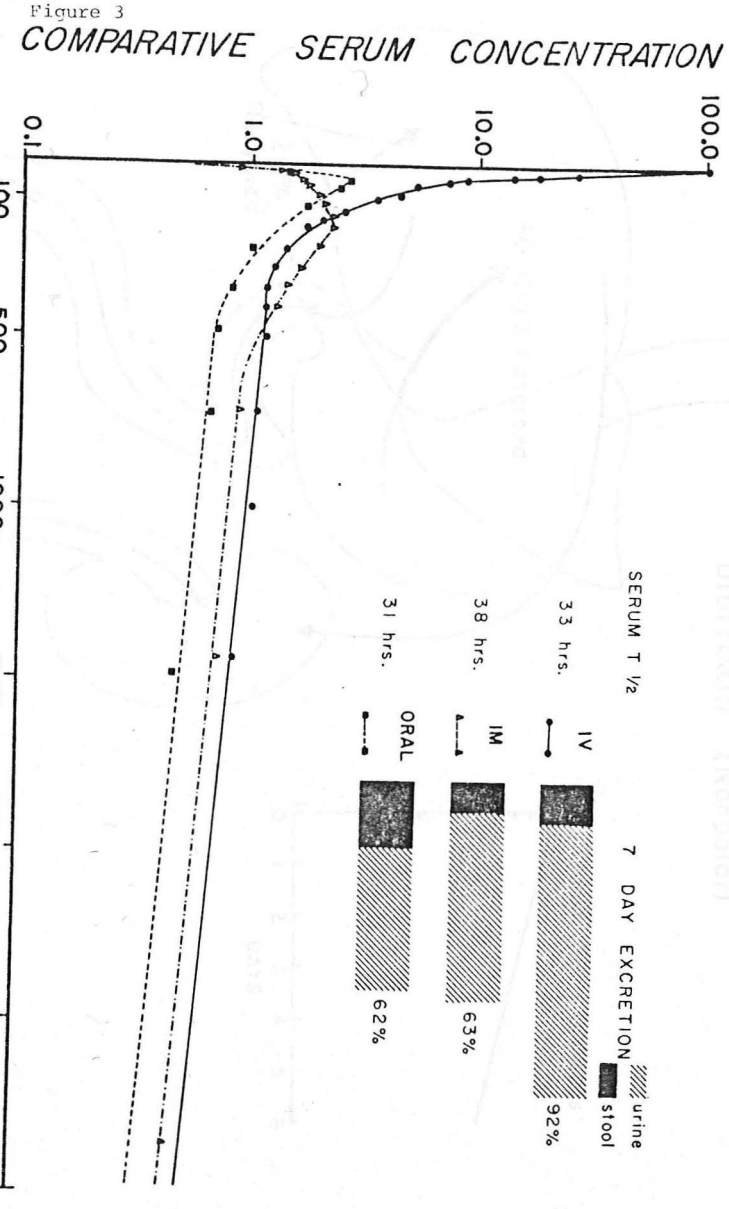

DIGOXIN (Polar)
(12-Hydroxydigitoxin)
Serum T 1/2 = 1.5-1.7 days
75% Absorbed
6.8% Recycled
0 1 2 3 4 5 6
Days
3%
Stool
Daily
30%
Urine
Daily
= 33% of total body stores
excreted per day
30% as Digoxin
3% as Metabolites

Figure 2

(4)

Figure 3


COMPARATIVE SERUM CONCENTRATION
100.0
10.0
1.0
0.1
100
500
1000
1500
2000
2500
3000
TIME IN MINUTES
SERUM T ½
IV
33 hrs.
IM
38 hrs.
ORAL
31 hrs.
7 DAY EXCRETION
urine
stool
92%
63%
62%

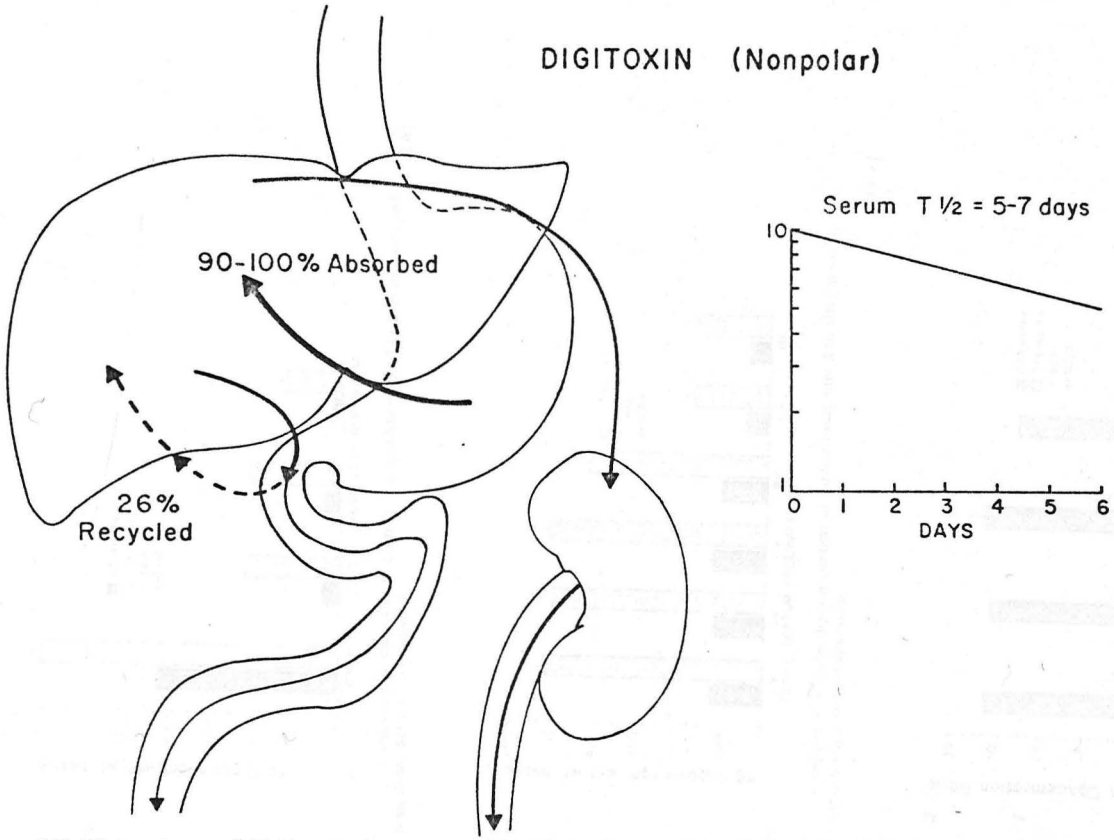
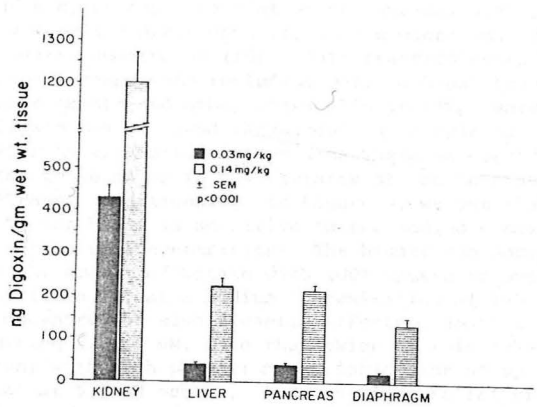

DIGITOXIN (Nonpolar)
90-100% Absorbed
26% Recycled
Serum T ½ = 5-7 days
10
1
0 1 2 3 4 5 6
DAYS
2% Digitoxin
8% Metabolites
4% Digitoxin = 14% OF TOTAL BODY STORES EXCRETED/DAY

Figure 4

(9)

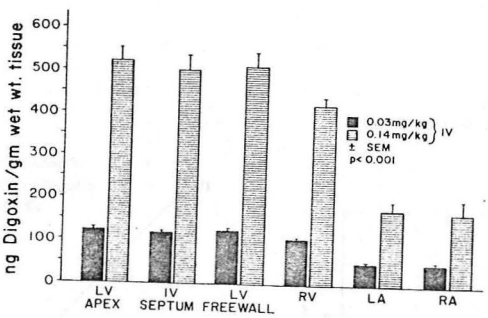
Figure 5



Comparison of mean digoxin content of noncardiac tissues 2 hr after inotropic and toxic doses. See text for discussion.

(14)

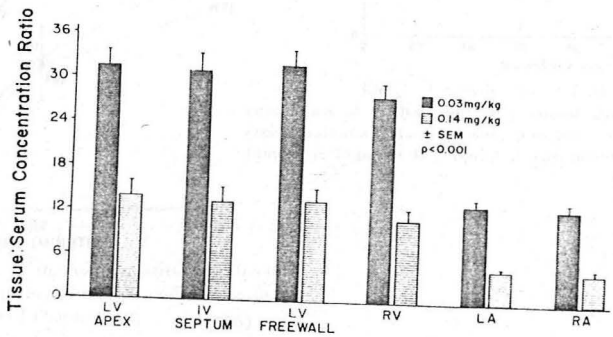
Figure 6



Comparison of mean digoxin content of cardiac tissue sites 2 hr after inotropic and toxic doses. See text for discussion.

(14)

Figure 7

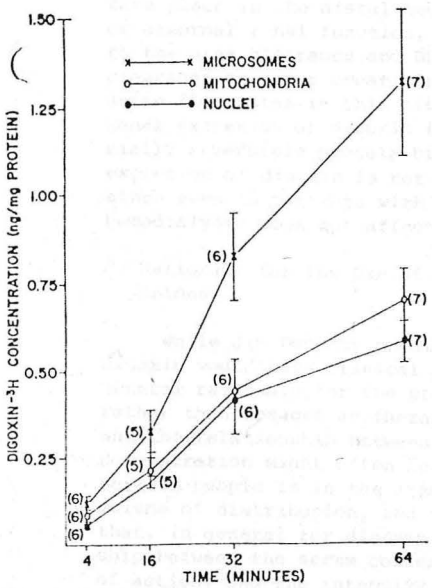


Comparison of mean tissue to serum concentration ratios of cardiac tissue sites 2 hr after inotropic and toxic doses. See text for discussion.

(14)

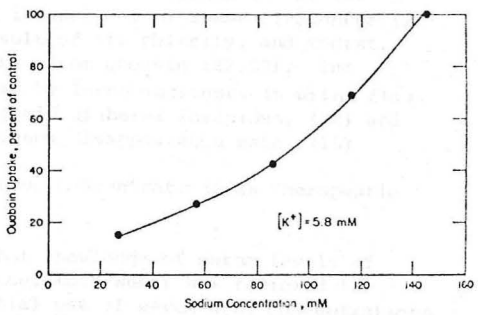
In Figure 8, we can note that at the sub-cellular level digoxin appears to accumulate preferentially in the microsomal fraction of guinea pig heart homogenates (16). This fraction contains all the light membranous components including cell membrane fragments, sarcotubular elements and other intracellular components. Thus, although digoxin may be found throughout the myocardial cell, it does seem to prefer to accumulate in the area where we consider its active binding sites to be on or in the vicinity of the membrane sodium potassium ATPase. Additionally, in Figure 9, we see that the uptake of ouabain by the heart is sensitive to the sodium concentration at a constant potassium concentration. The higher the sodium concentration the greater the amount of uptake with 100% uptake at approximately 140 mM. In Figure 10, at a sodium concentration of 145 mM, variable potassium concentration significantly affects ouabain uptake with 100% uptake occurring at 5.8 mM, more than twice that is taken up at 1 mM concentration; with high potassium, an inhibition of uptake to less than 50% that at 5.8 mM occurs. And, as might be inferred from these data, we see in the next figure, 11, the relationship of perfusion medium sodium/potassium ratio and uptake of ouabain by the perfused guinea pig heart demonstrating the inhibiting effects of low ratios and the enhanced uptake with high ratios.

Figure 8



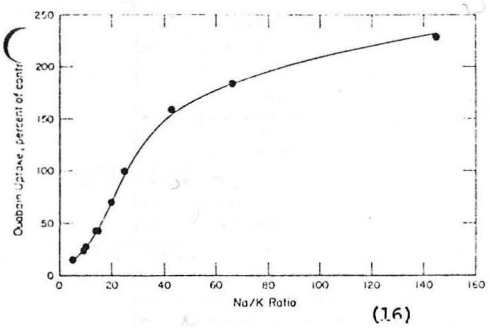
Digoxin concentration in the various particulate fractions of a pig heart after various perfusion times. Conditions as in Figure nted with permission from J Pharmacology. (16)

Figure 9



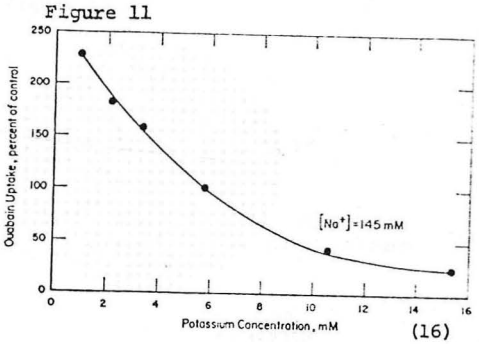
Effect of varying the sodium ion concentration on the accumulation of ouabain by the perfused guinea pig heart. Potassium ion concentration constant, osmotic pressure maintained with sucrose. Conditions as in Figure 4-4. (Reprinted with permission from J Pharmacology. (16)

Figure 10



(16)

Figure 11



(16)

Since digoxin excretion is dependent upon the kidneys, it should be clear that the rate of excretion is sensitive to renal function (17,18). In normal subjects the digoxin body clearance has been estimated to be 188 $\pm$ 44 ml/minute/1.73 meters^2 B.S.A. (19). There is a significant correlation between both the creatinine clearance and the BUN with digoxin disappearance time and with the amount that appears in the urine each day. Digoxin renal clearance is greater than inulin clearance indicating active tubular secretion (20), presumed to take place in the distal segment of the renal tubule. With borderline or abnormal renal function, digoxin clearance appears to be related to the urea clearance and BUN better than it is to creatinine clearance or serum creatinine. It also can be related to the low urine flow rates in this situation independent of these clearances (21). Renal excretion of digoxin is a result of its polarity, and modest, easily reversible protein binding by serum protein (22,23). The excretion of digoxin is not enhanced by large increases in urine flow since even in patients with nephrogenic diabetes insipidus, (24) and hemodialysis does not affect the plasma disappearance rate. (18)

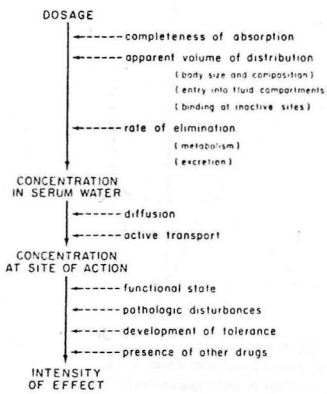
C. Rationale for the Use of Serum Drug Concentrations as Therapeutic Guides:

While Jim Doherty predicted that knowledge of serum levels of digoxin would have clinical relevance, Koch-Weser has reviewed the general rationale for the preferential use of serum drug concentrations rather than dosages as therapeutic guides. (25) Figure 12 illustrates why the relationship between dose of drug and the actual serum concentration might often be poor. The largest source of variability between people is in the area of completeness of absorption, apparent volume of distribution, and the rate of elimination. He pointed out that, in general for digoxin and many other drugs, that the relationship between the serum concentration, the concentrations at the site of action, and the intensity of effect tend to be well correlated, and that, in fact, the serum level of a drug may often be used as a useful index of the degree of receptor occupancy.

D. Bioavailability:

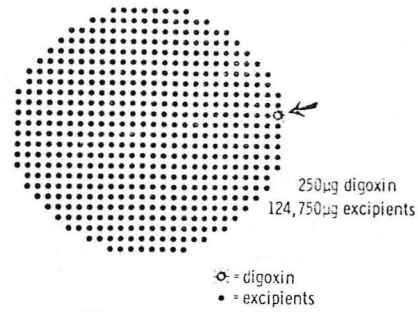
The discovery and continuing investigation of the bioavailability problem illustrates the usefulness of easily performed, precise methods for measurement of digoxin in serum and urine.

Figure 12



Dose-Effect Relation of Drugs in Man and the Factors That Influence It. (25)

Figure 13

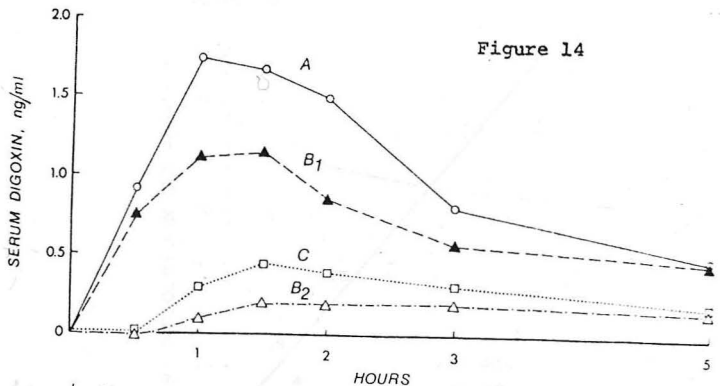


Schematic representation of a typical 0.25 mg digoxin tablet. Tablet weighs 125 mg (125,000 µg). White circle depicts 0.25 mg (250 µg) digoxin. Black circles represent various excipients. (26)

This problem may be divided into two parts. First, is the question of tablet content; the US Pharmacopeia requires that tablets contain between 92 and 108 percent of the stated amount of glycoside (26). In the early 70s it was found by the FDA that 20 of 32 firms failed content uniformity standards, and that as many as 47% of digitalis tablets had to be recalled (27,28). This problem seems to be under control now, but the errant manufacturers have not been publicly identified. The largest digoxin manufacturer, Burroughs Wellcome, as well as some others, have never had a lot of tablets recalled (26). The second is bioavailability or the facility with which a tablet releases its active ingredient. Figure 13 illustrates the problem. A 0.25 mg digoxin tablet actually weighs about 125 mg so that only 1 part in 500 by weight is digoxin and the remaining 499 parts are a variety of excipients. From the manufacturing standpoint, therefore, when a single quarter ton batch of 2 million digoxin tablets is prepared it is a challenge to insure equal distribution of the active ingredient, digoxin, so that every individual tablet contains the same amount and will be formulated in a manner that it will effectively and predictably release its active ingredient for absorption (26). The bulk of the tablet is made up of fillers, granulating agents, lubricants, disintegrants. Disintegration time depends on these factors plus the granule size, surfactants, compressional pressure, particle size of active drug as well as age and condition of storage (28). Even solutions or elixirs of digoxin are less bioavailable than a comparable intravenous dose (29). This seems to be dependent upon such factors as motility, intestional tissue degradation, unfavorable in vivo partition coefficients between membranes and GI fluids, the pH of the gastric juice, and possibly still others.

In 1971, Lindenbaum and his colleagues encountered several patients with rapid atrial fibrillation with no evidence of thyroid or GI disease who were taking 0.75 to 1 mg of digoxin daily with poor rate control (30). Their serum digoxin levels were unexpectedly low and they wondered about the adequacy of their digoxin tablets and carried out the experiment illustrated in Figure 14. It can be

Figure 14

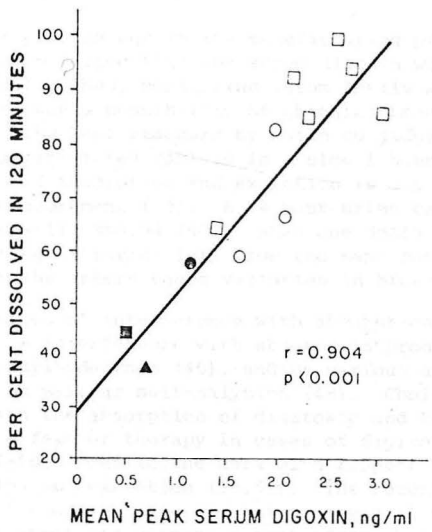


Mean serum digoxin concentrations after oral administration of digoxin products from three manufacturers (including two lots from company "B") to four normal subjects. Serum levels after A differed significantly from those after B_2 and C at each time interval except at 3 hours; the same was true when B_1 and B_2 were compared. From Lindenbaum et

seen that peak blood levels after administration of 0.5 mg tablets from 3 different companies, there was a 7-fold difference in peak level between Brand A and Brand B2. As might be expected, these results gave rise to a great flurry of activity and FDA sponsored conferences looking for the solution to this problem. The unflappable Dr. Doherty editorialized that 70 to 80% of already available digoxin was "good" digoxin, that is, it was Brand A or Burroughs Wellcome Lanoxin, and that the problem was really soluble (31). Other observers recommended switching to digitoxin since it was 100% absorbed when administered orally (13). Dr. Koch-Weser recommended that variation in bioavailability should be limited to less than 20 percent, and that complete predictability would be ideal (32). The regulators, in consultation with clinicians and backed by a NY Heart Association Task Force on Digitalis Preparations, feared the hazard of unanticipated changes in potency of tablets (27,32). Thus, all agreed to set for the time being upper limits on tablet dissolution rates which seemed to be so critical in determination of bioavailablity. They would then require a 55 to 95% dissolution rate while studies were continuing. Preparations which had faster rates of dissolution would be considered new drugs and tested for their safety.

Lindenbaum and colleagues had fortunately found that there was an excellent correlation between tablet dissolution in 6% HCL and in vivo bioavailability (34). The good correlation with peak serum digoxin level is seen in Figure 15. If there is less than 50% dissolution in 2 hours, relatively little digoxin from a tablet is effectively released for absorption in the GI tract. Figure 16 compares the serum digoxin concentrations after administration of elixir, the standard, on the left with those seen after rapid dissolution tablets and on the right after slow dissolution tablets (35). A sizeable number of human studies have utilized various techniques to test for bioavailability including short term serum levels, 6 hour and 24 hour urinary cumulative excretion and 6 and 9 day cumulative urinary excretions (36,37).

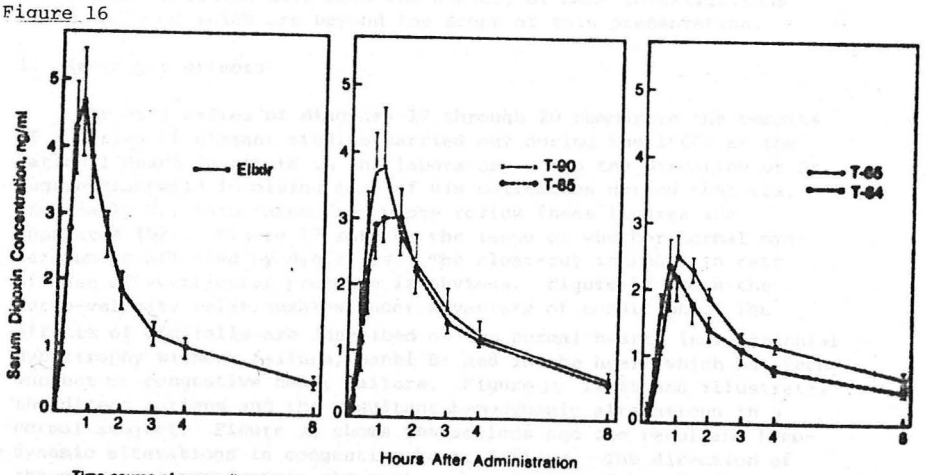
Figure 15



Correlation between dissolution rate of 12 lots of digoxin from 9 companies and peak serum levels in volunteers after a single 0.5 mg dose. The solid symbols indicate lots of digoxin found to be therapeutically ineffective in patients. From Lindenbaum et al. (26)

(14)

Figure 16



—Time course of serum digoxin concentration after administration of 0.75 mg of digoxin elixir (left), rapid-dissolution tablets (middle), or slow-dissolution tablets (right) to eight subjects. Each point represents mean (±SE) for all subjects. (35)

In England, after a change in the manufacturing process, serum level assessment demonstrated that the serum digoxin was 2/3 higher after the change (38). Thus, monitoring serum levels would be necessary when there was a possibility of changing brands or manufacturing methods. The best standard by which to judge bioavailability of all the orally administered tablets is a slow 1 hour infusion, and the most stable measure of absorption and excretion is a 6 day cumulative urinary excretion measurement (39). A 24 hour urine can be substituted and correlates very well, R=0.94 (40). When one deals with "good" digoxin and is testing different lots from the same manufacturer, it has been found that the intersubject variation in bioavailability

Additional sources of interference with absorption of tablets actually taken is the interference with absorption produced by neomycin (45), diphenylhydantoin (46), and by various antacids and kaolin-pectin (47) as well as sulfasalyzine (48). Cholestyramine, which interferes with the absorption of digitoxin and has therfore been recommended as a form of therapy in cases of digitoxin intoxication (49), has yielded conflicting data with respect to its effect on digoxin absorption and excretion (50,51). The recent impressive study from Little Rock using tracer technics showed increased variation in serum levels and stool and urinary output after cholestyramine, but that it had no net short term effect on these three variables and only a minor increase in stool content after one month's administration (50).

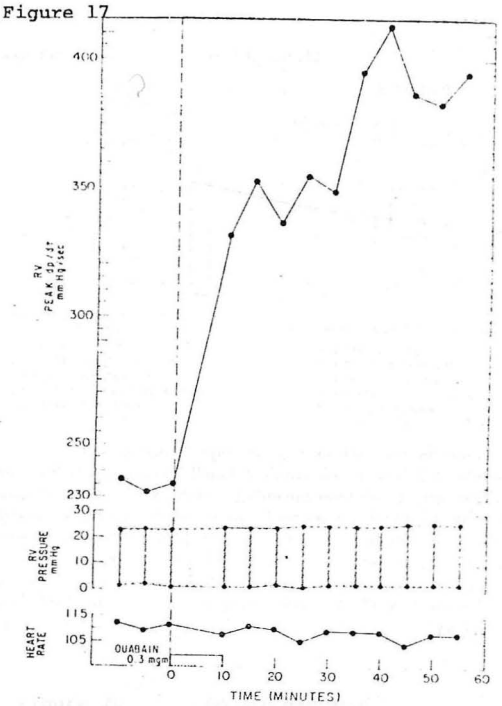
E. Summary of Inotropic and Electrophysiological Effects:

The principal effects of glycosides for which they are applied in clinical medicine have been the subject of many investigations the details of which are beyond the scope of this presentation.

1. Inotropic effects:

The next series of diagrams 17 through 20 summarize the results of a series of elegant studies carried out during the 1960s at the National Heart Institute in the laboratory under the direction of Dr. Eugene Braunwald involving many of his colleagues during that era, especially Dr. Dean Mason from whose review these figures are reprinted (52). Figure 17 settles the issue of whether normal myocardium is affected by digitalis. The clear-cut increase in rate of rise of ventricular pressure is obvious. Figure 18 shows the force-velocity relationships under a variety of conditions. The effects of digitalis are described on the normal heart, in ventricular hypertrophy without failure, panel B; and in the heart which has been subject to congestive heart failure. Figure 19 lists and illustrates the direct actions and the resultant hemodynamic alterations in a normal subject. Figure 20 shows the actions and the resultant hemodynamic alterations in congestive heart failure. The direction of changes under hemodynamic alterations are indicated by the direction of the arrow, and I think we can agree that there are a variety of effects which would be beneficial to the victim of congestive heart failure. In an outstanding series of independent investigations utilizing noninvasive techniques, Weissler and his colleagues carried out a series of parallel, confirmatory studies. (53,54) One major point made in this series of investigations which had been fuzzy in the older literature was the clear cut dose response curve that

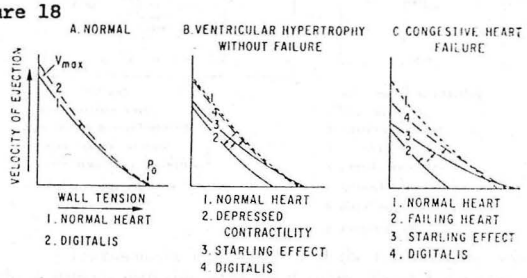
Figure 17



Sequential measurements of the peak rate of change (dp/dt) of right ventricular (RV) pressure in a patient with a normal cardiovascular system. (Reprinted with permission from J Clin Invest 42:1105, 1963.)

(52)

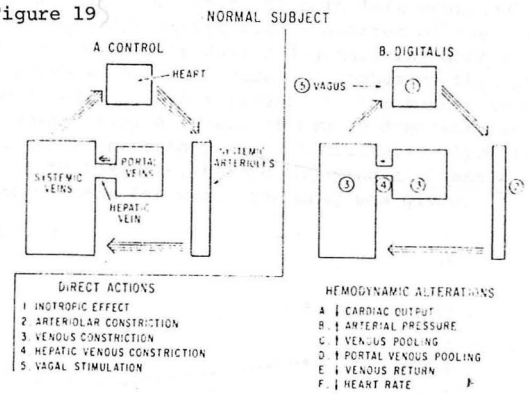
Figure 18



Force-velocity relations of the intact ventricle in (*A*) the normal heart, (*B*) ventricular hypertrophy without heart failure, and (*C*) congestive heart failure. P_o-maximal isometric tension development. (Reprinted with permission from Progr Cardiov Dis 11:143, 1969.)

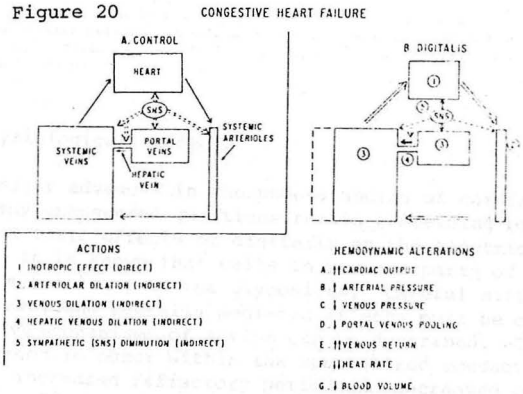
(52)

Figure 19



Diagrammatic representation of the hemodynamic action of digitalis in normal subjects. Panel A shows the control state of the circulation and Panel B the circulation following digitalis. In the bottom panels are shown the direct actions of the drug on the heart, peripheral vessels, and vagus nerve *(left)* and the hemodynamic alterations resulting from these actions *(right)*. The circled numbers in Panel B refer to the direct actions of the drug. The width of the arrows indicate the relative amounts of blood flow. (Reprinted with permission from Progr Cardio Dis 11:443, 1969.) **(52)**

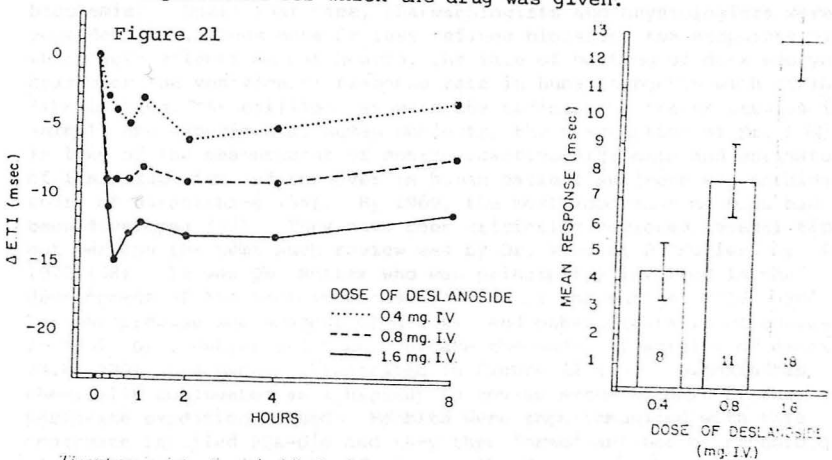
Figure 20



Diagrammatic representation of the hemodynamic actions of digitalis in patients with congestive heart failure. Panel A depicts the control state and Panel B the circulation following digitalis. In the bottom panels are given the actions of the drug on the heart, peripheral vessels and sympathetic nervous system (SNS) *(left)*, and the hemodynamic changes induced by these actions *(right)*. The width of the solid arrows indicate relative amounts of blood flow. The broken arrow represents increased activity of the SNS on the heart and peripheral blood vessels; the double broken arrows in Panel A depict greater activity than the single broken arrows in Panel B. The circled numbers in Panel B refer to the direct and indirect actions of digitalis. The broken line indicating expansion of the systemic venous reservoir represents an initial increase of blood volume in this compartment; at a later point in time, the size of this compartment is reduced following diuresis and a fall in total blood volume. (Reprinted with permission from Progr Cardiov Dis 11:443, 1969.) **(52)**

could be demonstrated, and is illustrated in Figure 21. What we see here is a definite shortening of both left ventricular ejection time and Q-S_2 time demonstrable with a quarter of the full digitalizing dose, a median response with half a digitalizing dose and then the completed response with a full dose. I emphasize this particular point because I think it has relevance to the manner in which we tend to utilize digoxin clinically and of course demonstrates that it generally may not be necessary to push digitalis glycosides to their limits, that is to toxicity, before enjoying at least a good deal of the needed improvement for which the drug was given. (18)

Figure 21



The response in ejection time index following deslanoside at three dose levels. The response curves during the [illegible] hours corrected for diurnal effect and the mean response for this period are illustrated. The crossbars represent standard error of the mean eight hour response. Deslanoside was administered at 0 time. The number of hours in each group is indicated in the bars.

(53)

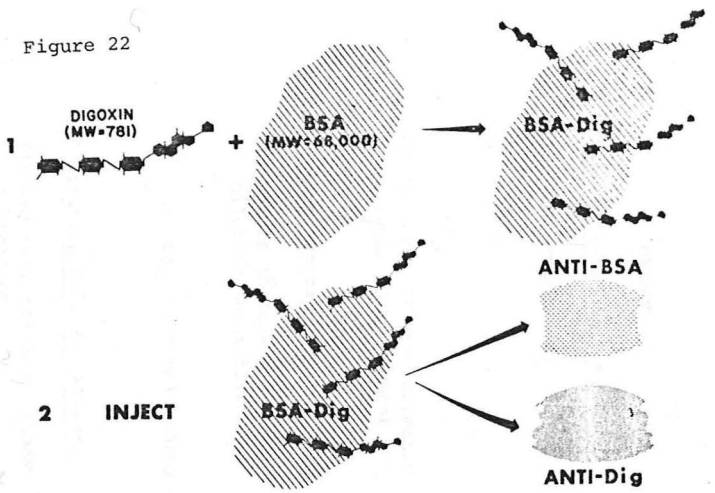
2. Electrophysiological effects:

Despite major advances in the understanding of cardiac electrophysiology, many unanswered questions remain concerning both the therapeutic and toxic effects of digitalis on the electrical activity of the heart. It is known that cells in various parts of the heart show variable sensitivity to the glycosides. Careful differentiation between the direct and neurally mediated effects must be carried out before definitive mechanisms of action can be described. The following effects are agreed to occur within the specialized conduction tissues of the heart: increased refractory period and decreased conduction velocity; these effects slow the ventricular response to atrial fibrillation and atrial flutter and prolong the PR interval in the presence of normal sinus rhythm. These effects are summarized in the resulting prolongation of A to H time in His bundle conduction studies indicating that these principal effects of digitalis affect the conduction tissue above the His bundle predominantly since the H-V time is insignificantly changed. We do know that in the atrial and ventricular myocardial tissue, however, the refractory period tends to be shortened and this more rapid recovery results in the typical shortening of the QT interval. With increased amounts of digitalis in model experiments, it appears that both increased automaticity as well as conditions favoring reentry occur. Both mechanisms must be considered as potentially capable of producing the arrhythmias associated with digitalis overdosage (55).

F. Methods for measurement of digoxin in the serum

The problem of direct measurement of therapeutic concentrations of digoxin in serum prior to the mid-60s resulted from the fact that the measurement of a billionth of a gram of steroid (less than 1% is present in the vascular compartment) was beyond the abilities of the biochemist. Until that time, pharmacologists and physiologists were dependent on various more or less refined bioassays the endpoints of which were effects on cat hearts, the rate of beating of duck embryo hearts or the ventricular response rate in human subjects with atrial fibrillation. As brilliant as were the radioactive tracer studies in animals and experimental human subjects, the description of Dr. Lukas in 1966 of the measurement of non-radioactive digitoxin and estimates of its metabolism and turnover in human patient subjects was nothing short of astonishing (56). By 1969, the most important methods had been developed (57). They have been critically reviewed several times but perhaps the best such review was by Dr. Vincent P. Butler, Jr. in 1972 (58). It was Dr. Butler who was principally involved in the development of the radioimmunoassay which is the current gold standard for the precise measurement of digoxin and other digitalis glycosides. In 1967, Drs. Butler and Chen overcame the non-antigenicity of digoxin (M.W. 500) in a manner illustrated in Figure 22 (59). Digoxin has chemically conjugated as a haptene to bovine serum albumin by the periodate oxidation method. Rabbits were then immunized with this conjugate labelled BSA-Dig and they then formed antibodies capable of binding digoxin. They also formed antibodies to the bovine serum albumin, but this did not interfere with the digoxin immunoassay procedure later developed. Additionally, in their classic paper they also demonstrated that non-radioactive digoxin inhibited the binding of tritiated digoxin by anti-digoxin antibody. They thought that development of a practical radioimmunoassay capable of precise measurement of digoxin in the small amounts present in blood was quite likely. They were inspired to pursue this goal by the results of Doherty's studies in which he found a relative constancy of myocardium to serum concentration ratios (mean 29 to 1) and stated in his 1967 paper that the relative constancy of these ratios in the face of large differences in total body digoxin stores "indicates that the serum-digoxin level is related to the cardiac muscle digoxin level in that a serum digoxin determination... should be of definite value in clinical assessment of digoxin cardiac content" (15). Despite the potential excitement of these developments, Dr. Butler found it impossible, despite his most pleasant personality, to find collaborators at his medical center in New York. He overcame this by finding willing and able collaboration at the Massachusetts General Hospital in the form of Drs. Thomas Smith and Edgar Haber. Their work resulted in the landmark paper authored by Smith, Butler and Haber entitled "Determination of Therapeutic and Toxic Serum Digoxin Concentrations by Radioimmunoassay" published in the New England Journal of Medicine in 1969 (57). This radioimmunoassay was based on methods developed by Berson and Yalow for the assay of insulin and other peptide hormones. Since the amount of labeled glycoside bound by a standard amount of antibody will decrease as increasing amounts of unlabeled glycoside are added, a

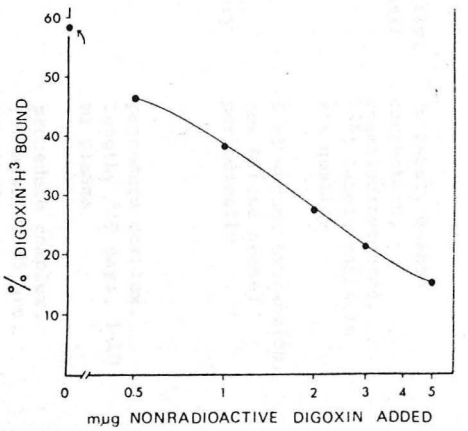
Figure 22



. *Production of antibodies to digoxin.* ***Top,*** *digoxin (Dig) was chemically conjugated as a hapten to bovine serum albumin (BSA) by the periodate oxidation method.* ***Bottom,*** *rabbits were immunized with BSA-Dig conjugates and formed antibodies capable of binding digoxin, as indicated by bivalent antidigoxin antibody molecule; antibodies to BSA were also formed, but did not interfere with digoxin immunoassay procedure. From Butler* (26)

standard curve, such as the one illustrated in Figure 23, can then be constructed from which the concentrations of digitalis in a given patient's serum can be determined on the basis of the decrease it causes in the binding of radioactive glycoside by specific antibody. Since it would be unfair not to acknowledge other methods, we have adapted Table 2 to show the several more or less acceptable methods available for digitalis assay in plasma or serum. The radioammuno-assay method is the most precise and best adapted for wide-scale clinical determinations and investigative procedures requiring large numbers of determinations and not too fussy about the small amount of digoxin metabolites which may be available and inaccurately determined. The red blood cell rubidium 86 uptake inhibition method deserves special mention. It was described by a lone worker in San Francisco (60) and later underwent many modifications which brought it close to adequate sensitivity and specificity. (61,62) We were able to make some reasonable observations with it (63,64) and it is still used in modified form by some European workers. As one puruses the advantages and disadvantages of each of the methods, I think we would all agree that the RIA method is the clear current winner.

Figure 23



(26)

Table 2 Serum or Plasma Digitalis Assay Methods

METHOD	GLYCOSIDE	ADVANTAGES	DISADVANTAGES
A. Competitive Protein Binding:			
(1) Radioimmunoassay	digoxin, digitoxin, deslanoside, ouabain, acetyl strophanthidin	simple, rapid, sensitive specific, long AB shelf life, 0.1-1 ml.	^{3}H label: quench correction, chemiluminescence. ^{125}I label: variable kit quality
(2) Na^+, K^+, ATPase enzymatic isotopic displacement	digoxin, digitoxin	rapid, sensitive, specific, quench correction unnecessary	5 ml serum, extraction, new ATPase needed periodically
B. Physicochemical:			
(1) Double isotope dilution derivative	digitoxin	sensitive specific	procedure complex, lengthy >10 days, 3-10 ml plasma
(2) Gas-liquid chromatography	digoxin	sensitive specific	procedure complex, few assays, >5 hrs, 10 ml plasma
C. Inhibition Na^+, K^+, ATPase:			
(1) Red cell rubidium uptake inhibition	digoxin, digitoxin	sensitivity and specificity only fair	extraction, lengthy >7 hrs.
(2) Microsomal Na^+, K^+, ATPase inhibition	digoxin, digitoxin	specificity good, no isotopic counting equipment	extraction, insensitive (5-10 ng/ml), lengthy >4 hrs, 3 ml plasma

Commercial laboratories have refined these RIA methods and offer them in the form of kits. By utilizing an iodinated label instead of the tritiated label the technique has been further simplified. Although initially there was some question as to the accuracy and precision of the iodinated technique, (65) a number of recent papers have validated its precision and accuracy sufficiently that it is useful both for clinical and investigative purposes. (66-69)

An illustrative example of such a kit evaluation from our laboratory also demonstrates the talent of our technicians, Table 3. In reproducibility studies with a low content sample the coefficient of variation was 8% around a mean of 0.25 ng/ml, whereas with the 0.93 mean value sample the coefficient of variation was close to 1% as it was with the P92 sample mean of 3.81 ng/ml. In recovery studies, the variations of percent recovery in the range of clinical interest was from 98.5% to 108.8%. The correlation of 100 samples between the kit which we have used and validated clinically for a few years with a new kit is shown in Figure 24 with a near perfect correlation coefficient.

Reproducibility Studies Table 3

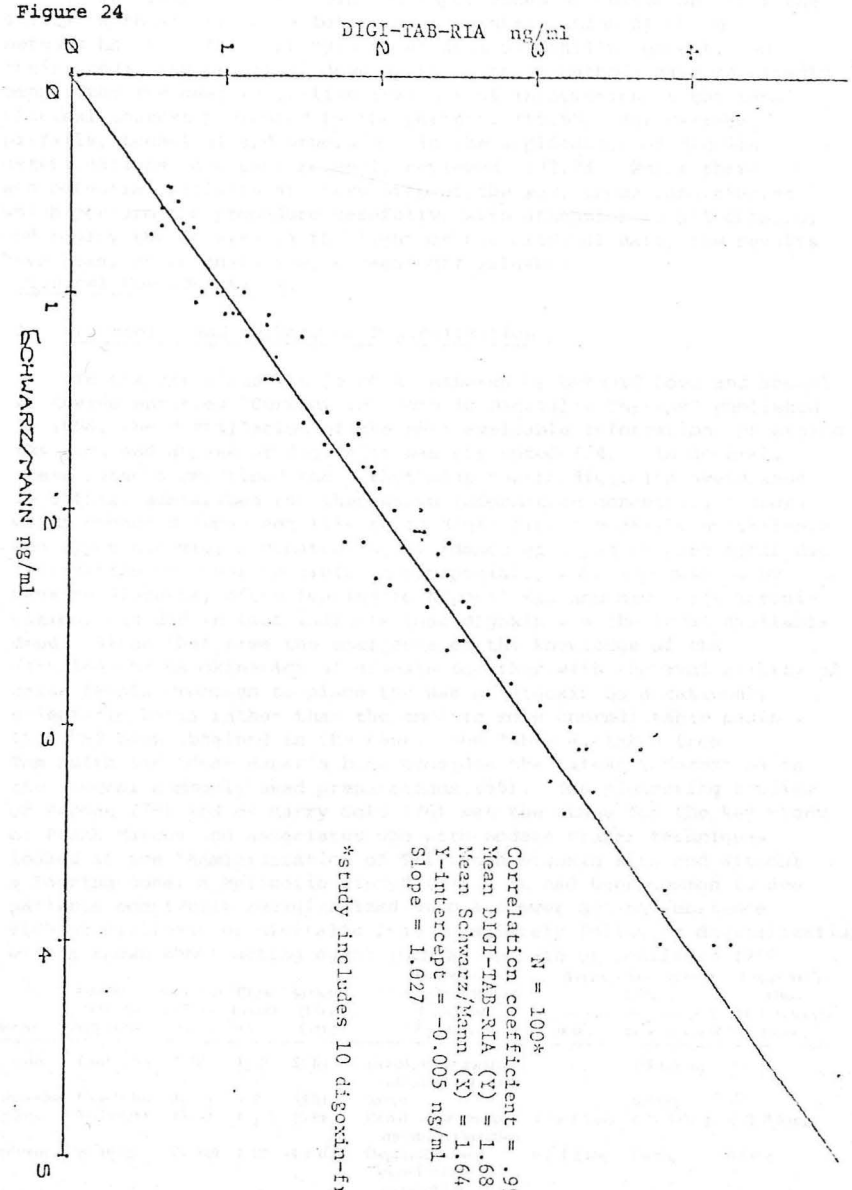
	P90	P91	P92
N	20	20	20
Mean	0.25	0.93	3.81
Highest value	0.28	0.94	3.92
Lowest value	0.20	0.91	3.75
S.D.	0.02	0.01	0.04
C.V. (%)	8.0	1.1	1.1

Recovery Studies

Digoxin Added	Digoxin Recovered	Percent Recovery
1 ng/ml	1.05 ng/ml	105.0%
2 ng/ml	1.97 ng/ml	98.5%
3 ng/ml	2.99 ng/ml	99.7%
4 ng/ml	4.35 ng/ml	108.8%

The practical advantage of utilizing an iodinated label allows one to use gamma counters which are simpler and less expensive than liquid scintillation counters. Further, liquid scintillation counting requires an additional step to correct for luminescence called quenching. This further series of pipettings and rinsings prolongs the procedure and provides opportunities for technical error. It is necessary to note that the presence of similar types of radioactivity in the blood from other diagnostic tests can interfere with the determination. Also low serum albumin may sometimes lead to spuriously low results (70) and the presence of digitoxin may be picked up to the extent of about 9% of the digitoxin present by the digoxin-specific antibodies. (71) An exciting new prospect is the potential practicality of the enzyme multiplied immunoassay technic or EMIT. (72) This technique does away with the disadvantages inherent to all radioisotopic methods when used in routine clinical laboratories; specialized isotope safety considerations, licensure requirements, decay of radiolabeled reagents, need for radioisotopic counting equipment, and the obligatory separation of antibody bound from unbound isotope. Preliminary results with this method are quite promising. (71)

Figure 24


DIGI-TAB-RIA ng/ml
0
1
2
3
4
5
SCHWARZ/MANN ng/ml
N = 100*
Correlation coefficient = .9912
Mean DIGI-TAB-RIA (Y) = 1.68 ng/ml
Mean Schwarz/Mann (X) = 1.64 ng/ml
Y-intercept = -0.005 ng/ml
Slope = 1.027
*study includes 10 digoxin-free samples

It is clear from the clinical experiences of physicians that the initial enthusiastic wave following the introduction of these methods has been followed by a great deal of disillusionment. To their credit the principal developers of these methods have repeatedly emphasized the need to utilize this bit of information in the total clinical context presented by the patient. (55,59) The various pitfalls, technical and otherwise, in the application of digoxin determinations have been recently reviewed. (72,73) While there are potential pitfalls at every step of the way, those laboratories which perform the procedure carefully, with attention to all details, and employ the results in the light of the clinical data, the results have been, as we shall see, exceedingly valuable. (24)

Clinical Considerations:

A. Principles and Methods of Digitalization

In the marvelous little book authored by Bernard Lown and Samuel A. Levine entitled "Current Concepts in Digitalis Therapy" published in 1954, the distillation of the best available information concerning the uses and abuses of digitalis was presented (74). In general, these authors described the arrhythmias due to digitalis overdosage in detail, summarized the then known information concerning factors which enhanced human sensitivity to digitalis, especially hypokalemia and hypercalcemia, advocated the avoidance of rapid or parenteral digitalization wherever possible, and especially when accompanied by massive diuresis, often leading to hypokalemia and digitalis intoxication, and did in fact indicate that digoxin was the ideal available drug. Since that time the emergence of the knowledge of the detailed pharmacokinetics of digoxin together with the availability of serum levels promises to place the use of digoxin on a rational, scientific basis rather than the empiric more unpredictable basis that had been obtained in the past. The Table 4, taken from Tom Smith and Edgar Haber's book provides the latest information on the several commonly used preparations (55). The pioneering studies of Pardee (75) and of Harry Gold (76) set the stage for the key study of Frank Marcus and associates who with modern tracer techniques looked at the "Administration of Tritiated Digoxin With and Without a Loading Dose: a Metabolic Study" (77). It had been common to see patients completely redigitalized with a slower acting substance such as digitoxin or digitalis leaf immediately following digitalization with a known short acting agent such as ouabain or cedilanid (78).

Table 4

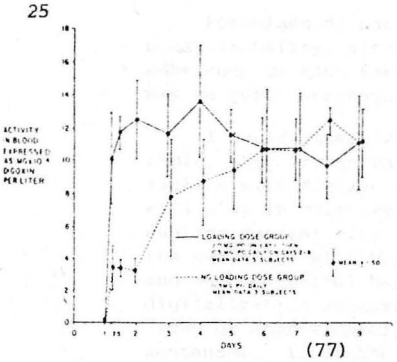
Agent	Gastrointestinal Absorption	Onset of Action† (min)	Peak Effect (hr)	Average Half-Life‡	Principal Metabolic Route (Excretory Pathway)	Average Digitalizing Dose: Oral§	Average Digitalizing Dose: Intravenous¶	Usual Daily Oral Maintenance Dose‖
Ouabain	Unreliable	5–10	½–2	21 hr	Renal; some gastrointestinal excretion	—	0.3–0.5 mg	—
Deslanoside	Unreliable	10–30	1–2	33 hr	Renal	—	0.8 mg	—
Digoxin	55–75%**	15–30	1½–5	36 hr	Renal; some gastrointestinal excretion	1.25–1.5 mg	0.75–1.0 mg	0.25–0.5 mg
Digitoxin	90–100%	25–120	4–12	4–6 days	Hepatic††; renal excretion of metabolites	0.7–1.2 mg	1.0 mg	0.1 mg
Digitalis leaf	About 40%	—	—	4–6 days	Similar to digitoxin	0.8–1.2 g	—	0.1 g

• Table modified slightly from Smith.[154]
† For intravenous dose.
‡ For normal subjects (prolonged by renal impairment with digoxin, ouabain and deslanoside, and probably by severe hepatic disease with digitoxin and digitalis leaf).
‖ Average for adult patients without renal or hepatic impairment; varies widely among individual patients and requires close medical supervision.
§ Divided doses over 12–24 hours at intervals of 6–8 hours.
¶ Given in increments for initial subcomplete digitalization, to be supplemented by further small increments as necessary.
** For tablet form of administration (may be less in malabsorption syndromes and in formulations with poor bioavailability).
†† Enterohepatic cycle exists. (55)

Rosenblum noted that toxic effects occurred in about 50% of those who were completely redigitalized, and that those who, after digitalization with a short acting agent, were given only a mainenance dose had good clinical effects with a much lower incidence of toxicity (79). (25)

Cardiac glycosides will accumulate in the body when given as a daily maintenance dose without a loading dose, and the same serum level will occur as if a loading were given. The accumulated body dose at the plateau, after 4 to 5 half-lives, is directly related to the half-life and to the maintenance dose. When half-life is constant, the accumulated dose is a function of the maintenance dose. When a loading dose is given, to gain a rapid effect, the loading dose should be appropriate to the estimated maintenance dose. For a 0.25 mg maintenance dose, the loading dose should be 0.75 mg divided over 24 hours. Excretion of 0.25 mg (33% of 0.75) will occur, and the total body dose would be 0.5 mg without a loading dose, the same amount would accumulate on 0.25 mg/day in 4-5 half-lives or 1 week. If 1.5 mg were given, 1 mg would accumulate. If this was followed by 0.25 mg 1 day, the body dose would gradually diminish to 0.5 mg. This is illustrated in Figure 25, and some data from the original study in Table 5. Generally, the loading dose should be three times the expected maintenance dose in patients with normal renal function. In atrial fibrillation and flutter the ventricular response may guide therapy. The non-loading dose method has also been found to reduce toxicity. These principles are further illustrated in Figure 26 taken from a paper by Bigger in which they are applied to the substitution of digoxin for digitoxin (80). One can predict a period of toxicity, panel A, if one begins digoxin the next day since digitoxin excretion is slower. If digoxin is begun 3 days after discontinuation of digitoxin, as in panel B, the problem is avoided.

Figure 25



(77)

Table 5

Seven-Day Cumulative Retention of Digoxin and Metabolites

No-loading-dose group			
Subject	Digoxin retained* (mg)	Subject	[illegible] (mg)
W.B.	0.74	R.F.	1.09
R.T.	0.82	B.M.	1.13
A.J.	1.04	J.C.	1.20
B.M.	1.20	A.S.	1.60
F.P.	1.22	A.J.	1.87
Mean ± 1 SD	1.01 ± 0.22		1.38 ± 0.

*Calculated as total 7-day dose administered minus amount excreted. Excretion of activ[illegible] was converted to equivalent milligrams of digoxin.

(77)

Severe renal disease may prolong the half-life up to a maximum of 4.4 days, and, therefore, the period required to reach a steady state plateau to a maximum of about 3 weeks (55). Doherty has recommended that the necessary loading dose be given followed by maintenance doses reduced to one-quarter or one-half of what they would be in the presence of normal renal function (18). It is possible to reduce these approximations to formulae. Suggested formulae:

(1) Men: % daily loss = $11.6 = \frac{20}{C}$; (2) Women: % daily loss = $12.6 = \frac{16}{C}$

Figure 26

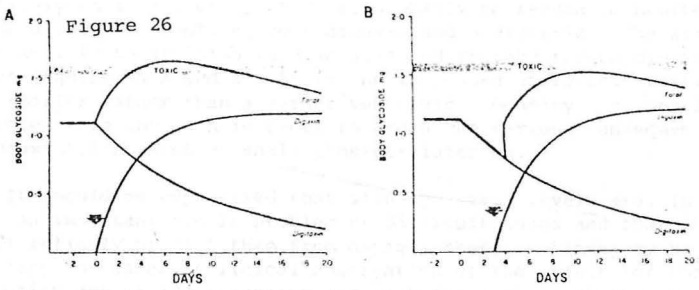


Fig. 1. Digitalis toxicity resulting from a change from digitoxin to digoxin maintenance. The hypothetical patient weighs 90 kg and has normal values for BUN and serum creatinine but a creatinine clearance of 50 ml/min. He had been on digitoxin 0.1 mg/day and had a steady state total body glycoside content of 1.1 mg (12.2 μg/kg). He was switched to an equivalent dose of digoxin 0.375 mg/day, a dose that ultimately produces an identical steady state body glycoside content. (A) A daily maintenance dose of digoxin is substituted for digitoxin on day 0 (arrow). Since the elimination half-life of digoxin (2.4 day) is shorter than that of digitoxin (7.2 day), the body stores of digoxin accumulate faster than the decline in body digitoxin stores. This leads to an increase in total body stores that reach a peak value of 1.64 mg (18.3 μg/kg) on day 6 after the change. This amount of total glycoside is very likely to produce clinical toxicity. Note that the total body glycoside content remains higher than the ultimate steady state value of 1.1 mg for longer than 3 wk. (B) A simple method for avoiding transient toxicity when changing from maintenance with digitoxin to digoxin. Digitoxin is discontinued on day 0 as in (A), but no glycoside is given until the third day when maintenance doses of digoxin are begun (arrow). This method avoids the use of a complicated digoxin dosage schedule, but the total body glycoside content neither falls to ineffective amounts nor reaches the toxic range during the transition period. Again, it takes several weeks to reach the ultimate steady state value to total body glycoside.

(80)

where c=serum creatinine mg/100 ml. These values for daily percent loss multiplied by the loading dose that produced a satisfactory therapeutic response gives a reasonable approximation of the proper daily maintenance dose (55).

Formulaes do not take into account patient compliance, absorption, bioavailability, altered metabolism and hepatic function so that rigid adherence to such formulae as well as computer estimates of dosage may be quite erroneous indeed.

I would summarize as follows: Wherever possible avoid rapid, that is, intravenous digitalization. Intramuscular digitalization with digoxin seems to be contra-indicated because of inefficency in delivery to the vasulcar compartment. Since the average patient with congestive failure took a long time to develop the condition with which he presents, there is no particular benefit and much potential harm in reversing it instantly. Thus, slow digitalization achieving full therapeutic levels in 4 to 5 half-lives or approximately a week for digoxin would seem adequate in most instances. If at the end of this time one has not achieved optimal dosage, one can check the serum digoxin level and revise the dose upward. It probably continues to make sense to specifically ascertain whether the patient actually requires diurectics or whether the full clinical benefit can be achieved by utilizing digoxin alone. Where intravenous digitalization seems indicated, this should be done in increments. Prior to each incremental dose, check the patient at no less than 2 hour intervals, to see if there are signs of intoxication or the desired effect has been achieved. With the knowledge that there is a dose response curve, be aware that one is obtaining some of the desired effect with some digoxin. I do not believe that there is any contraindication to deliberately under-shooting, so to speak, and then gradually comming to a monitored, optimal serum level and clinical effect. Finally, in this world of potent reliable and

relatively cheap diuretics there is probably no reason to hesitate to use a regimen involving both digoxin and a diuretic. The aim, after all, is to diminish cardiac size and thereby reduce myocardial oxygen requirements and to attain the increased efficiency realized by a smaller rather than a larger ventricle. Doherty has subtely advocated this approach in order to avoid the serious consequences of intoxication which we shall consider later on. (27)

It should be emphasized that although serum levels are, in my view, an important aid in problem or difficult cases and that one cannot reliably predict them from dosage, there continues to be the necessity for careful clinical observation of the effects of the drug which one is administering and evaluation as to whether its optimal effects have been achieved.

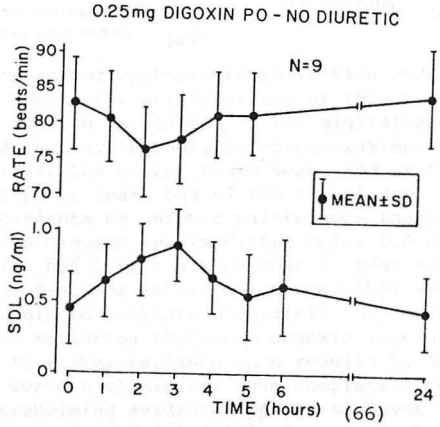
B. Serum Digoxin Levels: Clinical Observation.

In Table 6, we see the mean serum digoxin levels attained by our patients maintained on 0.125, .25 and .5 mg per day and compared to those in patients judged clinically toxic (66). It is clear that there were significant differences between the serum levels seen at each dosage level and that these in turn were signficiantly less than the mean value in toxic patients. The accepted upper limit of the therapeutic range in our lab is 2.2 ng/ml. As illustrated in the Figure 27, the absorption of a maintenance dose of digoxin is sufficient to maintain that given glycoside level for a 24 hour period. Note that 24 hours after routine administration of a 0.25 mg. tablet, the SDL is equal to the initial pre-administration level (66). To measure the "steady state" level, one must

Table 6 Mean serum values for patients on various daily doses of digoxin (66)

	No digitalis	*0.125 mg./day*	*0.25 mg./day*	*0.5 mg./day*	*Intoxication*
Number of patients	14	56	275	25	34
Mean	0	0.80	0.93	1.35	3.86
S. D.	0	0.44	0.51	0.47	1.40
P values for group comparison			<.05	<.001	<.001

Figure 27



either take a blood sample before or at least 6 hours after administration of such a tablet. In contrast to patients who have not previously received glycoside, the gradual rise and fall in blood level following administration of drug is accompanied by some enhancement of digitalis effect, in this case measured by the average slowing and then return to control of the pulse rate. Indeed in some patients following the administration of larger doses and generally in those who have higher levels transient toxic symptoms including transient arrhythmias have been observed during the post-absorptive period. (81,81a) Also of importance are our observations of the correlation of serum level changes and myocardial effects after acute administration of an intravenous dose, (63), Figure 28. There were initially very high levels during the plasma: tissue equilibration phase during which onset of myocardial effect is indicated by the diminution in the left ventricular ejection time index. At about 3 to 4 hours the myocardial effect has achieved its maximum and the serum level is now turning the corner to the slow excretion slope. During subsequent observations there was the parallel offset of myocardial effects as serum digoxin disappeared. In Figure 29, the inverse correlation between the myocardial effects and the serum blood levels during the first 4 hours after administration of an intravenous dose is seen. Thus, measurement of blood levels during plasma tissue: equilibration will give spuriously high levels inversely related to the cardiac effect. To avoid false alarms, one should draw a blood sample immediately before administration of drug or 6 or more hours after administration. These considerations must be taken into account in any evaluation of studies of serum levels.

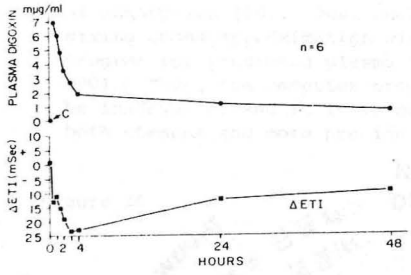


Figure 28

Mean values for plasma digoxin and simultaneous alterations in LVETI in six patients followed 48 hours after 1 mg of digoxin was given intravenously. (63)

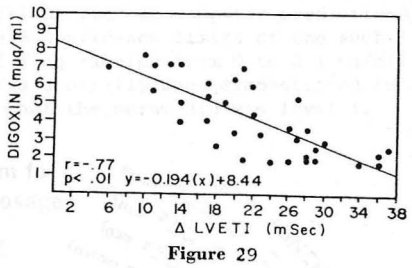


Figure 29

Correlation of individual plasma digoxin and ΔLVETI values during the initial 4 hours following administration of digoxin. (63)

If one can assume appropriate collection and determination of serum digoxin level, the principal use of this laboratory test is as an aid in the precise regulation of the digitalized patient. It has been estimated that at therapeutic concentrations a patient is receiving at least 50% of the toxic dose, and at toxicity he has probably received at least 60% of the lethal dose (81b). A careful study of 101 patients on chronic maintenance therapy revealed that 58 of 101 had serum digoxin levels either below 0.8 or above 2.0 ng/ml (82). About 25% had levels higher than 2 ng/ml and over half of these had clinical evidence of intoxication when they were further examined. It is not possible to estimate accurately the amount of delivered digoxin without measuring the serum dogoxin levels. There has been some reaction from over reliance upon results of serum digoxin levels, and, in fact, certain clinicians have completely rejected their value (83). The overwhelming evidence appears to favor their use for optimizing patient management. A fairly large recent study has confirmed

their utility in general evaluation of the clinical response of patients (84). The serum digoxin levels related more closely to clinical status than did the dose, body weight, creatinine clearance, and other factors. The specific clinical questions that can be largely answered by well done serum digoxin measurements are: 1) assessment of patient compliance; 2) identification of absorptive problems; 3) support or make very unlikely the diagnosis of digoxin intoxication; 4) better assess patients who cannot give a history; 5) disginguish between digoxin and digitoxin; 6) aid the physician in assessing the effects of a change in dose. (29)

The serum digoxin levels do relate to the myocardial response both after acute digitalization following plasma: tissue equilibration (63), and after alterations in serum levels in chronically maintained patients (85,86). The general technique of correlating non-invasive measures of inotropic response with the steady state serum digoxin levels has been particularly useful in domonstrating this point.

There has been considerable interest in utilization of known pharmacokinetic principles and deriving mathematical and computer programs for the prediction of digitalizing and maintenance doses (87, 88). Newer programs have provisions for the feedback of information through the computer of several types of alterations in the patient's status (89). An example of a neat nomogram for this purpose is presented in Figure 30 (88). Some authors have claimed reduction in incidence of digoxin toxicity when such systems are used (87). A typical recent system depends on patients being euthyroid adults with normal hepatic function, normal electrolytes and without abnormalities of absorption (88). Just such limitations lead to computer predictions giving gross approximation with the 95% confidence limits of one such program for predicted plasma level of 1 ng ranging from 0 to 2.1 ng/ml (90). Thus, the computer programs have generally been demonstrated to be inadequate, and it is to be noted that the serum digoxin level is both cheaper and more precise (84).

Figure 30

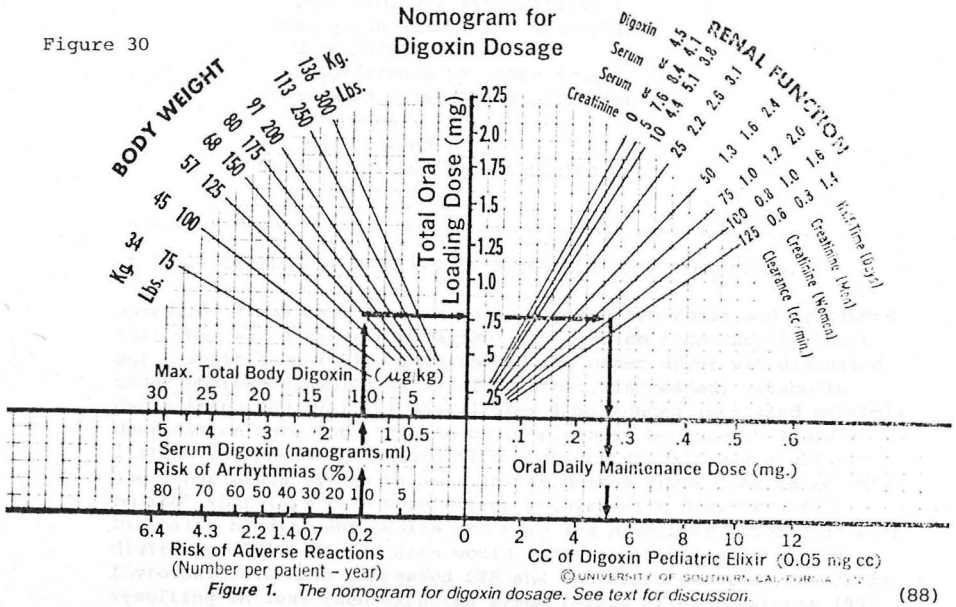


Figure 1. The nomogram for digoxin dosage. See text for discussion. (88)

I would be remiss in not mentioning the fact that there does seem to be an excellent linear correlation between serum digoxin concentrations and that in the saliva, $r = 0.988$, $p < .001$ (91). The salivary concentration could be used to monitor digoxin therapy if one can obtain good saliva, extract it with chloroform and recall that the saliva: serum ratio was $0.78 \pm .07$ (suggesting that only the unbound drug appeared in the saliva). The $K^{+}xCa^{++}$ index in saliva has been touted as a means for estimating therapeutic versus toxic serum digoxin concentrations. There has not been much correlation of this technique with actual serum level measurements and there has been considerable sentiment stating that this technique is impractical for clinical purposes providing no advantages over direct serum glycoside measurement (92).

C. Apparent and Real Resistance to Digoxin:

In Table 7 we have listed the causes of apparent digoxin resistence, or, conditions in which the serum levels are low relative to the dose presecribed. (93) We have previously discussed patient compliance and inadequate tablets. Heizer and colleagues found that patients with various intestinal malabsorption syndromes other than pancreatic insufficiency had low serum digoxin levels and ascribed this to their intestinal defects. (94) Absorption has been found to be unchanged after Billroth 1 or Billroth II partial gastrectomies. (95) Changing from tablets to elixir cured a patient with radiation induced malabsorption. (96) Doherty found only slight

Table 7 Causes of Apparent Digitalis Resistance*

Failure to take digitalis as prescribed
Inadequate digitalis tablets
Low digitalis content
Poor biologic availability
Inadequate intestinal absorption
Malabsorption
Interference by other drugs
Increased metabolic degradation
Idiopathic
Drug-induced
Digitalis-binding antibodies (rare)
Thyrotoxicosis

* Serum levels low relative to digitalis dose prescribed.

excessive fecal excretion in malabsorption syndromes and concluded that this was a minor bioavailability problem secondary to short gut transit time (97). Interference by other drugs was discussed under pharmacodynamics as was idiopathic, increased, metabolic degradation (80,97a). I have listed drug induced increased metabolic degradation more for the sake of completness because in Table 8 listing all the known interactions between digoxin and digitoxin and other drugs it can be seen in the bottom under "increased metabolism" that this is a more common problem with digitoxin (80). Digitalis binding antibodies are rare and have been associated with digitoxin (98). Recent data would indicate that patients with thyrotoxicosis have increased GFR and shortened disappearence time resulting in less then expected serum levels after treatment (99).

Table 8 Interactions Between the Cardiac Glycosides Digoxin or Digitoxin and Other Drugs

Mechanisms of Interaction	Interacting Drugs	Digoxin	Digitoxin
GI absorption			
Decreased	Cathartics	++	Unknown
	Neomycin	++	Unknown
	Cholestyramine	+++	+++
	Colestipol	+++	+++
Trapping of glycosides in the enterohepatic circulation			
Increased Fecal Excretion	Cholestyramine	0 or +	++
	Colestipol	0 or +	+++
Protein binding			
Decreased	Phenylbutazone	0	0
	Sulfadimethoxine	0	0
	Phenobarbital	0	0
	Chlorophenoxyisobutyric acid (clofibrate)	0	0 to +
	Tolbutamide	0	0 to +
Binding to cardiac tissues			
Decreased	Reserpine	+	Unknown
	Hyperkalemia (potassium salts and spironolactone)	++	Unknown
Increased	Hypokalemia (chlorothiazide (Diuril), furosemide (Lasix), ethacrynic acid (Edecrin), etc)	+	Unknown
Renal excretion			
Increased GFR	Hyperthyroidism (T_3 or T_4)	+	0 to +
Decreased GFR	Antihypertensive agents hydralazine (Apresoline), guanethidine (Ismelin), α-methyldopa (Aldomet)	+++	0 to +
	Diuretics (chlorothiazide, ethacrynic acid, furosemide)	+++	0 to +
Increased Urine Flow	Diuretics (saline, furosemide, ethacrynic acid)	0	0 to +
Metabolism			
Increased	Phenobarbital	Unknown	+ or 0
	Diphenylhydantoin	Unknown	+ or 0
	Phenylbutazone	Unknown	+ or 0
	Hyperthyroidism (T_3 or T_4)	Unknown	Unknown

The magnitude of the maximal effect is indicated on a scale of 0 to +++. 0 = no effect, + = slight effect, ++ = moderate effect, +++ = large effect. The magnitude of effect listed in the table is the maximum likely to be seen clinically; variables such as time, concentration, dose, individual patient responsiveness, and so on, would modify the effect seen in a given patient.

(80)

Table 9 Causes of True Digitalis Resistance*

Supraventricular arrhythmias
Diffuse myocardial disease
Infancy

* Relatively high serum digitalis concentration required for beneficial therapeutic effect.

Hypertrophy of the Na^+, K^+, ATPase system may be present and require more glycoside. But dose adjustment with serum levels as a guide usually overcomes any problems.

In Table 9 are listed the causes of real digitalis resistance, or, conditions in which relatively high serum digitalis concentrations are required for a beneficial therapeutic effect. Atrial fibrillation and other ventricular arrhythmias have long been known to require more than the usual doses for their control and this can result in high serum levels which are tolerated. A number of studies have demonstrated either rough or poor correlations between resting heart rate and serum digoxin levels (100). Nevertheless, Redfors felt that the serum digoxin levels were a useful guide to therapy which could result in safer achievement of decreased resting and exercise heart rates and improvement in symptoms at an average daily maintenance dose of between 0.4 - 0.5 mg/day (101,102). The poor correlation between serum digoxin level and heart rate is shown in the next series of illustrations 31, 32, 33 for stable chronic fibrillation, unstable chronic atrial fibrillation, and acute atrial fibrillation (103). These authors felt that the failure to control the heart rate below 100 per minute in atrial fibrillation was especially likely when infection, hypoxia, recent thoracotomy, or acute onset of atrial fibrillation was the clinical setting. While they did not observe serious toxicity in patients who had levels above 2 ng/ml they felt that the autonomic nervous system and catecholamine secretion probably antagonized the effects of digoxin and cautioned against pushing digoxin with too much enthusiasm before a) trying to treat the underlying condition, b) utilizing additional anti-arrhythmic agents especially propranolol, and c) attempting cardioversion.

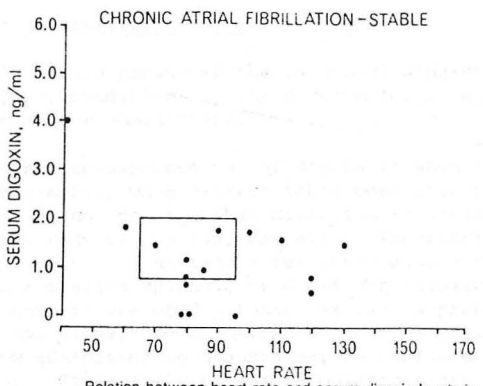
When planning electrocardioversion in patients with atrial fibrillation with high serum digoxin levels, even in the absence of signs of toxicity, I would allow the level to fall to the range of about 1 ng/ml prior to cardioversion. It is very important to begin cardioversion with low doses of electricity in order to avoid the production of digitoxic rhythms following conversion.

Patients with idiopathic cardiomyopathy may benefit with additional digoxin and levels at or over 2 ng/ml. In contrast, patients with amyloid heart disease may show no benefit and may show toxic signs at levels below 1 ng/ml (104). Thus, etiology of cardiomyopathy may help estimate needed therapy, but careful correlation of dose, serum level and response appears to be necessary.

Infants less than one year of age tolerate higher doses of digoxin then older children or adults (105,106). Although some have questioned whether these high levels are necessary or useful most pediatricians feel that neonates and infants do require more digoxin for optimal effects. Most cases of reported toxicity in this age group have then occured at still higher levels. In one such study, the average for a non-toxic neonate was 2.7 ± 1.2 and the mean for neonates who were toxic was 4.5 ± 2.5 (106). The precise mechanism is still incompletely defined. There appears to be no measurable alteration in absorption, metabolism or excretion (107-112). But, studies on human neonates are sparse. In some animal work carried out in Bill Miller's lab in our Dept. of Pediatrics, the suggestion was made, in comparing unborn and neonatal puppies with their mothers, that there was immaturity in the myocardial Na^+, K^+, ATPase leading to increased digoxin requirement for the desired effects (113).

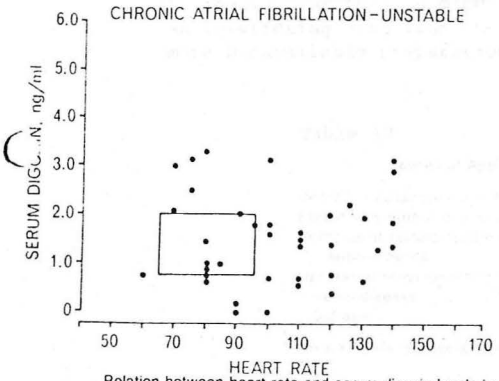
Figure 31

DIGITALIS AND ATRIAL FIBRILLATION—GOLDMAN ET AL. (33)



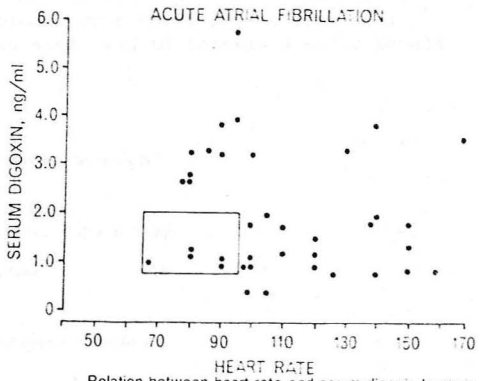
Relation between heart rate and serum digoxin levels in 14 patients in Group IA (chronic fibrillation, clinically stable condition). Dots falling within the box represent those with "therapeutic" serum digoxin concentrations (0.8 to 2.0 ng/ml) in combination with "controlled" ventricular rates (65 to 95/min). (103)

Figure 32



Relation between heart rate and serum digoxin levels in Group IB (chronic fibrillation with complicating, serious illness). (103)

Figure 33



Relation between heart rate and serum digoxin levels in Group II (acute atrial fibrillation). (103)

D. Apparent Sensitivity to Digoxin:

In Table 10 are presented the causes of apparent digitalis sensitivity, or, conditions in which serum levels appeared relatively high for the dosage administered.

The recent, unsuspected use of digitalis when the history is poor or unobtainable, when patient takes more than prescribed, or when patients do not realize that digitalis is included in medications such as weight reduction pills, may all be important causes of unsuspected high levels. In Holland a few years ago, a manufacturing error led to a massive epidemic of digitoxin intoxication (114). Unsuspected chronic use of digitoxin has been a problem since you will recall the digoxin serum method detects 9% of it, and the physician now administering digoxin may be confused about the actual status. Excessively potent formulations are examplified by the Holland experience I just described, and with digoxin one must recall that oral talbets are absorbed less well then elixirs or aqueous solutions which in turn provide only 80% of intravenous dose. So that if the physician is shifting modes of administration he should bear this in mind in order to avoid problems. Removal of an interfering drug from the regimen, or a shift from a less to a more bioavailable preparation can also lead to increased serum levels.

Table 10

Causes of Apparent Digitalis Sensitivity*

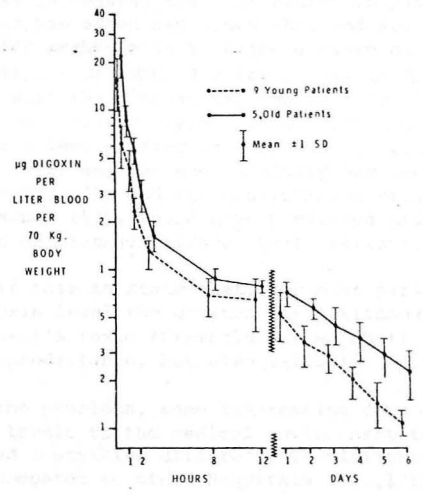
Recent unsuspected use of digitalis
Excessively potent digitalis formulations
Removal of factors contributing to high digitalis dosage requirements
Decreased renal excretion of digitalis
Renal disease
Old age

* Serum levels relatively high for dosage administered.

In our discussion of pharmacokinetics of digoxin we emphasized the sensitivity of digoxin excretion to the status of renal function. While increased urine output due to diuretics or nephrogenic diabetes insipidus do not increase excretion, diminutions in renal function do sensitivly slow the disappearence time of digoxin. Hemodialysis does not alter or remove significant digoxin. Excellent recent reviews have detailed those alterations seen in renal disease (17, 18), and suggestions for dosing were discussed previously. Digitoxin has the fortunate characteristic of not having a change in its disappearence time in renal disease so that the dose should be more predictable and constant (13). Nevertheless, Doherty points out that the excretion time of digoxin in renal disease is, when maximally prolonged, roughly equal to that of digitoxin. Thus, there appears to be no basic reason for preferring digitoxin to digoxin in renal disease provided that the necessary adjustments in dosage are made (17).

A rather nice study by Ewy and colleagues documented the fact that elderly patients not in congestive heart failure with a mean age of 77 had, a) decreased body size and therefore decreased volume of distribution when compared to normals and, b) the normal decrease in renal function seen with aging (115). These two factors combine to slow excretion time and therefore result in higher serum digoxin levels on average doses. This could result in toxicity. The essential data from this study are shown in Figure 34 demonstrating the significantly slower excretion times in the elderly patients after the first 24 hours following administration of a dose of digoxin. In Table 11 are the details of the observed alterations in renal function and digoxin clearance. These facts are critical in the management of elderly patients, and any persual of the literature of digoxin intoxication will readily document the elevated mean ages of the victums and the frequent coexistence of overt renal dysfunction.

Figure 34



Concentration of digoxin in micrograms (µg) per liter of blood per 70 kg of body weight at intervals after the injection of tritiated digoxin. P values were less than 0.1 during the first 24 hr, but less than 0.01 thereafter.

(115)

Comparison of Laboratory Data in Young and Elderly Subjects

Table 11

	Age (yr)	BUN (mg%)	Serum creatinine (mg%)	Creatinine clearance (ml/min/1.73 m²)	Digoxin clearance (ml/min/1.73 m²)
Young Mean ±1 SD	27 ±4	14 ± 5	1.00 ± 0.16	122 ± 19	83 ± 17
Old Mean ±1 SD	77 ±4	24 ± 3	1.24 ± 0.11	56 ± 17	53 ±9
P		<0.001	NS	<0.001	<0.001

(115)

E. Real Sensitivity to Digoxin and the Question of Digoxin Intoxication:

One of the key issues and frequent sources of disappointment is the precision with which serum levels may identify toxic patients. Early studies indicated the likelihood of such a separation (60-62), but as methods became more precise a real over-lap in values has persisted between toxic and non-toxic patients which has required explanation and study (57, 115a, 116). Recently, the results of the test as having any diagnostic importance in toxicity has been challenged (117). While it is possible to explain some of the over-lap data as being problems in sampling time or concomitant drug therapy (118), the recent review of Noble and associates emphasizes some clinical points that are worth repeating (119). 1) The diagnosis of digitalis intoxication is a clinical, never a laboratory diagnosis (Smith and his colleagues have emphasized this from the beginning of their ability to measure serum concentrations (57)). 2) There is no optimal serum level of digitalis for any specific arrhythmia or for arrhythmias in general (Vincent Butler in particular in literature reviews has often mentioned this and we, or course, list supraventricular arrhythmias as being a cause of true resistance to digoxin (58)). 3) When the levels are in flux prior to their equilibration with the myocardium, the test is often misleading. (Even without the inverse correlations between myocardial response and serum levels after intravenous digitalization presented by us in 1970 (63), any one who carefully reviewed the tracer studies of Doherty (3), and the non-invasive studies of Weissler and his colleagues (53), would have predicted disparities prior to the completion of plasma: tissue equilibration).

I think it fair to state that, for most patients, the higher the serum digoxin level the greater the liklihood of toxicity. Any given patient's toxic threshold, as we shall see later, may be not only unpredictable, but also variable.

Despite the problems, some interesting data on the value of serum digoxin levels to the medical environment is available. The data showed a striking difference in digitoxic reactions at the MGH when compared to other hospitals (120,121)

A prospective monitoring of digoxin toxicity comparing the Brigham with the MGH was carried out because of their many similarities save for the fact that during that period the serum digoxin concentration measurement was routinely available at the MGH and was only occasionally utilized at the Brigham (and those determinations were made at the MGH and usually reported some days after the samples were drawn). In the prospective study, dose related adverse reactions were confirmed in 10% of 272 patients at the Brigham and in only 4% of 291 patients at the MGH $p < .02$. Differences in digoxin dosage, and of other drugs, patient characteristics, or other factors predisposing to digoxin toxicity did not account for the different adverse reaction rates. Serum digoxin concentrations were measured in more digoxin recipients at the MGH, 40%, than at the Brigham, 12%, $p < .001$. The mean levels were lower at the MGH, 0.98 ng/ml, than at the Brigham, 1.82 ng/ml, $p < .001$, reflecting the use of the assay at MGH for therapeutic guidence in nontoxic patients. The authors believed that the use of serum digoxin assays in clinical practice could decrease the frequency of adverse reactions to digoxin and improve management as do others (122,123). In the past few years, I think we've had a similar experience.

I should like to briefly review the causes of true digitalis sensitivity, that is, toxicity associated with relatively low serum digitalis levels. Documentation of the sensitivity of amyloid heart disease has been discussed (104). Others who recurrently get into trouble at low levels are elderly patients with severe heart failure and often conduction system disturbances (116,118). This milieu often includes overt renal dysfunction just to complicate matters.

Table 12 Causes of True Digitalis Sensitivity*

Diffuse myocardial disease
Myocardial ischemia
Hypoxemia
Electrolyte abnormalities
a) Hypomagnesemia
b) Hypokalemia

* Toxicity associated with relatively low serum digitalis levels.

Morrison and Killip demonstrated sensitivity during the first 24 hours after myocardial infarction and then this susceptibility subsided (124). Some authors agreed (125,126) while others could not demonstrate sensitivity (127,128). A number of hemodynamic studies indicate that the most extensive infarctions and/or cardiogenic shock do not respond significantly to glycosides, whereas those with mildest forms of infarction do respond hemodynamically (129,130). This type of divergent cardiac response can lead to excessive administration when empiric criteria are being followed. In any case there are electrophysiological studies which also show that the ischemic myocardium seethes with the conditions necessary for production of re-entrant arrhythmias, and that the several electrophysiologic effects of the glycosides would tend to aggravate this (131). On the basis of present data, after myocardial infarction we avoid the use of glycoside therapy whenever possible, but supraventricular arrhythmias occasionally force our hand.

Hypoxia per se appears to sensitize the heart to the effects of the glycosides even in the presence of constant serum digoxin concentrations below 2 ng/ml, and constant, normal serum postassiums (132). The threshold of this effect and its clinical frequency is not known.

Hypomagnesemia has been reported as a potential cause of digoxin intoxication with usual doses of digoxin (133), but a recent study failed to confirm this in toxic patients with SDLs < 2 ng/ml (134). This latter study found increased serum magnesium in 18% of their toxic patients most of whom were uremic and cautioned against routine use of magnesium therapy.

(38)

Dr. John Sampson of San Francisco pointed out many years ago that hypokalemia enhanced the toxic effects of digitalis glycosides. These clinical observations were highly refined by Lown and Levine (74). Acute human experiments became possible with the routine use of hemodialysis. Glenn Lubash in particular showed that induced acute hypokalemia in patients who were on maintenance glycosides resulted in digitoxic arrhythmias which were suppressed by potassium repletion (135). This type of observation was common in the 50s (136).Marcus (137) infused normokalemic and hypokalemic dogs with digoxin at a constant rate until ventricular tachycardia ensued at which time they were sacrificed. See Table 13. The hypokalemic dogs required a mean of 39% less digoxin for the onset of ventricular tachycardia and the mean myocardial concentration in hypokalemic dogs at the time of toxicity was 35% less than the controls. The mean rate of myocardial uptake of digoxin was no different for the two groups. This was interpreted to demonstrate that the heart was truly sensitive to smaller doses of digoxin under hypokalemic conditions.

In a recent well planned study from Scandinavia, patients on maintenance digoxin were deliberately made hypokalemic (138). The appearance of hypokalemia with constant serum digoxin levels

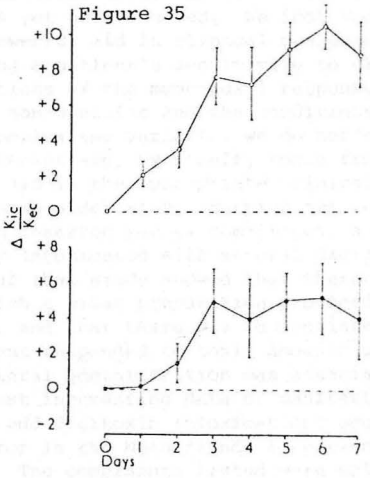
Table 13

DOGS INFUSED WITH H³ DIGOXIN AND SACRIFICED AT ONSET OF VENTRICULAR TACHYCARDIA

	6 Normokalemic Dogs	*6 Hypokalemic Dogs*
H³ digoxin infused (mg)	1.09 ± .21	.67 ± .15
Mean rate of myocardial uptake of H³ digoxin (mg/min)	.00867	.00875
Myocardial concentration of H³ digoxin (ng/gm ± 1 S.D.)	467 ± 60	302 ± 31
Blood concentration of H³ digoxin (ng ml)	97 ± 53	77 ± 12
Heart:blood ratio	5:1	4:1

(137)

Figure 35



Changes in intra-/extracellular K gradients in 10 patients receiving a K depleting regimen for 7 days. Mean values (± SEM) are given. The upper panel shows the myocardial K gradient (calculated on the assumption of an unchanged intracellular K concentration); the lower panel shows the K gradient for the whole body. (138)

lead to signs and symptoms of digoxin intoxication. In Figure 35, changes in the intra-/extracellular potassium gradients in the ten patients are plotted. The upper panel shows the myocardial potassium gradient calculated on the assumption of an unchanged intracellular potassium concentration, and the lower panel shows the potassium gradient for the whole body. By their calculations the changes in gradient affecting the heart were much more severely altered than the total body gradient. Six of 12 patients developed cardiac arrhythmias fulfilling the criteria of digitalis toxicity. This would seem to satisfy a raging argument published in Lancet in 1975 (139) stating that hypokalemia did not enhance digitalis toxicity which had been challenged by some of our data (140). In Table 14, we present data from our own experience collected in the following manner. Patients presenting with acceptable electrocardiographic criteria for digitalis intoxication (and these are outlined in Table 15 adapted from Smith) had measurements of serum digoxin concentrations, electrolytes and BUN, and electrocardiograms documenting their arrhythmia. Of 79 patients, 55 were normokalemic and 24 hypokalemic. There were no significant differences in their age, BUN or in type of arrhythmias. The expected significant difference in potassium is obvious and the mean and standard errors for the digoxin concentrations in each group were significantly different. These data demonstrate the enhancement of digitalis sensitivity by hypokalemia and provide one explanation for some of the overlap reported between toxic and nontoxic patients. Patients with similar degrees of hypokalemia not taking digoxin did not demonstrate these arrhythmias.

The problem of intoxication is a complex one with many factors operative, including those listed as causes of true sensitivity and others as yet unrecognized. We look upon the serum digoxin level as a powerful aid in clinical management which can be an aid in gauging a patient's sensitivity to glycosides when correlated with observations of the myocardial response. Since toxic symptoms are commonly non-specific and the conditions for arrhythmia production complex and variable, we do not expect a certain serum level to differentiate, by itself, toxic from non-toxic patients. It can be an aid in the appropriate clinical setting, in diagnosing toxicity. In an older study, carried out in Baltimore before the days of human research review committees, a group of patients were serially intoxicated with several digitalis preparations (141). The essence of that study showed that there was no consistant manner in which a given preparation produced its first signs of intoxication, and that there was no consistent manner in which a given patient responded to toxic amounts of the glycosides though parenteral administration was associated with fewer GI symptoms. Most interesting data of manifestations of toxicity from the 170 odd digitoxin intoxications occurring after a manufacturing error in the Netherlands is presented in Tables 16, 17 and 18 (142). The complaints listed were well associated with the mass digitoxin intoxication. It is easy to see how nearly all of

Table 14 Summary of data* from 79 patients presenting with "digtoxic-like" arrhythmias who had been taking prescribed maintenance doses of digoxin classified into normo- and hypokalemic groups.

	Normokalemic (Serum K^+ > 3.5mEq/l)	Hypokalemic (Serum K^+ < 3.5mEq/l)	p
number	55		
age	63.5 ± 1.7	62.2 ± 2.2	N.S.
serum K^+, mEq/l	4.73 ± 0.08	3.02 ± 0.06	<.001
blood urea N, mg%	35.1 ± 3.6	24.6 ± 3.0	N.S.
serum digoxin level, ng/ml	3.68 ± 0.17	1.13 ± 0.14	<.001
incidence & type of arrhythmias:†			
VEA	60%	75%	
PAT with block	12.7%	12.5%	
AF <50/min	10.9%	-----	
A-V Dissociation	9.1%	12.5%	
Junctional rhythm	7.3%	-----	

* Mean ± standard error of mean

† VEA = Ventricular Ectopic Activity, PAT = Paroxysmal Atrial Tachycardia, AF = Atrial Fibrillation

CRITERIA FOR ABSENCE OR PRESENCE OF DIGITALIS INTOXICATION

Table 15

Absence of Toxicity

Electrocardiographically documented stable sinus rhythm with PR interval 0.20 sec or less, atrial fibrillation with ventricular response between 70 and 100 beats per min, or atrial flutter with degree of atrioventricular block in the 2:1 to 4:1 range.

Presence of Digoxin or Digitoxin Intoxication

One or More of the Following Disturbances of Impulse Formation or Conduction:

A. Supraventricular tachycardia (atrial or atrioventricular junctional) with atrioventricular block
B. Frequent or multifocal ventricular premature beats, ventricular bigeminy, or ventricular tachycardia
C. Atrial fibrillation with high grade atrioventricular block (ventricular response less than 50 per min) and ventricular premature beats
D. Sinus rhythm with second or third degree atrioventricular block

Disappearance of the Rhythm Disturbance When Digoxin or Digitoxin Was Withheld.*

* Two patients died while continuing to show classical manifestations of digoxin intoxication, and thus represented exceptions to this criterion. (55)

Duration of the Complaints after Cessation of the Faultily Composed Tablets in 160 Patients

Table 16

No. of weeks	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10
No. of patients	22	44	46	24	6	11	4	1	1	1

(114)

Symptoms of 179 Patients with Digitoxin Intoxication

Table 17

Symptoms	Percentage	
	Positive	Negative
Fatigue	95	5
Visual complaints	95	5
Muscular weakness	82	18
Nausea	81	19
Anorexia	80	20
Psychic complaints	65	35
Abdominal pains.	65	35
Dizziness	59	41
Dreams	54	46
Headache	45	55
Diarrhoea	41	59
Vomiting	40	60
Retrosternal pains	9	91

(114)

Separate Disturbances in Rhythm or in Atrioventricular Conduction Observed on Electrocardiograms of 48 Patients with Digitoxin Intoxication

Table 18

Sinus arrhythmia	2
Sino-auricular block	3
Sinus bradycardia	4
Coronary sinus rhythm	1
Supraventricular tachycardia	1
Atrial tachycardia with block	4
Atrial fibrillation	4
Atrial flutter	1
Atrial extrasystoles	5
Atrial bigeminy	1
Nodal rhythm	6
Nodal tachycardia	6
First-degree block	21
Second-degree block	1
Total block	5
Changing A.V. conduction	2
Wenckebach phenomenon	1
Ventricular bradycardia with atrial fibrillation	6
Unifocal ventricular extrasystoles	14
Multifocal ventricular extrasystoles	8
Ventricular bigeminy	7
Ventricular tachycardia	2
	(114)

them can be confused with generalized signs and/or symptoms of disease.

In Table 19, is a comparison of data from a consecutive series of normokalemic patients with initially elevated serum glycoside levels who were studied on a daily basis and classified according to presence or absence of digitoxic arrhythmias disappearing after withdrawal of glycoside and within 24 hours of return of the serum glycoside level to 2 or less ng/ml. There were no significant clinical distinctions in age, renal function, or serum potassium. Serum digoxin was higher in those with arrhythmias and the time for normalization of serum digoxin level, that is for it to drop to 2 or less ng/ml was longer. These differences were not accounted for by the incidence of atrial fibrillation. The percent of hospital deaths in the two groups was strikingly different but not significant by chi square analysis. Some, but not all, of the patients without arrhythmias had nausea and/or vomiting. Based on this series, the Specificity of SDL was 62% and the Predictive Accuracy was 38% for the diagnosis of toxicity in normokalemic, high level patients.

In Table 20, are data during and after disappearance of arrhythmia in initially hypokalemic patients. This is the reverse of Steiness and Oleson's (138) experiment and demonstrates that disappearance of arrhythmia was associated with potassium repletion with, in most cases, relative constancy of SDL.

Table 19 Comparison of data from normokalemic patients with initially elevated serum glycoside levels studies serially classified according to presence or absence of digtoxic arrhythmias disappearing after withdrawal of glycoside and within 24 hours of return of serum glycoside level to therapeutic range.

	Arrhythmias		No Arrhythmias		P
n	17		28		----
age	62.2 ± 3.1		59.5 ± 2.2		N.S.
blood urea N, mg%	33.4 ± 6.7		33.6 ± 5.1		N.S.
serum K^+, mEq/l	4.7 ± 0.14		4.6 ± 0.15		N.S.
serum digoxin, ng/ml n=14	4.2 ± 0.33	n=26	3.6 ± 0.16	=	.05
serum digitoxin, ng/ml n=3	60.3 ± 10.1	n=2	75 ± 5.0		----
time to normal, digoxin, days	4.1 ± 0.5		2.1 ± 0.3		<.01
time to normal, digitoxin, days	7		----------		
% atrial fibrillation	41%		36%		----
% deaths	29%		10.7%		N.S.

Table 20 Data during and immediately after arrhythmia in 6 hypokalemic patients.

Patient	During Arrhythmia K meq/l	During Arrhythmia SDL ng/ml	Other Sx	Days between observations	After Arrhythmia K meq/l	After Arrhythmia SDL ng/ml	Digoxin therapy
1	2.7	0.2	---	1	3.9	0.2	Discontinued
1A*	3.3	0.3	---	2	3.9	0.3	Discontinued
2	2.5	1.0	Nausea	2	4.3	1.2	Continued†
3	2.9	1.2	---	0.5	4.6	0.8	Continued
4	3.1	1.3	---	2	‡		Continued
6	2.8	2.8	Chest pain	3	3.5	1.2	Continued 1 day
10	3.4-3.1	6.0-4.0	Nausea Vomiting	2	3.6	3.3	Discontinued

* Studied on 2 occasions during hospitalization

† Pacemaker, temporary used with benefit

‡ Arrhythmia persisted after normal serum K^+ achieved

Finally, I'd like to show Table 21 which contains data from 2 or 3 episodes of high SDLs in 7 patients for a total of 16 episodes only 3 of which were associated with arrhythmia. Arrhythmia occurred no more than once in any given patient. In the next figure (Figure 36), is an illustrative case. This man had 3 separate episodes of high levels and a digitoxin arrhythmia only once. My conclusion is that since all of the heart diseases in which glycosides are used form a continuous spectrum of severity and, at each point in the spectrum, susceptibility to arrhythmias will depend on the interplay of multiple factors, there is no reason to expect that any arbitrary serum glycoside level would independently distinguish toxic from non-toxic patients. I hasten to add that this in no way diminishes the value of well done SDLs in patient management as well as one of the points to be considered in finding actual toxicity.

Table 21 Data from 16 discrete episodes of serum digoxin level elevations (>2 ng/ml) in 7 patients.

Patient No.	Cardiac Rhythm	Arrhythmia Present Serum K^+	SDL	Arrhythmia Absent Serum K^+	SDL
1	AF	4.4	4.2*	4.4	5.2
2	ST	3.6	2.8†	4.7	2.3
3	AF	4.5	3.9‡	---	5.0
				4.0	5.0
4	ST			5.1	2.6
				---	3.9
				---	2.7
5	ST			2.9	3.2+
				---	3.1
6	ST			4.8	3.2
				5.5	4.4
7	AF			---	4.6
				6.1	5.9
Mean Values		4.17	3.63	4.69	3.93

AF = atrial fibrillation; ST = sinus tachycardia

* AF at 46/min; † ST with 2:1 A-V Block after carotid massage

‡ AF at 40 with 3" pauses; + High SDL and hypokalemia

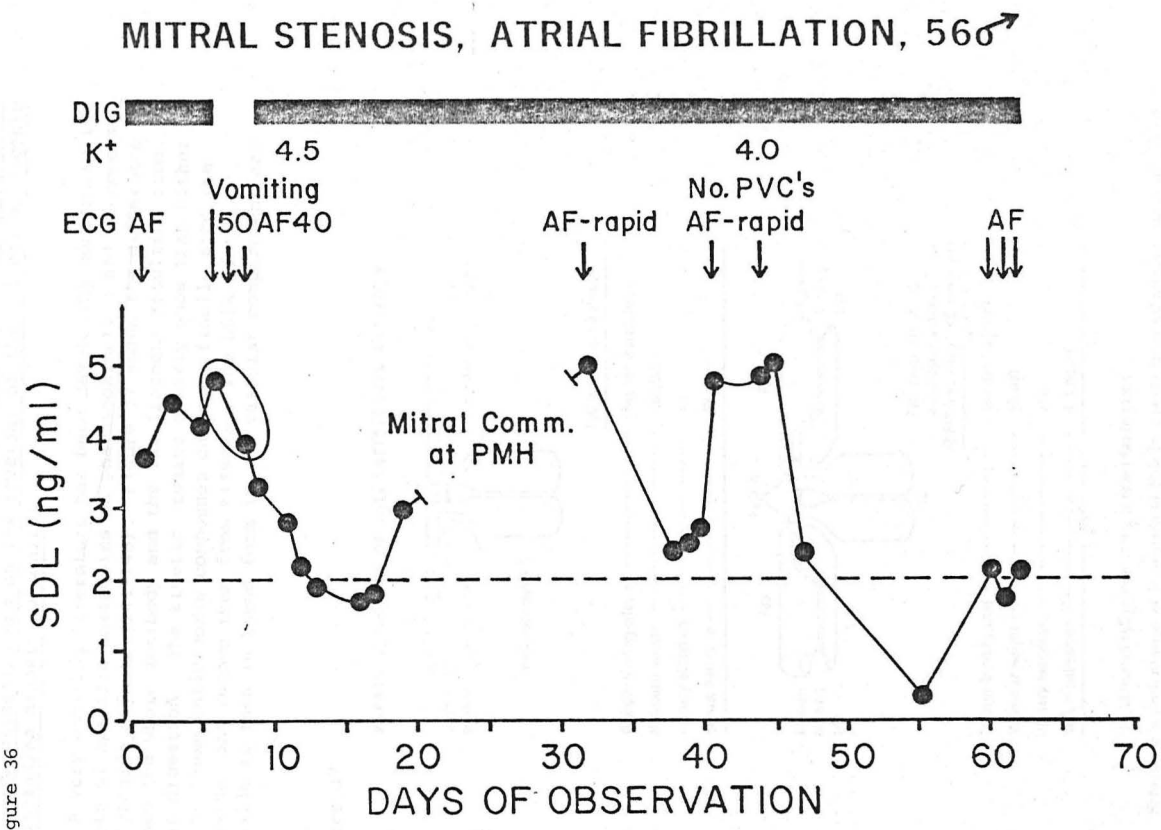

MITRAL STENOSIS, ATRIAL FIBRILLATION, 56♂
DIG
K+
4.5
4.0
Vomiting
No. PVC's
ECG AF
50AF40
AF-rapid
AF-rapid
AF
Mitral Comm.
at PMH
SDL (ng/ml)
0
1
2
3
4
5
0
10
20
30
40
50
60
70
DAYS OF OBSERVATION

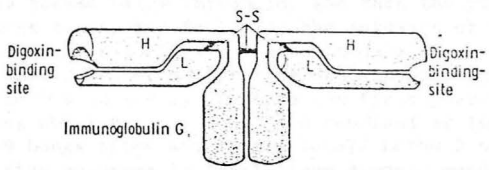
Figure 36

F. The effect of digoxin specific antibodies and fab fragments on pharmacokinetics and on the reversal of the effects of digoxin including digoxin poisoning:

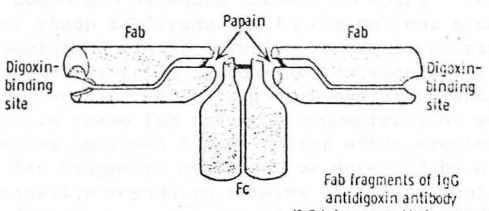
A very exciting literature has been developing concerning the effects of specific antibodies on pharmacokinetics and on reversal of glycoside effects (144-148). Figure 37 shows the difference between the whole antibody and the fab fragment resulting from papain digestion. The kinetic studies clearly show that either form of these antidigoxin compounds can specifically bind the glycosides and remove them from tissues. The bulk of the glycoside is then in bound form in the vascular compartment and

Figure 37

PAPAIN DIGESTION OF *IgG* ANTIDIGOXIN ANTIBODY



	IgG antidigoxin antibody
Digoxin-binding sites	two per molecule
Molecular weight	160,000
Urinary excretion	no
Serum half-time	23 days*



	Fab fragments of IgG antidigoxin antibody (2 Fab fragments / IgG molecule)
Digoxin-binding sites	one per fragment
Molecular weight	50,000
Urinary excretion	yes
Serum half-time	4.3 hours **

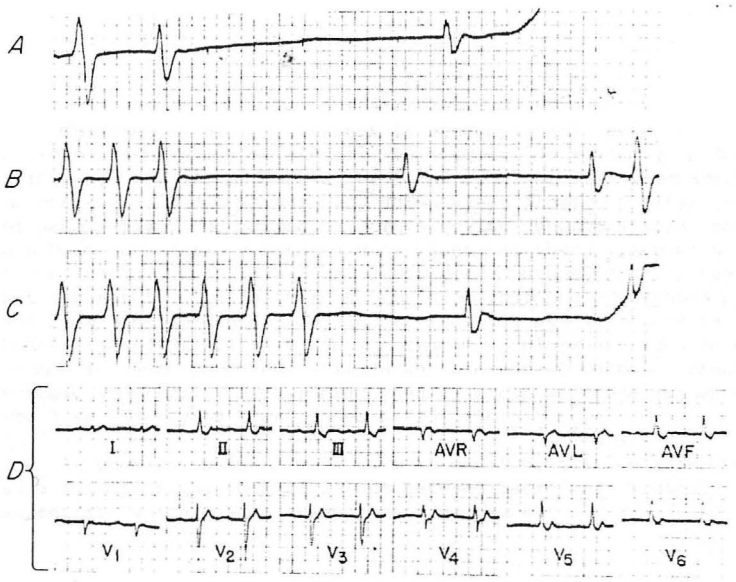
*$t_{1/2}$ of human IgG in man **$t_{1/2}$ of rabbit Fab in rabbit

Schematic representation of formation of Fab fragments from antidigoxin antibody, based on model of Nisonoff (41). When IgG antidigoxin antibody is treated with papain, it is cleaved into three parts: one Fc fragment and two Fab fragments. Each Fab fragment (Ab = "antigen-binding") contains one digoxin-binding site.

inactive. The total antibody with a molecular weight of about 150,000 is slowly excreted and degraded so that the disappearance rate of the whole antibody complex is slow. As the antibody molecule becomes metabolically degraded, a portion of the bound digoxin is re-released into the circulation. The smaller fab fragments, molecular weight 50,000, are excreted quite rapidly and take the bound digoxin (and the same trick can be done with digitoxin) with them at a rapid rate. Although immunogenicity to either of these compounds has not occurred in animals, it seems more likely that the entire antibody would be more immunogenic than the fab fragment (149). In the April 8, 1976 issue of the New England Journal of Medicine, Smith and his group reported the first instance in a patient of reversal of digoxin poisoning by utilization of sheep fab fragments (150). Sequential electrocardiograms from this paper are shown in Figure 38, demonstrating the prelethal arrhythmia which was present when the temporary pacer was turned below threshold, and then the progressive improvement during and following the infusion of the fab fragments which bound the digoxin. The kinetic data is shown in Figure 39. It should be noted that free digoxin concentration in serum dropped to low levels by the time the first post-treatment serum sample was obtained in 1 hour, and remained at levels below 1 ng/ml through 9 hours after which only levels below 2 ng/ml were recorded. A sharp rise occurred in total serum digoxin concentration from 176 ng/ml immediately before infusion to 223 ng/ml one hour after fab infusion was started. Despite a continuing rise in sheep fab fragment concentration from 60 mcg/ml at one hour to 98 at 2 hours, total serum digoxin plateaued at values of 223 and 226 ng/ml, respectively, and remained at about that level for 12 hours after infusion when an exponential decline with a half-life of 20 hours began and extended through 56 hours. The peak concentration of sheep fab fragments in the patient's serum occurred at the completion of the infusion and declined rapidly, at first reflecting distribution through the extracellular space, then more slowly, presumably, reflecting both excretion and catabolism. No detectable sheep fab fragment concentrations were present in serum samples obtained 9 and 21 days after treatment. Antibodies to sheep fab fragments could not be detected by a sensitive hemagglutination method in samples of the patient's serum obtained 1, 3 and 4 weeks after treatment. Urine collections documented substantial renal digoxin excretion which was as high as 969 ng/ml during the initial 24 hours of observation. Initially after the beginning of the fab infusion and 6 hours later, there were undetectable amounts of free digoxin in the urine while the total digoxin was 155 to 660 ng/ml indicating that the digoxin was excreted by the kidney bound to the specific fab fragments. Subsequently, the fraction of total urinary digoxin present in the free state increased gradually to 100% by 30 hours after fab infusion. These data are consistent with the time course of fab excretion in the urine as measured by radioimmunoassay. Initial urinary fab concentrations after administration were as high as 42.5 mcgms/ml falling to less than 2 mcgm/ml in the urine sample collected 30 to 52 hours after fab infusion.

(49)

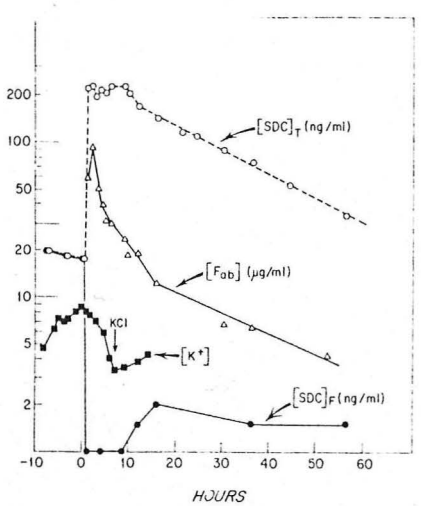
Figure 38



Sequential Electrocardiograms Recorded before, during, and after Treatment with Digoxin-Specific Fab Fragments.

In A, the tracing recorded immediately before the start of Fab infusion, serum potassium is 8.7 meq per liter; the escape interval when pacer stimulus is reduced below threshold is 4.60 seconds. In B, the tracing recorded 15 minutes after the start of Fab infusion, serum potassium is 8.0 meq per liter; the escape interval is 3.96 seconds. In C, the tracing recorded 30 minutes after the start of Fab infusion, the escape interval is 2.76 seconds. In D, the tracing recorded two hours after the start of Fab infusion, serum potassium is 7.4 meq per liter; a sinus mechanism is present at a rate of 75 per minute, with first-degree atrioventricular block (PR interval of 0.24 second). (150)

Figure 39



Time Course of Serum Potassium Concentration in meq/liter, $[K^+]$ (■—■), Total Serum Digoxin Concentration $[SDC]_T$ (O----O), Free Serum Digoxin Concentration $[SDC]_F$ (●—●), and Serum Concentration of Sheep Digoxin-Specific Fab Fragments [Fab] (△—△).

The scale on the vertical axis is logarithmic. On the horizontal axis, 0 denotes the time at which administration of digoxin-specific Fab fragments was started. (150)

This remarkable achievement is now applicable also to digitoxin (Smith et al: unpublished reversal of toxicity in dogs). This could readily be applied by these sophisticated laboratories to other glycosides as well and holds great promise for the treatment of severe glycoside poisoning. This vexing, unpredictable problem has been successfully managed with pacemaker therapy and with reduction in the toxic elevations of serum potassium which can occur, but has resulted in death in a number of profoundly poisoned patients who have developed unmanageable hyperkalemia and unresponsive heart block (151-154). Various forms of AV block are much more common in those poisoned patients who had normal hearts whereas ectopic ventricular arrhythmias tend to occur in those patients who have underlying heart disease (155,156).

In summary, Digoxin 1977 is more exciting than ever before as a result of the collaborations between basic and clinical scientists which I have attempted to describe.

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