CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18118

MEDICAL REVIEW(S)

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MEDICAL OFFICER'S REVIEW AND EVALUATION OF CLINICAL DATA

NDA 18-118

APPLICANT: Burroughs Wellcome

I. General Information

a. Name of drug:

(1) Digoxin
(2) Lanoxicaps
(3) 3B-[(O-2,6-dideoxy-B-D-ribo-hexopyranosyl-(1 4)
-O-2,6-deoxy-B-D-ribo-hexyopyranosyl-(1 4)
-2,6-dideoxy-B-D-ribohexopyranosyl)oxy]-12B,14-dihydroxy-5B-
card-20(22)-enolide

b. Pharmacologic Category; cardiac glycoside

c. Proposed Indications:

(1) Congestive heart failure
(2) Atrial fibrillation
(3) Atrial flutter
(4) Paroxysmal atrial tachycardia

d. Dosage forms and route of administration:

50 mcg capsules (red), 100 mcg capsules (yellow) and 200 mcg capsules (green) for oral administration

II. Manufacturing Controls

See Chemist's review.

III. Pharmacology

Digoxin is a member of a closely related group of cardiac (digitalis) glycosides. These drugs are found in several plants and animals and their use dates back as far as 2000 B.C. Members of the group have a steroid nucleus with a lactone ring at C-17 and one or more sugars linked at C-3. Modern usage traces directly back to William Withering's classical "Account of the Foxglove and Some of its Medical Uses" published in 1785 (Majors, R. H., Classic Descriptions of Disease, 440-443, Charles C. Thomas, Springfield, Illinois, 1959).

The therapeutic effects of the cardiac glycosides are qualitatively similar although their exact mechanism(s) of action remain obscure. Their influence on the electrophysiologic properties of the myocardium are dose related, and involve both a direct action on cardiac muscle and the specialized conduction system, and an indirect action mediated by the autonomic nervous system. The direct action on cardiac muscle is probably mediated through the effects of the cardiac glycosides on the ATP dependent myocardial "sodium-potassium pump" which regulates intracellular cation concentrations; conversely, cations play a major role in contributing to both the beneficial and toxic manifestations of digoxin.

The indirect actions mediated by the autonomic nervous system involve a vagomimetic action, which is responsible for effects on the sinus and atrioventricular (AV) nodes; and also a baroreceptor sensitization which results in increased carotid sinus nerve activity and enhanced sympathetic withdrawal for any given increment in mean arterial pressure.

The pharmacological consequences of these direct and indirect effects are:

(1) an increase in the force and velocity of myocardial systolic contraction (positive inotropic action);
(2) a slowing of heart rate (negative chronotropic effect), and
(3) decreased conduction velocity through the AV node.

In higher doses, cardiac glycosides increases sympathetic outflow from the central nervous system (CNS), to both cardiac and peripheral sympathetic nerves. This increase in sympathetic activity is responsible for most of the extra cardiac manifestations of toxicity and may be an important factor as well in cardiac toxicity.

Other actions:

Cardiac glycosides may cause other dose related effects on the central nervous system, eye, skeletal muscles, peripheral vascular tree and kidneys.

Nausea, vomiting and probably diarrhea and salivation are CNS mediated. Also headache, fatigue, malaise and drowsiness are probably CNS mediated; whereas, muscle weakness which may accompany these symptoms may be due to effects on skeletal muscle cell cations. Mental symptoms associated with cardiac glycosides include disorientation, confusion, aphasia, delirium and hallucinations. Visual symptoms include white borders or halos around dark objects, chromalopsea most common for yellow and green but may be for red, brown or blue and transitory amblyopia, diplopia and scotomata.

In animal models cardiac glycosides can be shown to increase peripheral vascular resistance particularly of the splanchnic bed. Whether this has any clinical significance is not clear, although abdominal pain and ischemic necroses of the bowel has been attributed to acute digitalization of patients with marginal mesenteric perfusion. Changes in the tubular reabsorption of sodium (inhibition) probably is due to an effect on Na, K-ATPase.

Less commonly occurring effects of the cardiac glycosides may be due to idiosyncratic or allergic reactions which only occur in predisposed individuals. These reactions involving the CNS include neurologic pain and paratheslas, retrobulbar neuritis and convulsions. The etiology of such reactions is not clear. Skin rashes and eosinophilia which can occur with the cardiac glycosides are infrequent and may be specific for only one of the drugs in the class. The most likely explanation for these reactions is an allergic basis. Gynecomastia may occur in men and is thought to be due to some estrogenic effect of the steroid nucleus or one of its metabolites. Suppression of follicle-stimulating hormone secretion and cornification of vaginal epithelium occurring in postmenopausal women is thought to be caused by the same mechanism.

Although in animals cardiac glycosides can increase blood coagulability it has not been shown to have any clinically significant consequences in therapeutic doses. Thrombocytopenia has been reported with cardiac glycosides presumably on an immunologic basis.

IV. Clinical Background

There is extensive literature on the pharmacodynamics of digoxin in man. The studies relating to onset of effect and time of peak effect to dosing, serum digoxin levels and myocardial digoxin levels have been studied by succeeding generations of physicians as new techniques for quantitating pharmacologic effects and measuring digoxin and its metabolites have been developed.

Patients with auricular fibrillation were used by Gold, H.; Cattell, M.; Greener, T.; Hanlon, L. W.; Kevit, N. T; Modell, W.; Cottore, E.; Benton, J. and Otto, H. L., Clinical Pharmacology of Digoxin, Jour. of Phar. Exptl. Ther. 109:45, 1953, to assess the bioavailability of the oral preparation versus the same dose intravenously. They anticipated correctly the results obtained 2 decades later with serum digoxin levels (2/3 of the oral dose bioavailable). The pharmacologic time effect curves they developed showed significant rate slowing by 15 minutes after 1.2 mg of digoxin I.V. The same effect was achieved about 5 hours after 1.2 mg of digoxin orally. The maximum effect after the oral dose occurred at about 6 hours and persisted until the following day. The maximum response to the I.V. dose was 10 beats/min

greater, but was reached at about the same time. By the next day the rate was only 5 beats/min less than the oral dose. A differential of 3-4 beats/min between the oral and intravenous group's ventricular rates then persisted for the week they followed their patients.

In the paper by Gold, et al, they also related the control of the apical rate between 65 and 85 beats per minute to dose as well as the occurrance of nausea and vomiting to dose. At daily doses of .25, .5, .75, 1.0 and 1.5 mg for an average of 5.9 weeks they found the apical rate was "controlled" in 28, 47, 71, 80 and 92% of their patients respectively. They found 0, 0, 4, 26, and 72% incidences of nausea and vomiting in each group (N/group 24-49 patients).

With the development of methodology for measuring serum digoxin levels and changes in the timing of the sequence of events occurring during ventricular contraction the pharmacokinetics of digoxin and pharmacodynamics of the inotropic effects have been studied and correlated.

Among the initial pharmacokinetic discoveries was that there was a bioequivalency problem between different manufacturer's tablets and probably between different lots from the same manufacturer. The FDA in cooperation with the New York Heart Association and the United States Pharmacopecia established dissolution standards for all marketed digoxin tablets (1972) and new recommended dosage levels (1974) for the standardized tablets. (A result of this change in the marketed products is that dosage forms used orally before 1972 as in the Gold, et al, study referenced above had a lower bioavailability - i.e. less than 65% absorbed - than tablets marketed after 1972).

The application of systolic time interval measurements to studies in patients and normals to evaluate the positive inotropic effects of digoxin have essentially confirmed the pharmacological time course observed by Gold in auricular fibrillation; namely, that significant digoxin effects appear within 10 minutes after I.V. dosing (1.6 mg) reach a peak at around 6 hours and return to normal at a rate approximating the serum half-life. Oral dosing (3.25 mg) shows slower onset with peak effect of about the same time as I.V.

Studies of the beneficial effects of digoxin on heart failure in patients with normal sinus rhythm are less clear cut than those of the effect on failure associated with auricular tachyarrthymias. Beneficial hemodynamic effects, effects on systolic timing and on heart size can be shown in both acute and chronic studies in both situations. The heart does not appear to become refractory or fast to these digoxin effects. However, the symptomatology of congestive heart failure related to fluid retention edema and exertional dyspnea, can be effectively treated in many patients with normal sinus ryhthm by diuretics alone. In studies where diuretics are used concurrently and either held constant or pushed to maximum effective doses, the majority of patients can be maintained without digoxin. The differences in other patient characteristics, in patients with normal

sinus rhythm, which determine whether or not digoxin is necessary in addtion to diuretics such as initial NYH functional class and control of hypertension have not yet been well established. However, based on the patient populations studied with differences in proportions of patients needing digoxin the most important characteristic seems to be the circumstances in which congestive heart failure was first diagnosed. If the diagnosis was unequivocal and failure was not associated with some other precipitating factor like pneumonia, which can be successfully treated, then the likelihood of continuing to require digoxin is probably better than fifty-fifty.

The clinical pharmacokinetics of digoxin show it is widely distributed through body tissues and has a high apparent volume of distribution (mean value in healthy subjects about 6L/kg). In patients with renal impairment the apparent volume of distribution (Vd) may be lowered and values below 3L/kg have been observed (Szefler, J. J. and Jusko, W. J.. Decreased volume of distribution of digoxin in a patient with renal failure. Res. Comm. in Chem. Path & Pharm. 6:1095, 1973; Aronson, J. K. and Graham-Smith, D. G. "Altered Distribution of Digoxin in Renal Failure — A Cause of Digoxin Toxicity?" Br. J. Clin. Pharm. 3:No. 6, 1045, 1976). The reasons for this reduction are unknown, but may be related to altered tissue binding in the presence of diminished activity of membrane Na+, K+ -ATPase. Volume of distribution returns towards normal when renal function improves (Aronson and Grahame-Smith). The volume of distribution of digoxin is also related to age, decreasing in adults with increasing age (Aronson, J. K. and Grahame-Smith, D. G. Monitoring Digoxin Therapy. II Determinants of the Apparent volume of distribution. Brit. J. Clin. Pharm. 4:223, 1977; Cusack, B.; Kelly, J., et. al., "Digoxin in the Elderly: Pharmacokinetic Consequences of Old Age", Clin. Pharm. Ther., 25:772, 1979).

The distribution of digoxin to various tissues (calculated from data of Doherty, J. E.; Perkins, W. H.; Flanegan, W. J. The distribution and concentration of tritiated digoxin in human tissues. Ann. Intern. Med. 66:116, 1967) is skeletal muscle, 65%; liver, 13%; heart, 4%; brain, 3%; kidneys, 1.5%. There have been numerous studies of the relationship between myocardial tissue concentrations of digoxin and corresponding plasma concentrations. There is great variation from study to study in the correlation between myocardial and plasma digoxin concentrations. The variation undoubtedly arises from both differences in techniques as well as differences in patient population. For example, the 2 studies (Gullner, H. G.; Stinson, E. B.; Harrison, A. Correlation of Serum Concentration with Heart Concentrations of Digoxin in Human Subjects. Circ. 50:653, 1974; Hartel, G.; Kyllonen, K.; Merikallio, E.; Ojala, K.; Manninen, V., Reissell, P. Human serum and myocardium digoxin. Clin. Pharm. & Therap. 19:153, 1976) in which the least variation in ratio from patient to patient within the studies was found, showed widely different mean ratios (24:1 and 67:1 respectively) probably because of different sampling sites (left atrial appendage and papillary muscle

respectively). The relatively poor correlation found by Jusko, W. J. and Weintraub, M.(Myocardial distribution of digoxin and renal function, Clin Pharmacol. Ther. 16:449, 1974) was attributed to, and would be corrected by, differences in their patients' renal function; and their data suggest that values in the presence of normal renal function are at or above 60:1. Such values agree with those of Hartel, et al, all of whose patients had normal renal function.

The distribution of digoxin to central nervous tissue is of interest in view of the suggestion that some of the effects of cardiac glycosides may occur as a result of effects on central nervous tissue (Levitt, B; Cagen, N.; Kleid, J.; Somberg, J. and Gillis, R. Role of the nervous system in the genesis of cardiac rhythym disorders. Am. J. Cardiol. 37:1111, 1976). Digoxin has been detected in cerebrospinal fluid in adults during steady-state administration (Allonen, H.; Anderson, K. E.; Iesolo, L. E.; Kanto, J.; Stromblad, L. G. and Wettrell, G. Passage of digoxin into cerebrospinal fluid in man. Acta Pharmacologia et Toxicologeca 41:193, 1977; Gayes, J. M.; Greenblatt, D. J.; Lloyd, B. L., Hormatz, J. S. and Smith, T. W. Cerebrospinal fluid digoxin concentrations in humans. J. Clin. Pharmacol. 18:16, 1978). The ratio of serum to CSF concentrations ranged between 1.2:1 and 20:1 during steady-state treatment, with mean serum concentrations of 1.1 ng/ml. Digoxin was barely detectable in the CSF after a single dose in most patients (Allonen, et al). The concentration of digoxin (ng/g tissue) in the chorold plexus (Bertler, A.; Andersson, K. E. and Wettrell, G. Concentrations of digoxin in chorold plexus. Lancet 2:1453, 1973; Anderson, K. E.; Bertler, A. and Wettrell, G. Post-mortem distribution and tissue concentrations of digoxins in infants and adults. Acta Paediatrica Scandinavia 64:497, 1975; Krakauer, R. and Steiness, E. Digoxin concentration in chorold plexus, brain and myocardium in old age. Clin. Pharmacol. & Therap. 24:454, 1978) has been found to be at least as high as that in ventricular myocardium. Concentrations in the rest of the brain were much lower and in about one third of patients were undetectable (Krakauer and Steiness). The significance of high concentrations of digoxin in the CSF in relation to effects on the myocardium has not been established. Concentrations in autonomic nervous tissue have not been reported.

Although it is generally stated that digoxin is mostly excreted unchanged in the urine some evidence suggests that in some cases metabolism may be extensive.

The first hint that this might be so came from a study of a single patient with atrial fibrillation who had unusually large requirements of digoxin (Luchi, R. J. and Gruber, J. W. Unusually large digitalis requirements - study of altered digoxin metabolism. Am. J. of Med. 45:322, 1968). In chromatograms of urine digoxigenin and dihydrodigoxigenin were detected in relatively large amounts (18% and 15% of total glucoside detected respectively). In a study of the

urine of 50 patients, dihydrodigoxin was detectable in 48 and was found to constitute between 1 and 47% of total glycoside (mean 17%) (Clark, D. R. and Kalman, S. M. Dehydrodigoxin: A common metabolite of digoxin in man. Drug Metabolism & Disposition 2:148, 1974). In 3 patients, less than 51% of total glycoside in the urine was digoxin, the rest being accounted for by the presence not only of dihydrodigoxin but also of other metabolites. Of 2 normal volunteers given oral digoxin, one was found to have digoxigenin in the serum in concentrations of 1.0 to 1.3 ng/ml 0.5 to 1 hour after a single dose of digoxin (0.5 mg); the corresponding serum digoxin conetrations were 2.5 to 3.4 ng/ml (Loo, J. C. K.; McGilveray, I. J. and Jordan, N. Quantitation of digoxigenin in serum following oral administration of digoxin in humans. Res. Comm. in Chem. Path. and Pharmacol. 16:497, 1977). In a study of 100 patients (Peters, V. Falk, I. C. and Kalman, S. M. Digoxin metabolism in Patients. Arch. Int. Med. 138:1074, 1978), between 2.2 and 52% (mean 12.4%) of total glycoside in the urine was found to consist of metabolites, principally dihydrodigoxin. The majority (77%) of patients had less than 15% metabolites. In 11%, between 15 and 20% of total glycoside was excreted as metabolite and in the remaining 12% values ranged between 20 and 55%. The degree of metabolism was not related to renal function.

In 7 patients with digitalis toxicity, there was no increase in the formation of metabolites above the mean value for the whole group. If metabolites of digoxin have a longer half-time of elimination than digoxin itself, then accumulation would occur over a period of weeks and that would explain the failure of earlier workers to detect substantial quantities of metabolites during short term study. Peters, et al, found a higher proportion of metabolites in patients who had been taking digoxin for more than 20 days than in those who had taken it for less than 10 days. They also found that the half-time of clearance of hydrolytic metabolites in a normal volunteer was 65 hours (considerably longer than that of digoxin).

It is important to relate these findings to the interpretation of plasma (or serum) digoxin concentrations in patients. The different metabolites cross-react to a different extent with anti-digoxin antibody used in radioimmunoassay. Furthermore, the different metabolites have differing pharmacodynamic potencies. Thus a plasma 'digoxin' estimation which is contaminated by metabolites may not yield an accurate reflection of the quantity of cardioactive glycoside actually present in the plasma.

Studies of the degree to which different antibodies may bind different glycosides, of how the plasma concentrations of different glycosides relate to the tissue concentrations and of the pharmacokinetic properties of the individual glycosides are necessary for a more complete understanding of the problem.

Because of the good correlation between creatinine and digoxin clearances, it has been generally accepted that digoxin is excreted by glomerular filtration; however, the demonstration of an active tubular secretion of digoxin in man (Steiness, E. Renal tubular secretion of digoxin. Circ. 50:103, 1974) and other species (Rasmussen, F.; Nowaz, M. and Steiness, E. Renal excretion of digoxin in swine and goats. Acta Vet. Scand. 16:525, 1975; and Roman, R. J. and Kauker, M. L. Renal tubular transport of 3H-digoxin in saline diureses in rats. Evaluation by meropuncture Circ. Res. 38:185, 1976) has not only raised questions about this traditional concept, but also offered a potential explanation for drug interactions, like with spironolactone (Steiness, 1974, and Steiness, E.; Andersen, J. D.; Meeboll-Nielsen, N.; Nielsen, O. G.; Molkte, E. and Sorensen, U. Spyonolaltone-induced changes in digoxin pharmacokinetics in humans [to be published]) (see Abshagen, V.; Cardiac Glycosides, ed. Bodem, G. and Dengler, H. J.; Springer-Verlag Berlin, Heidelberg, New York, 1978, Chapter 33, 392-400 for some conflicting data), since active tubular excretion has a capacity which can potentially be saturated and/or competively inhibited. Data in 4 patients with hypokalemia (Steiness, E. Suppression of renal excretion of digoxin in hypokalemic patients. Clin. Pharm. Ther. 23:511, 1978) suggests hypokalemia also reduces active tubular secretion of digoxin. (The postulated mechanism is through increased aldosterone and competitive inhibition of the tubular secretion mechanism.)

Considerable investigation of the pharmacokinetics of digoxin in premature and full-term infants as compared to the adult has resulted in only partial clarification. The absorption, serum half-life and excretion of digoxin in urine and stool were found to be similar in infants and adults in some of the earlier studies by Hernandex, A.; Burton, R. M.; Pagtakhan, R. D. and Goldring, D. (Pharmacodynamics of ^{3}H-digoxin in infants. Pediatrics 44:418, 1969) and by Dugan, W. T.; Doherty, J. E.; Harvey, C.; Char, F. and Dalrymple, G. V. (Tritiated digoxin, XVIII: Studies in infants and children. Circ. 46:983, 1972). More recent studies have found an increased mean half-life of 57 hours in the premature newborns as compared to a mean of 35 hours in the mature newborns. This increased half-life in the premature infant has been attributed, in part, to a decrease in the renal clearance of digoxin The increase in biologic half-life may explain the increased serum concentration of digoxin per dose in premature infants. The pediatric dosing recommendations reflect that both the loading and the maintenance dose must be decreased in the premature infant to avoid toxicity.

There also appears to be an increase in the volume of distribution in the newborn. Contributory to this increase in the volume of distribution may be an increased tissue and red cell binding in the newborn. The observation of an increased volume of distribution in the newborn has been used to explain the relatively lower serum concentrations per unit digoxin administered and the need for higher doses of digoxin per kilogram body weight in infants.

The serum concetration may have to be interpreted differently in the infant than in the adult, since it has been found at post mortem that the myocardial-serum concentraion ratio was twice as high in the former as in the latter. In these studies, both the infants and the adults received digoxin for at least 5 days and therefore could be said to be at least approaching steady state. There was no evidence of toxicity in any of these infants. Experimental evidence to support the hypothesis of myocardial resistance to digitalis toxicity in the newborn has been provided by Rosen and co-workers. Clinically, digoxin levels in excess of 2 ng/ml are frequently found in infants receiving standard maintenance therapy without any ECG evidence of toxicity. Conversely, digoxin intoxication is unlikely to be present in infants when serum digoxin concentrations are less than 2 ng/ml. Digoxin toxicity appears to be fairly common when the serum concentraion is in excess of 3.5 ng/ml. Serum digoxin levels up to and even in excess of 5 ng/ml have been reported in children who have shown no evidence of digitalis toxicity.

It is generally recognized that elderly patients develop digitalis intoxication if they are maintained on doses of digoxin that are well tolerated in younger individuals. There are conflicting data on whether the myocardium in the elderly is more sensitive to digitalis glycosides.

Pharmacokinetic studies provide another explanation for digitalis intolerance in the aged. Ewy, G. A.; Kapadia, G. G.; Yao, L.; Lullen, M. and Marcus, F. I. (Digoxin metabolism in the elderly. Circulation 39:449, 1969) found that a single dose of tritiated digoxin injected intravenously into elderly patients resulted in a higher serum concentration than in the younger control subjects. The higher serum concentration of digoxin in the elderly may be due to changes in two factors rather than just one. The first is a decrease in renal function, as measured by decrease in glomerular filtration rate, that regularly accompanies the aging process. This is associated with a concomitant decrease in digoxin renal clearance. In addition, elderly patients are smaller and have a decreased skeletal muscle mass, and have a decrease in the apparent volume of distribution. If volume of distribution and clearance change proportionally, the net effect is no change in serum half-life, but the steady-state serum levels are increased as compared to serum levels in younger patients given the same dose of digoxin. Generally renal clearance decreases more than apparent volume of distribution so that older patients have a net increase in half-life.

IV. Clinical Studies

The primary indications for digoxin are management of congestive heart failure and control of ventricular rate in patients with supraventricular tachyarrhythmias, principally atrial fibrillation. For this reason, this review will be in two divisions - congestive heart failure and ventricular rate control.

Twelve studies are reviewed in the section dealing with congestive heart failure and 9 in the section dealing with ventricular rate control. Seven of the 12 studies regarding congestive heart failure and 6 of the 9 regarding ventricular rate control were supplied by the sponsor who also supplied 8 text book citations which contained no data and are not included in this review.

CONGESTIVE HEART FAILURE

The clinical signs and symptoms of congestive heart failure (e.g. fatigue and reduced exercise tolerance; dyspnea and other respiratory symptoms and their respiratory and radiographic signs; nocturia [early] and oliguria [late]; edema; venous congestion with hepatomegaly, ascites and hydrothorax; signs of increased adrenergic activity and reduced cardiac output; cardiomegaly with gallops, pulsus alternans, accentuation of P2; fever; cachexia; Cheyne-Stokes respiration, etc.) are the end product of the complex interactions of the various components that regulate the circulation and its pump, the heart and secondary effects on other vital organ systems (e.g. see Braunwald, E., Regulation of the Circulation. NEJM 290:1124, 1420. 1974; Benge, W. et al Exercise Capacity in Patients with Severe Left Ventricular Dysfunction. Circ 61:955, 1980). Expert recommendations for treatment of congestive heart failure have been changing over the last 5-10 years (e.g. see Chapter 33, AMA Drug Evaluations, 4th Ed., 1980). Previously, digitalis preparations and a low sodium diet were the primary treatment for uncomplicated cases of congestive heart failure. Patients started on cardiac glycosides during an acute illness involving any of the signs or symptoms of heart failure were often left on their glycoside indefinitely although signs and symptoms were absent. In recent years, the concepts that digitalis should be given to all patients with congestive heart failure (e.g. see Cohn, J. N., Indications for digitalis therapy: A new look JAMA 229:1911, 1974) or should be given as the initial treatment in patients in normal sinus rhythm (e.g. see editorial, Digoxin in sinus rhythm. Br. Med. J. 1:1103, 1979) or should be continued indefinitely once it is started for whatever reason have all been questioned (e.g. Spector, R., Digitalis Therapy in Heart Failure: A Rational Approach J. Clin. Pharmacol. 19:692, 1979) based essentially on the observations that drugs with better toxic/therapeutic ratios can control the clinical signs and symptoms of congestive heart failure without an absolute necessity for digitalis therapy in a large proportion of patients initially digitalized because of "heart failure" -- (representative studies of this type will be reviewed later in this section).

It becomes obvious from reviewing clinical studies on digitalis in congestive heart failure secondary to arteriosclerotic heart disease and hypertension in patients in normal sinus rhythm that how patients are selected and heart failure defined and evaluated will in large measure determine whether or not one can demonstrate the effectiveness of digoxin.

This is demonstrated by the following 2 well-controlled studies submitted by the sponsor as the pivotal proof of efficacy of digoxin for the treatment of congestive heart failure.

1. Arnold, S. B.; Byrd, R. C.; Meister, W.; Melmon, K.; Cheitlin, M. D.; Bristow, J. D.; Parmley, W. W.; Chatterjee, K.: Long-term digitalis therapy improves left-ventricular failure. New England Journal of Medicine 303:1443, 1980.

This is a baseline-controlled, open-label study to determine the long-term effectiveness of digoxin in the treatment of congestive heart failure (CHF). Ten patients entered and nine patients, 6 males and 3 females, aged 27-67 years (mean 51 years), with chronic CHF completed the protocol. CHF was secondary to idiopathic congestive cardiomyopathy in 4 of the patients, ischemic heart disease in 3, long-standing hypertension in 1 and valvular disease in 1. All patients had been on a stable dose of digoxin (125-250 ug/day) for at least 2 months. The indications for initiation of long-term digitalis therapy included presence of clinical and radiologic evidence of CHF with S_3, cardiomegaly, and pulmonary and sytemic venous hypertension. The criteria for entry into the study included a history of CHF; at least one documented episode of pulmonary edema, in the past; and a degree of compensation of CHF while receiving long-term digoxin and diuretic therapy. At the time of study, four patients were in New York Heart Association (NYHA) Class II and five in Class III. These patients thus had unequivocal CHF. Patients in NYHA Class I or who were unstable clinically or not in normal sinus rhythm were excluded. All patients took stable doses of diuretics before the study and the diuretic regimen was not altered during the study except in one patient (reasons and dose alterations not stated). All other medications were maintained at the same dose during the study.

Two to four clinical evaluations were performed during a 2-4 week period prior to the first hemodynamic investigation. Digoxin dosage, weight and clinical status were unchanged during this period. The initial serum digoxin level, obtained 4-6 hours after the A.M. dose 1-4 days prior to the hemodynamic studies, was between 0.4-1.7 ng/ml (mean $\pm$ SD = 1.1 $\pm$ 0.4 ng/ml). Gated blood pool ejection fraction were performed 1-4 days before the hemodynamic study in 7/9 patients to further assess the effects of long-term digoxin on myocardial function.

The hemodynamic studies were performed in the A.M. in the post-absorptive state by right heart catheterization. Hemodynamics were studied at rest and during supine exercise using a bicycle ergometer. The workload was increased every 3 minutes until symptoms (dyspnea or fatigue) limited continuing at which time the hemodynamic measurements were repeated. Patients then rested for 1 hour during which 250-500 ug digoxin (depending on initial digoxin level) was infused. Resting and exercise hemodynamics at the same workload were repeated in 4-5 hours.

Digoxin was then discontinued, the other medications continued, and the patients were observed weekly for determinations of changes in clinical status. Four patients were rehospitalized in 12-31 days due to recurrence of CHF. The other 5 were rehospitalized 6-7 weeks after termination of digoxin. 7/9 had repeated blood pool ejection fractions 1-4 days before rehospitalization and 5/9 had repeat creatinine clearance determinations.

Resting and exercise hemodynamic measurements were again performed, as during the first hospitalization, with exercise hemodynamics measured at the workload used during the first study. One mg of digoxin was then infused and the hemodynamic parameters obtained 4-5 hours later. Pairwise comparisons were made of hemodynamic values measured at baseline (long-term digoxin) after the acute additional dose of digoxin, after digoxin withdrawal, and then after acute readministration. The hemodynamic values are tabulated in Table 1-1 (page 13) with the statistical significance of the comparisons indicated. It is clear that long-term digoxin and acute digoxin were associated with a higher cardiac index, stroke-work index, and ejection fractions, and a lower wedge pressure, both at rest and exercise.

One of the patients in NYHA Class II and 4 in Class III had clinical deterioration in association with worsened hemodynamic status after digoxin withdrawal. There was no change in the symptomatic status of the other four. After digoxin withdrawal, cardiac output (CO) decreased in 7/9, stroke volume decreased in 8/9, left ventricular stroke work index (LVSWI) decreased in 9/9, and pulmonary capillary wedge pressure (PCW) increased in 9/9. Following reinstitution of digoxin, stroke volume, stroke volume index and LVSWI increased and PCW decreased in 9/9. Total systemic resistance and blood pressure did not change after withdrawal nor with reintroduction of digoxin. Individual ventricular function curves (LVSWI vs PCW) were shifted up and to the left by digoxin indicating improved cardiac function.

As no change in vascular resistance was noted, the only mechanism to support the increased stroke volume and CO and decreased PCW is the positive inotropic effect of digoxin. The decrease in ejection fraction in 5/7 patients following digoxin termination further supports this conclusion.

In this population appropriately selected on the basis of a careful review of the indications for digoxin and hemo-dynamic findings, it is clear that a positive inotropic effect of digoxin was present during long-term digoxin therapy, as indicated by deterioration of the measured indices upon drug withdrawal and recovery upon readministration. It is noteworthy that in terms of symptomatology in 4 out of the 9 patients the observed deterioration and improvement in cardiac function could not be detected clinically despite the unblinded nature of the study.

Table 1-1

	Baseline	Additional Digoxin	After Withdrawal*	Acute Digoxin Administration**
Cardiac Index (L/min)				
Rest	2.4 ± 0.7	2.5 ± 0.6	2.1 ± 0.6(p 0.025)	2.5 ± 0.5(p 0.025)
Exercise	3.5 ± 0.9	3.9 ± 1.4	3.1 ± 1.2(p 0.05)	3.8 ± 1.1(p 0.01)
PCW (mm H_2g)				
Rest	21 ± 7.7	19 ± 5.7	29 ± 9.5(p 0.001)	22 ± 9.4(p 0.001)
Exercise	33 ± 7	31 ± 9	42 ± 5 (p 0.001)	35 ± 6 (p 0.01)
Heart Rate (beat/min)				
Rest	77 ± 12.6	73 ± 14.1	85 ± 13.3	77 ± 14
Exercise	111 ± 17	115 ± 23	121 ± 16	117 ± 25
Stroke Work Index ($g.m/m^2$)				
Rest	38 ± 17.7	44 ± 14.6	26 ± 14.2(p 0.001)	40 ± 14.4(p 0.001)
Exercise	45 ± 22	50 ± 23	33 ± 22(p 0.005)	47 ± 29(p 0.005)
Ejection Fraction (%)	41± 44	--	30± 14(p 0.05)	--
Creatinine Clearance (ml/min/1.73m)	78± 15	--	55± 9(p 0.01)	--

Values are mean ± standard deviation

* p-values for comparison of baseline and withdrawal

** p-value for comparison of withdrawal and acute readministration.

The next study illustrates this point even more graphically.

2. Lee, D. C.; Johnson, R. A.; Bengham, J. B.; Leahy, M.; Dinsmore, R. E.; Goroll, A. H.; Newell, J. B.; Strauss, H. W.; Haber, E. Heart Failure in Outpatients: A Randomized Trial of Digoxin Versus Placebo (Manuscript from the Cardiac Unit, Massachusetts General Hospital, Boston, Massachusetts 02114 published as an abstract in Circulation, Vol. 62, Supp. III:325,1981).

This was a randomized double-blind, crossover evaluation of digoxin versus placebo in 25 patients with CHF in normal sinus rythym (NSR). Patients were selected on the basis of chart survey findings of clinical (10 of 13 possible points) and radiographic (3 of the 13 possible points) evidence of CHF. Thirty-five patients were enrolled. Twenty-five patients completed the study.

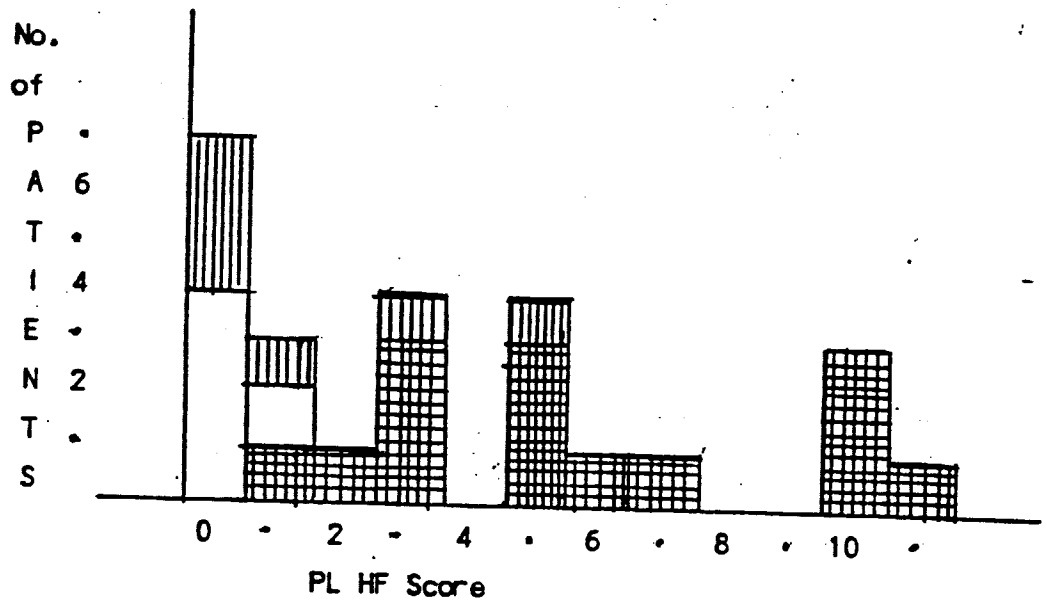
The patient population who completed the study consisted of 18 men and 7 women, aged 40 to 83 years of age. Ten had CHF on the basis of multiple myocardial infarcts, 3 had left ventricular aneurysms, 2 had recurrent ischemia, 6 had idiopathic cardiomyopathy (i.e., no basis could be established despite anglograms in 3) and 4 had left ventricular hypertrophy (LVH) from "long-standing" hypertension. They were all in NSR. None had valvular heart disease. None had heart failure (HF) only associated with an acute episode. None were in NYHA Class IV.

Patients were followed during a variable length lead in period where digoxin was administered to bring their serum level to 1.2 ng/ml ($\bar{X}$ dose required 0.435 mg, range 0.125-1.0 mg). Their diuretic dose was then adjusted until their weight, symptoms and physical findings "were stable." Patients were randomly assigned to treatment, A or B, and followed at 10 day intervals. If their status did not change after 8-10 weeks they were given an end of period evaluation (chest x-ray, spirometry, phonocardiogram, echocardiogram and radionuclide ventriculography) and then crossed over to the other treatment and followed similarly.

If CHF worsened in either period they had their end of period evaluation, the study treatment was discontinued, and they were given digoxin at their previous maintenance dose. Their diuretic was increased if necessary to bring them back to their previous baseline state, then it likewise was readministered at its previous dose and the other treatment was administered to complete the study (the study was terminated if they had already had the previous treatment). (? exceptions to this see their Figure 3).

The protocol data presentations in the manuscript does not distinguish between apriori and post-priori analyses so that it is difficult to differentiate between what hypothesis were tested by the experiment and which were generated by it. Fortunately, in the manuscript we have more data than will probably appear in the final paper because some of the figures and tables are not really crucial to the author's discussion. The data organization into Group I (the 14 "responders") and Group II (the 11 "non-responders") makes it particularly difficult to independently analyze the data and the results. The most crucial missing information which can not be derived from the data is the order in which patients got placebo or digoxin to look for the possible influence of the initial randomization and sequence of administration. I have prepared some additional graphs showing the relationship of the selection , placebo and digoxin HF scores.

Diff. in HF Score on DIG													Totals	
Increase	3	1	0	1	1	0	0	0	0				6 Group II	
Same	4	1	0	0	0	0	0	0	0				5 Group II	
Decrease	–	1	1	3	3	1	1	3	1				14 Group I	

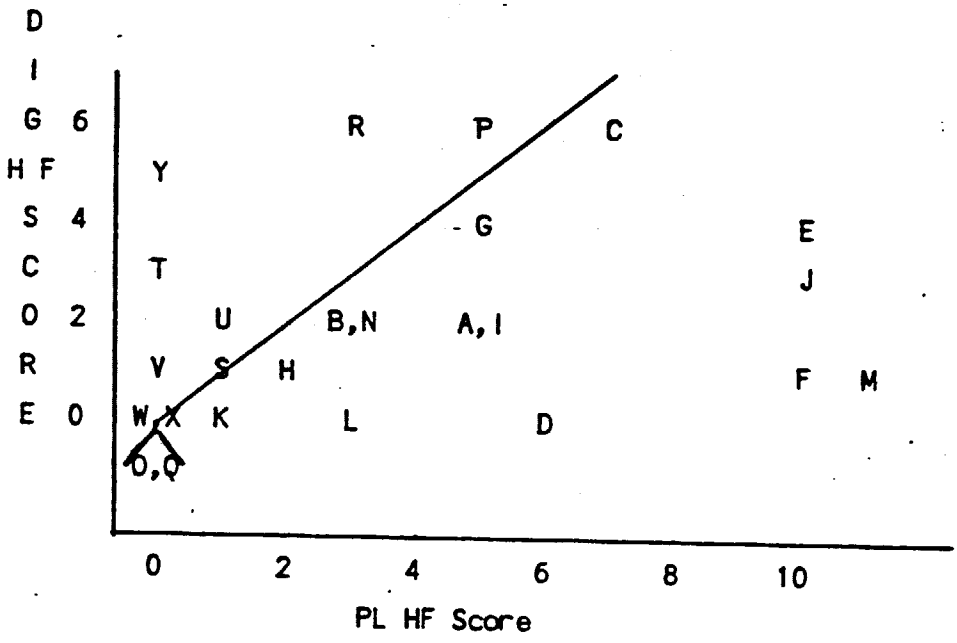


DIG = Digoxin

PL = Placebo

HF = Heart failure

Diff. in HF Score on DIG										Totals
Increase	3	1	0	1	1	0	0	0	0	6 Group II
Same	4	1	0	0	0	0	0	0	0	5 Group II
Decrease	-	1	1	3	3	1	1	3	1	14 Group I



DIG = Digoxin

PL = Placebo

HF = Heart failure

A...X = Patients

These data demonstrate the generic difficulty with and potential importance of patient selection criteria. In this case the selection HF scores correlated poorly with placebo HF scores. This poor correlation may reflect differences in the other elements involved in the patient's treatment or inherent differences in the patient's disease at different times. It emphasizes the difficulty in the clinical use of digoxin of trying to decide who needs digoxin indefinitely and who does not. It does not support the current dogma reflected in the current label that in general patients placed on digoxin for clear cut indications of CHF should be left on digoxin indefinitely.

It is clear that the 10 patients who had 0 or 1 HF scores on placebo bias the study against digoxin because their potential for improvement is much less (better score possibility of 0 to -1) than their potential for getting worse (worse score possibility of +13 to +12). Four of these 10 patients had higher HF scores on digoxin than placebo (patients T, U, V + U). Only 2 of the other 15 patients had higher scores on digoxin than placebo (patients R and P). No patient had a higher score on digoxon than their selection HF score (2 G + P had the same scores). Two patients had higher scores on placebo than their selection HF score (G + F).

If one looks at the 15 patients who's placebo HF scores were more than 1; their median score was 5 and the only 2 patients who's scores on digoxin were higher had placebo HF scores of 3 and 5 (patients R + P). The following table illustrates the influence of the placebo HF scores on the outcome and how the results are directly affected by including or excluding them from analysis.

Group II | I	CHANGE IN HF SCORE ON DIG		
PL HF SCORES	INCR.	SAME	DECR.
0 - 1	4	5	1 (K)
2 - 11	2 (R P)	0	13

The authors have placed 9/10 of the low (0-1) placebo HF score patients in Group II along with 2/15 of the higher (2-11) placebo HF score patients.

In reviewing the 3 patients involved (K, P and R) I don't believe it would change the basic conclusions so let us turn to the authors presentation of their results and conclusions.

In Table 3 (pages 22 and 23) in comparing results on digoxin and placebo the study did not show a statistically significant difference between responders (Group I) and non-responders (Group II) in anything except the cardiothoracic ratio. Both groups showed improvement in body weight and left ventricular internal diastolic dimension. Note that there was not a statistically significant difference between HF scores on digoxin and placebo in either group.

In Table 4 (pages 24, 25 and 26) in comparing the 2 groups the only baseline characteristic correlating with the favorable outcome with digoxin was the presense of a third heart sound. Although it is not explicitedly discussed in the manuscript, it can be presumed that this was a post priori finding because of the assignment of patient P to Group II (only patient in Group II with a third heart sound).

There are results presented on 6 patients (Fig. 3, pages 27 and 28) which are not part of the protocol and from the legend accompanying the figure, the results are not necessarily in the sequence of actual events. These patients would support the authors conclusions better than the data from the study itself; namely, that "long-term digoxin therapy is clinically beneficial in a subset of patients with heart failure and sinus rhythm." Such results from blinded randomized readministrations would define such a group. Unfortunately, this figure does not represent those circumstances.

These 2 recent studies are consistent with each other and with previous studies (summaries of some follow) which demonstrate the positive beneficial effects of digoxin on cardiac function as measured by a variety of techniques and the lack of a good correlation of such improvement with clinical improvement of the signs and symptoms of congestive heart failure in patients on stable multiple drug regimens.

The explanation for this apparent lack of the strong correlation one would expect between cardiac function and heart failure is reasonably straight forward although conjectural rather than established by direct experimentation in man. As pointed out in the beginning of this discussion there are complex inter-relations between a number of elements principally involving the cardio-vascular tree, renal-adrenal regulatory mechanisms and the central nervous system which determine circulatory function. A decrease in cardiac muscle's contractile force is initially compensated for by other elements of the system. If the system decompensates drugs affecting elements other than the heart per se, such as diuretics, may recompensate the system to an extent where the addition of a cardiac glycoside which can be shown to demonstrably affect cardiac function may produce no change (improvement) in overall system function. Experiments which conclusively established that digoxin alone is effective in correcting the signs and symptoms of "heart failure" secondary to decreased cardiac force of contraction might satisfy the strict letter of the regulations, but would not be as valuable medically as studies wich compared the long term risks and benefits of clinically apparently equal alternatives treatment regimens (equal in effect on signs and symptoms, but not hemodynamically equal).

ble 3. Digoxin vs Placebo

	Group *	Number of Patients	Digoxin+	Placebo+	p ‡
HF §	Total	25	2.0 ± 1.9	3.6 ± 3.6	>0.05 ¶
	I	14	2.0 ± 1.8	5.8 ± 3.3	
	II	11	1.9 ± 2.3	0.9 ± 1.6	
Heart rate (beats/min)	Total	23 **	81 ± 16	86 ± 17	>0.05
	I	13	81 ± 15	90 ± 16	
	II	10	81 ± 20	81 ± 18	
Mean blood pressure (mm Hg)	Total	25	99 ± 16	98 ± 15	>0.05
	I	14	97 ± 11	92 ± 11	
	II	11	102 ± 21	106 ± 16	
Body weight (kg)	Total	25	77 ± 36	78 ± 35	0.012
	I	14	72 ± 16	73 ± 16	>0.05
	II	11	82 ± 15	84 ± 15	>0.05
Vital capacity (l)	Total	25	2.5 ± 0.6	2.4 ± 0.5	>0.05
	I	14	2.7 ± 0.6	2.5 ± 0.6	
	II	11	2.3 ± 0.5	2.4 ± 0.5	
Cardiothoracic ratio ++	Total	25	0.51 ± 0.07	0.53 ± 0.07	0.00028
	I	14	0.52 ± 0.05	0.55 ± 0.05	0.0018
	II	11	0.50 ± 0.08	0.51 ± 0.09	>0.05
Left ventricular internal diastolic dimension (mm/m^2) ‡‡	Total	21 §§	31 ± 5.3	33 ± 5.3	0.0012
	I	12	35 ± 3.6	36 ± 3.4	0.042
	II	9	27 ± 4.0	29 ± 5.2	0.033
Left atrial diameter (mm/m^2) ‡‡	Total	22 §§	22 ± 2.8	22 ± 3.9	>0.05
	I	12	22 ± 2.9	23 ± 3.4	
	II	10	22 ± 3.1	22 ± 4.6	
Left ventricular ejection fraction ¶¶	Total	25	0.30 ± 0.19	0.29 ± 0.19	>0.05
	I	14	0.19 ± 0.07	0.19 ± 0.07	
	II	11	0.42 ± 0.20	0.44 ± 0.20	
Preejection period/left ventricular ejection time **	Total	24 §§	0.52 ± 0.19	0.54 ± 0.22	>0.05
	I	14	0.54 ± 0.19	0.59 ± 0.23	
	II	10	0.[illegible] ± 0.18	0.47 ± 0.20	

Footnotes to Table 3

*Groups I ($\Delta HF > 0$) and II ($\Delta HF \leq 0$), as defined in text.

†Mean ± S.D.

‡Paired t-test.

§HF = heart-failure score (Table 1).

¶T-test performed on a logarithmic transformation of HF.

**Excluding two patients with continuous ventricular pacing.

††Measured by posteroanterior chest radiography.

‡‡Measured by M-mode echocardiography.

§§Excluding patients in whom adequate data could not be obtained.

¶¶Measured by resting radionuclide ventriculography.

***Measured phonocardiographically in 23 patients and echocardiographically in 1 patien

GROUP I (ΔHF >0[1])

ENT	SEX	ENTRY AGE(y)	DIABETES MELLITUS[2]	ANGINA[3]	HYPERTENSION[4]	LVH[5]	MAXIMUM HF BEFORE ENTRY[1]	DURATION[6] (y)
	M	69	-	+	+	+	8	9
	F	70	-	+	+	+	8	2.5
	M	73	-	-	-	-	11	0.5
	M	63	-	-	-	+	10	4
	M	56	-	-	-	-	12	1
	M	63	-	+	-	-	5	1.5
	M	52	+	+	+	-	4	0.5
	M	45	-	-	-	+	7	3
	M	63	+	-	+	+	7	0.5
	F	47	+	-	-	-	12	6
	M	65	-	+	-	-	8	0.5
	M	70	-	-	-	+	11	1.5
	M	58	-	-	-	-	12	8.5
	M	60	-	+	-	+	7	21

GROUP II (ΔHF ≤ 0[1])

	F	53	+	-	+	+	4	1
	M	51	-	-	-	-	6	0.5
	M	65	-	-	+	+	4	2
	F	57	+	-	+	+	10	7.5
	F	59	+	+	-	+	9	0.5
	M	64	-	+	+	+	9	0.5
	F	72	-	-	+	+	6	2
	M	71	+	-	+	+	12	1.5
	M	55	-	+	-	-	10	0.5
	F	83	-	+	+	+	11	1.5
	M	40	-	-	-	+	6	5

L9 NDA48-118

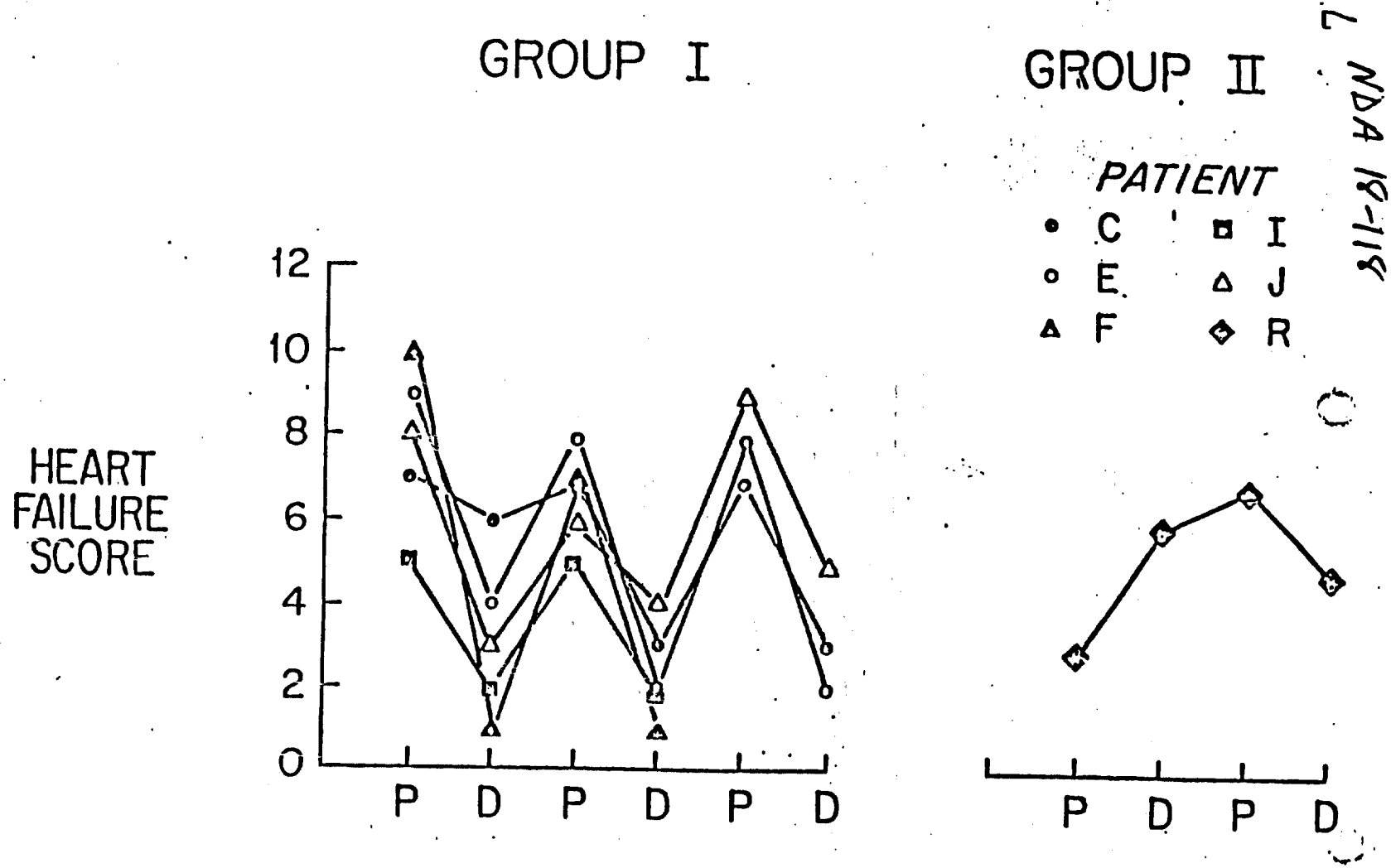
PULMONARY EDEMA[7]	CHRONICITY[8]	NYHA CLASS[9]	DIURETIC GRADE[10]	THIRD HEART SOUND[11]	LVEF[12]	CAUSE OF HEART FAILURE
1	C	III	2	+	0.17	myocardial infarctions
1	M	III	2	+	0.43	myocardial infarctions
1	C	II	3	+	0.19	myocardial infarctions
0	C	III	3	+	0.19	idiopathic cardiomyopathy
1	C	III	2	+	0.07	left ventricular aneurysm[13]
0	C	II	2	+	0.22	left ventricular aneurysm[13]
0	C	III	4	+	0.15	myocardial infarctions[13]
1	M	III	3	+	0.19	idiopathic cardiomyopathy
1	S	III	1	+	0.22	idiopathic cardiomyopathy
3	C	III	4	+	0.15	idiopathic cardiomyopathy[13]
0	C	I	2	+	0.18	myocardial infarctions[13]
2	M	I	3	+	0.24	left ventricular aneurysm
1	C	III	4	+	0.15	myocardial infarctions[13]
1	C	II	1	+	0.14	myocardial infarctions
0	S	I	1	-	0.53	hypertrophic cardiomyopathy[14]
0	M	III	3	+	0.13	idiopathic cardiomyopathy[13]
0	S	I	1	-	0.52	hypertrophic cardiomyopathy[14]
0	C	III	2	-	0.64	hypertrophic cardiomyopathy[14]
1	S	II	3	-	0.67	ischemia [13,15]
0	S	II	3	-	0.24	myocardial infarctions[13]
0	S	II	2	-	0.57	hypertrophic cardiomyopathy[13,14]
1	S	III	1	-	0.22	myocardial infarctions
1	S	I	1	-	0.61	ischemia [13,15]
1	M	III	2	-	0.18	myocardial infarctions
0	M	II	2	-	0.35	idiopathic cardiomyopathy[13]

(See footnotes on following page)

Footnotes to Table 4:

1. $\Delta HF = HF_{placebo} - HF_{digoxin}$, where HF = heart-failure score (Table 1).
2. Diabetic history positive (+) if a fasting glucose >150 mg/dl or persistent glycosuri had been documented.
3. History of typical angina present (+) or absent (-).
4. History of systemic hypertension positive (+) if 2 or more blood pressure recordings of at least 160 mm Hg systolic, 90 mm Hg diastolic, or both had been documented.
5. LVH = left ventricular hypertrophy, defined by a left ventricular posterior wall thickness $\geq$ 12 mm (M-mode echocardiography).
6. Duration = time since first diagnosis of heart failure.
7. Number of episodes of acute pulmonary edema (defined as the syndrome of acute respiratory distress requiring emergency treatment or radiographic alveolar edema) occurring before entry.
8. Chronicity: S = single episode; M = multiple episodes; and C = chronic (persistent symptoms or signs).
9. New York Heart Association Functional Class at entry.
10. Diuretic grade: 1 = less than 40 mg/d of furosemide; 2 = 40 to 80 mg/d; 3 = more than 80 mg/d; 4 = more than 80 mg/d, plus vasodilators or other diuretics (up to 100 mg/d of hydrochlorothiazide considered grade 1).
11. Third heart sound (or summation gallop) present (+) or absent (-) during placebo period.
12. LVEF = resting left ventricular ejection fraction, measured by radionuclide ventriculography.
13. Presence or absence of atherosclerotic coronary artery disease documented by coronary angiography.
14. Concentric left ventricular hypertrophy was the only apparent cause of heart failure.
15. In addition to documented coronary artery disease, the patient had an exercise-induced fall in left ventricular ejection fraction exceeding 0.10.

Fig. 3


GROUP I
GROUP II
PATIENT
C
E
F
I
J
R
HEART FAILURE SCORE
12
10
8
6
4
2
0
P
D
P
D
P
D
P
D
P
D

LEGENDS TO FIGURES

Fig. 3 Repetitive trials of digoxin (D) versus placebo (P). The heart-failure score (HF, see Table 1) is displayed for alternating P and D in 5 Group-I and 1 Group-II patients (see text). Where chest-radiographic data are not available in all repetitions, a modified score, omitting points in the radiographic category, is used (patients E and J). Letters identifying individual patients correspond to the designations in Tables 2 and 4. The displayed order of study periods is not necessarily the actual order of occurrence.