One additional study which lends strong support to the effectiveness of digoxin in some patients with congestive heart is:

Dobbs, S. N.; Kenyon, W. I.; Dobbs, R. J.: Maintenance digoxin after an episode of heart failure: placebo-controlled trial in outpatients. British Medical Journal 1:749, 1977.

This is a baseline and placebo-controlled, double-blind, randomized, crossover study in which 46 clinically stable patients who were receiving digoxin for heart failure were enrolled. 13/46 were in atrial fibrillation, but without history of ventricular rate more than 120. The causes of CHF were ischemic heart disease in 18, rheumatic heart disease in 11, chronic bronchitis and emphysema in 10, hypertension in 5, cardiomyopathy in 1 and SLE in 1. Twenty-eight patients received diuretics throughout the trial. Digoxin dosage was adjusted to provide minimum levels of 1 ug/ml (blood sample taken just prior to the next dose). After titration, patients were kept on a stable dosage for 3 months. They were then randomly assigned to digoxin or placebo for 6 weeks, after which they were crossed over to the other therapy. All other treatment remained unchanged, if possible. At each clinic visit, the patients completed a questionaire and were examined for signs/symptoms of CHF and graded according to NYHA functional class. Body weight, 12-lead ECG, FEV_1, FVC and chest x-ray were obtained. Left ventricular systolic time intervals were studied in a subgroup of 9 patients in sinus rhythm who did not deteriorate on placebo.

16/46 patients clinically deteriorated on placebo and none on digoxin (Tables 1 and 2, page 30). Three developed symptoms, 4 developed signs and 9 developed signs and symptoms of CHF. Deterioration of these 16 patients occurred 4 days to 3 weeks after digoxin withdrawal. Three of these patients showed radiologic evidence of pulmonary edema. Eight recovered rapidly with reinstitution of digoxin and 8 required short-term diuretics in addition to digoxin.

Patients in both groups, i.e., those who developed CHF(n=16) those who did not (n=30) had a significant increases in heart rate and decreases in FEV_1, and FEV_1,/FVC ratio when on placebo. Values (which ones are not stated) returned to baseline levels with reinstitution of digoxin and, if necessary, diuretics. In the 9 patients who did not deteriorate clinically and had systolic time intervals measured, all values were within the normal range on placebo but a significant decrease occurred in QS_2 and LVET when digoxin was resumed and it persisted suggesting a long-term positive inotropic effect.

TABLE I—*Clinical signs and symptoms that were assessed in each patient*

Signs	Grade	Definition	Symptoms	Grade	Definition
(a) Gallop rhythm	1	Absent	(a) Orthopnoea (No of pillows used)	1	<3
	2	Present		2	Between grades 1 and 3
				3	Enough to prop patients up at 90°
(b) Jugular venous pulse	1	2 cm	(b) Nocturnal dyspnoea (No of episodes/week)	1	None
	2	Between grades 1 and 3		2	Occasional
	3	To angle of jaw		3	Every night
(c) Oedema	1	Absent	(c) Ability to climb stairs (No of flights (12 steps) climbed without stopping)	1	≥2
	2	Between grades 1 and 3		2	1
	3	Constantly present		3	<1
(d) Central cyanosis	1	Absent	(d) Ability to walk briskly on flat (Distance walked without stopping)	1	≥100 yards (≥91 m)
	2	Present		2	50-99 yards (45·7-80·5 m)
(e) Tender hepatomegaly	1	Absent		3	<50 yards (<45·7 m)
	2	Present			
(f) Pulmonary oedema	1	Absent			
	2	Between grades 1 and 3			
	3	Extensive crepitations			
(g) Bronchospasm	1	Absent			
	2	Present			

Blood pressure, resting pulse and apex rate, and body weight were also measured.

TABLE II—*Clinical deterioration on placebo*

Case No	Symptom*				Functional classification	Sign*						
	a	b	c	d		a	b	c	d	e	f	g
3	—	—	—	—	—	1 →2(T)	—	—	—	—	1→2(N)	—
8	1 →3(P)	1 →3(N)	2 →3(T)	—	3 →4(T)	—	1 →2(T)	1 →3(T)	—	—	1 →2(T)	1→3(N)
9	1 →2(T)	1 →2(T)	—	—	1 →2(T)	—	—	—	—	—	1 →3(T)	—
10	—	2 →3(T)	—	—	3 →4(T)	—	—	—	—	—	2 →3(N)	—
15	—	—	—	—	3 →4(T)	—	—	—	—	—	2 →3(T)	—
18	2 →3(T)	2 →3(T)	—	—	—	—	1 →2(T)	—	—	—	1 →2(T)	1→2(N)
25	—	1 →2(T)	—	—	2 →3(T)	—	—	—	—	—	—	—
32	1 →3(T)	1 →3(T)	2 →3(N)	—	3 →4(T)	—	2 →3(T)	—	1 →2(T)	—	1 →3(T)	—
35	—	—	1 →3(T)	—	1 →2(T)	—	—	—	—	—	1 →2(T)	—
36	2 →3(T)	—	—	—	—	—	—	—	—	—	—	—
38	1 →2(T)	—	1 →2(T)	—	1 →2(T)	—	—	—	—	—	—	—
39	—	1 →2(T)	—	—	—	—	1 →3(T)	—	—	—	1 →2(T)	—
42	—	—	—	—	—	—	—	—	—	—	2 →3(N)	—
43	—	—	—	—	—	—	—	—	—	—	1 →2(T)	—
44	—	2 →3(T)	—	—	—	—	—	—	—	—	1→2(N)	1→2(N)
45	—	—	1 →2(T)	—	1 →2(T)	—	—	—	—	—	1→2(N)	—

*See table I for definition of grades. Numbers before and after arrows indicate grade before and during placebo phase.
— = No change. (T) = Rapid total recovery after restarting digoxin. (P) = Partial recovery. (N) = No improvement.

The data, collected in blinded fashion, conclusively demonstrates a beneficial long-term effect of digoxin in the treatment of CHF in some patients. Unfortunately, data are not provided as to which patients deteriorated in relation to the cause of CHF. It is possible that the patients who deteriorated the (16/46) included a disproportion of fibrillators (13/46). As no patients with atrial fibrillation had a history of ventricular rate exceeding 120/min. and the mean resting HR, while on placebo (in the group who deteriorated was 88.1 ± 11.3) the development of CHF is likely to have been due more to poor LV function than rate and thus the beneficial effects noted was due to digoxin's positive inotropic rather than negative chronotropic effects. Additional support for this interpretation comes from the investigator's statement that "there was no significant difference between the groups (i.e. those deteriorating and those not) in...cardiac rhythm..." and from a reference to this study by McHaffie, H.; Purcell, P.; Mitchell-Heggs, P. and Guz, A: The Clinical Value of Digoxin in Patients with Heart Failure and Sinus Rhythm, Quart. J. Med. 47:401, 1978, which says 4 of the 16 patients who deteriorated were fibrillators (on page 416: lines 7-10).

Three additional studies which were not performed to determine if digoxin was effective in the long-term therapy of CHF but rather to see whether most patients on digoxin (for whatever reason) really needed digoxin follow. These studies included all patients on digoxin irregardless of initial indication for digoxin. In some cases, it is clear, the drug was started and then continued inappropriately. The data support, in general, the effectiveness of digoxin in a subset of the population for whom the indicated use was appropriate. The studies do establish also, however, that some patients on digoxin for valid indications can not be shown to need or benefit from chronic administration. This to some extent departs from the old "once on digatalis, always on digitalis" philosophy which is reflected in the proposed and current labeling.

(1). Dall, J.L.C.: Maintenance digoxin in elderly patients. British Medical Journal 2:705, 1970.

This was a baseline-controlled study in which 80 patients, 18 men aged 58-99 years (mean 74.3 yrs) and 62 women aged 63-94 years (mean 78.9 yrs), who were on chronic digoxin therapy had digoxin discontinued. At baseline, 53/80 patients were symtomless and 27/80 had symptoms of digitalis intoxication. Patients were observed over 3 months and withdrawal was regarded as successful if signs of cardiac decompensation did not recur. The initial indications for digitalis in the 53 asymptomatic patients were: tachycardia (N=23); cardiac failure (N=12); edema (N=8); hypertension (N=6) and bronchitis (N=4). No information of this type was provided for the 27 patients exhibiting evidence of toxicity. Following digoxin withdrawal, no patients in the tachycardia, hypertension or bronchitis groups had signs or symptoms of cardiac decompensation. Of the 12 patients with the initial indication of cardiac failure, 8 had a history or evidence of coronary disease. Of these latter 8, 4 had reoccurrence of failure, evidence for such not stated, and were restated on digoxin. Also included in the "cardiac failure" group were 3 patients with respiratory infection, and 1 patient with pernicious anemia. None of these 4 patients had reoccurrence of CHF. Of the 8 patients with the initial indication of edema, only one patient had to be restarted on digoxin (reason not stated). This patient had coronary artery disease. The other 7 patients had multiple causes for edema - 2 had varicose veins, 2 had hypoproteinemia and 3 were immobilized due to rheumatoid arthritis or Parkinsonism.

Five of eight patients with coronary disease (4 in the cardiac failure group, 1 in the edema group) had recurrence of CHF following digoxin withdrawal. Although not specifically stated, it appears the CHF resolved with reintroduction of digoxin. Although the majority of patients could have digoxin discontinued successfully, the initial indications for the use of digoxin is questionable in many cases. Of the 9 patients given digoxin initially for congestive heart failure or edema associated primarily with cardiac disease 5 deteriorated and required redigitalization. Thus, the data support the continuous

necessity of digoxin in the long-term management of CHF for only a subset of patients for whom it was clearly indicated. Many patients receiving digoxin chronically, however, perhaps should not be, not only patients in whom it may have been inappropriately begun (the majority of the patients in this study) but also in perhaps half in whom the initial indication was considered appropriated.

(2) Johnston, G. D.; McDevitt, D. G.: Is maintenance digoxin necessary in patients with sinus rhythm? The Lancet 1:567, 1979.

A baseline-controlled therapy withdrawal study was undertaken in 56 patients, 26 males and 30 females with a mean age of 65.2 + 1.1 years, to determine if termination of their digoxin therapy resulted in cardiac decompensation. All patients were in sinus rhythm, had no previous history of atrial tachyarrythmia and did not show any clinical evidence of CHF at the time the study began.

The indications for starting digoxin initially were CHF secondary to ischemic heart disease in 29/56, hypertensive heart disease in 4/56, valvular heart disease in 5/56 and respiratory disease in 1/56. Ten of the 56 had digoxin initiated following myocardial infarction and 7/56 for unknown reasons. The patients were divided into two groups based on their digoxin level; 34/56 had levels less than 0.8 ng/ml and 22/56 had levels between 0.8-2.0 ng/ml. Forty-four of the 56 patients, 27 with digoxin levels less than 0.8 ng/ml and 17 with digoxin levels 0.8-2.0 ng/ml received diuretics throughout the study. Criteria for reintroduction of digoxin therapy were development of CHF, increases in PEP/LVET ratio, or development of atrial fibrillation or tachycardia. Evidence of digoxin effectiveness was if these abnormalities returned to the prewithdrawal state.

Thirty three of 34 patients with digoxin levels less than 0.8 ng/ml were successfully withdrawn from digoxin for at least 3 months. One of the 34 developed 2 episodes of atrial fibrillation requiring reinstitution of digoxin and the rhythm converted to atrial flutter with 3:1 AV block. Seven of 22 patients with digoxin levels 0.8-2.0 ng/ml had a return of signs and symptoms of CHF. Of the 22, only 14 had been given digoxin for CHF and all of the failures were in these 14. Five of the 7 developed atrial fibrillation 2 of those 5 developed concurrent CHF. The other 2 patients (2/7) developed CHF but stayed in sinus rhythm. All 5 patients who developed atrial fibrillation converted to sinus rhythm with reintroduction of digoxin. The two with CHF and sinus rhythm had control of the CHF with reinstitution of digoxin. In these 2 patients, the PEP/LVET ratio returned to the prewithdrawal values. Of the 7 patients who could not be withdrawn, all had a diagnosis of CHF; secondary to ischemic heart disease in 5/7, valvular heart disease in 1/7 and respiratory disease in 1/7.

The data suggest that patients with digoxin levels less than 0.8 ng/ml can be withdrawn from digoxin without ill effects. However, patients with a history of CHF and digoxin levels between 0.8-2.0 ng/ml were not withdrawn so readily. This was especially true if the CHF was secondary to ischemic heart disease as 5/9 could not be successfully withdrawn. An oddity of the study, however, is that 5/7 failures were due to development of atrial fibrillation despite no prior history of it. The two (of seven) who developed CHF but remained in sinus rhythm had diagnosis of valvular heart disease or respiratory disease. These latter facts are unique findings. No other investigators have reported this . The fact that two patients who remained in sinus rhythm required digoxin to control the CHF lends support to the long-term effectiveness of digoxin in the treatment of CHF in some patients.

(3). Fonrose, H.A.; Ahlbaum, N.; Bugatch, E.; Cohen, M.; Genovese, C.; Kelly, J.: The efficacy of digitalis withdrawal in an institutional aged population. Journal of the American Geriatrics Society 22:208, 1974.

A prospective, baseline-controlled, single-blind trial of 31 patients, 28 males and 3 females, aged 64-92 years (mean: 83yrs.) who had been receiving digoxin for at least 12 months were entered to determine the long-term effectiveness of digoxin. Eligibility for the study required digitalization at least 12 months prior to the trial, no evidence of CHF or atrial fibrillation, at the time of the study, no history of PAT or paroxysimal atrial fibrillation, no diagnosis of rheumatic heart disease, normal heart size on chest x-ray and absence of specific ECG changes of left bundle-branch block or recent myocardial infarction. The initial indications for digoxin therapy was CHF in 15 patients, atrial fibrillation in 2 and unknown in 14.

At baseline, prior to digoxin withdrawal, each patient had the following: ECG, chest x-ray, CBC, urinalysis, BUN, serum electrolytes, creatinine and digoxin and 16 patients had a creatinine clearance determined from 24 hour urine collection. Except for creatinine clearance and serum digoxin determinations, all of the above tests were repeated at the end of the 3 week trial. The patients were given placebo in place of digoxin and were clinically monitored every other day for 3 weeks to detect any signs/symptoms of CHF.

The principal signs used to assess cardiac decompenstaion were rales, effusion, hepatomegaly, ascites, neck vein distention and edema.

15/31 patients tolerated withdrawal of digoxin for at least 4 months without evidence of cardiac decompensation. However, 16/31 patients had evidence of decreased cardiac function 1-21 days following digoxin withdrawal. These patients and their symptoms (delected by physical examination) are shown below.

TABLE 2

Reasons for Returning to Digitalis Therapy — 16 Patients

Patient Age & Sex	Signs and Symptoms						No. of Days without Digitalis
	Chest Pain	Gallop Rhythm	Dyspnea	Pulm. Congest.	Venous Dil.	Recurr. Edema	
82F	1	1	1		1		1
86F	1						1
76F				1			1
83F				1			2
72F				1			2
83M				1			2
89F				1	1	1	3
87F				1	1		5
76F			1	1			5
84F		1		1		1	6
82M				1	1		7
81F			1		1	1	8
84F				1	1	1	9
70F		1					11
87F		1		1	1	1	15
86F		1		1	1	1	21

Following reinstitution of digoxin 0/16 patients had to be hospitalized. It is presumed that this indicates a resolution of the CHF. Using such a "soft" endpoint detracts from the study findings.

The recurrence of signs/symptoms of CHF within 48hrs. of digoxin discontinuation in 6 patients is difficult to explain. The long serum half-life of digoxin (36 hrs with normal renal function and longer with decreased renal clearance or increased age) and clinical experience suggest that it is uncommon to note such a rapid deterioration of cardiac function in patients who are clinically stable as these were supposed to be prior to the study.

No information is provided describing which patients, if any were receiving diuretics during the trial. We also cannot tell which of the patients who deteriorated were those put on digoxin initially because of CHF. Each of these variables could theoretically have directly influenced (biased) the outcome.

It should be noted that this study excluded patients who had current symptomatology of heart failure including increased heart size on chest x-ray. The effectiveness of digoxin in the treatment of ~~such a~~ selected subpopulation may be different than a symptomatic subgroup with cardiomegaly.

This study was not well controlled to avoid observer bias. This probably explaind why 6/16 patients developed CHF within 2 days of withdrawal. Even discarding the 6 patients with early symptoms, we are still left with a significant number of patients (10/31) who developed CHF. Five of the 6 with early CHF developed only 1 sign/symptom; whereas, 9/10 patients developing CHF later (3-21 days) had 2-4 signs/symptoms. It is possible the MD's "overread" the signs/symptoms of CHF and placed these six patients on digoxin prematurely or even placed some on digoxin who did not need it. Nothing is reported concerning the findings at baseline or after resumption of digoxin. No objective measurements (e.g. weight, chest x-ray, etc) were reported. The use of baseline control would have been more convincing if the baseline physical examination and other laboratory parameters (e.g. chest x-ray, ECG,etc) had beem reported at both time points and the observer(s) blinded. This would have avoided the potential for bias in overdiagnosing recurrent CHF and provided better evidence of worsening of CHF. With these reservations, 10-16/31 patients (depending whether the 6 patients relapsing within 48 hrs. are counted) required reinstitution of digoxin for recurrent CHF, if the findings and the "soft" endpoints used are accepted. This data is supportive of the long-term effectiveness of digoxin in CHF at least for a significant proportion of patients (i.e. 1/3-1/2 of them).

Two additional studies which do not demonstrate the effectiveness of digoxin in the subsets of patients studied follow:

(1) Hull, S. M.; MacIntosh, A.: Discontinuation of maintenance digoxin therapy in general practice. The Lancet 2:1054, 1977.

A baseline-controlled therapy withdrawal study was performed in 17 patients, 7 males aged 56-83 years and 10 females aged 60-97 years to determine if patients on chronic digoxin for CHF could be maintained without digoxin. The study was not designed to determine whether digoxin was effective, but rather to see if alternative management, such as adding or increasing diuretics, could be successful in these patients.

Seven other patients were enrolled but dropped, as six had atrial fibrillation and 1 had a ventricular aneurysm and refractory CHF and digoxin could not be discontinued. The original indications for digoxin in the remaining 17 patients were: left ventricular failure (LVF) in 7/17; congestive cardiac failure (CCF) in 7/17; palpitaions in 1/17, paroxysmal supraventricular tachycardia (SVT) in 1/17 and unknown in 1/17. Patients had been on digoxin for 3 months to 11 years. 12/17 were on diuretics at the start of the trial. All

patients tolerated digoxin withdrawal and 1/17 with either LVF or CCF required no ~~further~~ medications for control of the disease process. 9/17 required initiation of or increased doses of diuretics for control of LVF or CCF. The 2 with palpitations or SVT required a beta-blocking agent with/without a diuretic.

This study does support the effectiveness claim for digoxin in the long-term management of CHF in that 9/17 patients required additional diuretics to control their CHF. However, the study again shows that many patients (7/17) on chronic digoxin can have digoxin discontinued without any ill effects and that an additional subset of patients can be managed with increased doses of diuretics and their digoxin discontinued. The study did not include any patients with CHF who could not be managed without digoxin, (1 patient with a ventricular aneurysm and refractory CHF was excluded) under the conditions of the study, during which, presumably, there were no acute intercurrent illnesses superimposed on the patient's steady state.

(2) McHaffie, D.; Purcell, H.; Mitchell-Haggs, P.; Gug, A.: The clinical value of digoxin in patients with heart failure and sinus rhythm. Quarterly Journal of Medicine (New Series) 47:401, 1978.

This was an unusual combination parallel-crossover study design in which six patients were entered; 4 men aged 48-71 years and 2 women aged 40 and 59 years, all with clinical evidence of CHF and in sinus rhythm. Three of the 6 had CHF secondary to myocardial infarction (MI) and 3/6 had CHF due to congestive cardiomyopathy. Prior to the study, all patients were diuresed to "dry" weight with furosemide. After diuresis, a variable degree of exercise intolerance persisted and 4/6 still had a cardiothoracic ratio greater than 0.5. At the time of study 3/6 were maintained on digoxin and diuretics (2 MI patients and 1 cardiomyopathy patient) and 3/6 on diuretics only (2 cardiomyopathy patients and 1 MI patient). Diuretics were employed throughout the study.

The study employed both subjective and objective observations. Subjective assessment was based on changes in symptoms related to vascular congestion and exercise capacity using a visual analog scale. Measurements included various laboratory tests and a bicycle ergometer in which workloads were increased every 4 minutes until 85% maximal heart rate for age or the workload was 5 watts below what had previously stopped the test (chest pain, excess fatigue, breathlessness). The maximum level of exercise was established by testing prior to the study. In three patients, digoxin and diuretics were administered for weeks 1 and 2 and weeks 7-12 with diuretics only during weeks 3-6. The other 3 patients received diuretics only on weeks 1 & 2 and 7-12 and digoxin and diuretics during weeks 3-6. (Whether weeks 1 and 2 and 7-12 represented the usual treatment for each patient group or whether patients were randomly assigned to these treatment schedules is not clear.) Exercise testing and other laboratory tests were performed on weeks 1, 2, 5, 6, 11 and 12.

Five patients completed the trial. One completed the first pair of tests but was withdrawn after digoxin was discontinued as he developed frequent VPC's and angina. This patient was presumably redigitalized with amelioration of signs and symptoms but information is lacking on this point. Subjectively 5/6 patients did not note a beneficial effect of digoxin. Objectively, no difference was noted in heart rate, jugular venous pressure, cardiothoracic ratio, FEV_1, FVC, FEV_1/FVC ratio or other laboratory tests. Average systolic BP (lying and standing) was 10 mm/Hg higher with digoxin. The only possibly favorable effect of digoxin was a lower body weight and ECF volume in 4/5 patients on digoxin. This appeared to be a real finding, as weight rose then fell when digoxin was stopped and restarted. When digoxin was started, weight and ECF volume decreased and then rose when digoxin therapy was stopped.

There was no difference in the amount of work performed whether or not the patient was on digoxin. The serum digoxin levels were in the therapeutic range at all testing intervals, when the patients were receiving digoxin. Statistical analysis comparing heart rate, respiratory rate, ventilation and respiratory quotient at each level of exercise for each patient did not demonstrate a difference between treatments, although the small sample size would require a large difference in order to be detected.

Although no significant difference was noted with digoxin therapy, there are several aspects of the study which preclude its acceptance as establishing general lack of effectiveness. First, only 3 patients clinically required digoxin prior to the study (this is too small a group for generalization to all patients). Second, the patients workloads were limited since they were not permitted to exercise to the usual endpoint of exercise tolerance (i.e. fatigue, breathlessness, etc). Third, 3/6 patients had congestive cardiomyopathy and this process has been noted to be particularly difficult to manage with digoxin. The study did demonstrate consistent with the previous studies that subsets of patients exist who have heart failure and are unresponsive to digoxin. This study underlines the point made by each of the other studies, namely that not all patients with signs and symptoms of CHF can be expected to benefit from long term digoxin treatment.

Other Studies:

In 3 of the 4 additional studies which the sponsor submitted to support the congestive heart failure indication for digoxin the studies demonstrate hemodynamic and electromechanical effects as well as effects on heart size in patients with heart disease but without symptoms or signs of heart failure. In the 4th study, a 1949 early right heart catherization study in 5 patients judged to have "pure" left-sided failure ("this type of case is difficult to find. .") The patients were symptomatic (study antedates thiazide or even carbonic anhydride inhibitor diuretics), although none had rales. The data presented is again mainly hemodynamic with clinical findings reported only incidentally as summary statements.

The authors summaries of these 4 studies follows:

(A) Harvey, R. M.; Ferrer, M. I.; Cathcart, R. T.; Richard, D. W. and Cournard, A. Some Effects of Digoxin upon the Heart and Ciculation in Man. Am. J. Med. 7:439, 1949.

1. The early effect of intravenous digoxin is studied by the cardiac catherization procedure in five patients with left-sided heart failure.

2. Digoxin produced a significant rise in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure in each of these five patients. These changes were effected without alteration in the right ventricle end diastolic pressure and therefore cannot be ascribed to an action of the drug upon the systemic venous system but rather are interpreted as an action of digoxin upon the myocardium.

3. Similar changes in cardiac output, stroke volume and pulmonary arterial pressure were observed in a patient with left ventricular failure after the peripheral resistance had been lowered by quinidine.

4. The tentative conclusion can therefore be reached that regardless of the cause of the stroke volume increase--myocardial action or a reduction in peripheral vascular resistance--the pulmonary congestion in six patients with left ventricular failure was relieved as a result of more satisfactory emptying of the left ventricle.

5. The conclusion that ventricular ejection and ventricular filling are mutually dependent upon the functional state of the myocardium seems inescapable.

6. As a contrast to the patients with left ventricular failure the effect of digoxin upon pulmonary blood flow and blood pressure in a patient with cor pulmonale is presented.

(B) Carliner, N. H.; Gilbert, C. A.; Pruitt, A. W. and Goldberg, L. I. Effects of Maintenance Digoxin Theraphy on Systolic Time Intervals and Serum Digoxin Concentrations. Circulation 50:94, 1974.

Systolic time intervals (STI) and serum digoxin concentrations (SDC) were measured in eight patients with compensated atherosclerotic and/or hypertensive heart disease who received oral digoxin 0.25 mg/day or 0.5 mg/day for alternate two-week periods without a loading dose. Control data were obtained both before and after the four week of treatment. After 13 days treatment with digoxin, 0.5 mg/day there was a significant

decrease in total electromechanical systole corrected for heart rate (QS_2I), pre-ejection period (PEP), pre-ejection period corrected for heart rate ($PEP)_I$) and PEP/left ventricular ejection time (LVET). After the thirteenth dose of 0.25 mg/day there was significant shortening of (PEP_I) and PEP/LVET. Shortening of QS_2I correlated significantly with SDC 24 hours after the thirteenth dose of 0.5 mg. These data suggest that after 13 days of treatment with 0.25 and 0.5 mg/day of digoxin a positive inotropic effect occurs as reflected by STI shortening. A greater effect was recorded with the 0.5 mg dose.

(C) O'Rourke, R. A.; Henning, H.; Theroux, P.; Crawford, M. H.; Ross, J. Favorable Effects of Orally Administered Digoxin on Left Heart Size and Ventricular Wall Motion in Patients with Previous Myocardial Infarction. Am. J. Cardiol 37:708, 1976.

The effects of maintenance oral digoxin therapy on segmental left ventricular wall motion (wall motion videotracking) and left heart size (radiographic left heart dimension) were evaluated in 14 patients with a prior myocardial infarction but without clinical signs or sypmtoms of congestive heart failure. The left heart decreased in all six patients with cardiomegaly from an average of 55.0 ± 1.6 (standard deviation) to 52.2 ± 2.7 mm/m^2 body surface area (P less than 0.01) during digoxin therapy. However, there was no significant change in the eight patients with normal heart size. In the resting state, the average extent of shortening in normal segments increased significantly from 3.1 ± 0.8 to 4.2 ± 1.2 mm during digoxin therapy. During submaximal handgrip exercise, the extent of shortening in normal segments at rest and during handgrip exercise were similar. In all 14 patients, there was a decrease in the number of segments with abnormal wall motion at rest or with handgrip exercise during digoxin therapy. With therapy, the number of abnormal sites decreased from 52 to 35 in the resting state and from 84 to 49 during handgrip exercise. Thus, in patients 6 or more months after transmural myocardial infarction, orally administered digoxin decreases cardiomegaly, increases the extent and maximal velocity of shortening in normal left ventricular segments and often reduces the extent of abnormal wall motion at rest or during isometric exercise.

(D) Kleiman, J. H.; Ingles, N. B.; Daughters, G. II; Stinson, E. B.; Alderman, E. L. and Goldman, R. H. Left Ventricular Dynamics During Long-Term Digoxin Treatment in Patients With Stable Coronary Artery Disease. Am. J. Cardiol. 41:937, 1978.

Ten patients with stable coronary artery disease who did not have clinical congestive heart failure and had recovered (3 or more months) from coronary bypass graft surgery were given both intravenous and oral digoxin. Left ventricular performance was assessed weekly for 3 control weeks, during 4 weeks of long-term oral digoxin treatment, and during 2 to 3 weeks of recovery. Serial noninvasive measurements of velocity of circumferential fiber shortening, ejection fraction, end-diastolic volume and cardiac output were obtained with computer-assisted fluoroscopic analysis of the motion of surgically implanted mid wall myocardial markers that outline the left ventricular cavity. During 4 weeks of oral digoxin therapy, mean serum digoxin levels were maintained betweem 1.2 ± 0.1 and 1.4 ± 0.1 ng/ml (mean ± standard error of the mean). Mean velocity of circumferential fiber shortening increased 15.6 percent from 0.65 ± 0.05 to 0.75 ± 0.05 circumferences/sec (P less than 0.001) and ejection fraction increased 8.5 percent from 0.51 ± 0.03 to 0.55 ± 0.03 (P less than 0.001). End-diastolic volume and cardiac output were not changed significantly. The inotropic response to oral digoxin was similar during the 4th week of treatment to that seen during the first week, and the mean inotropic effect of chronic oral digoxin was not significantly less than that achieved by administration of 1 mg intravenouly over 15 minutes. These data suggest that chronic oral digoxin treatment exerts a sustained inotropic effect on the nonfailing heart that persists for at least 4 weeks and is equivalent to that achieved with rapid intravenous digitalization.

It is concluded that although these studies support the positive inotropic effect of digoxin on the heart they do not directly address the question of the usefulness of digoxin in treating patients with congestive heart failure.

CONCLUSIONS:

The studies, taken as a whole, provide adequate evidence of the short-term and long-term effectiveness of digoxin in improving cardiac function in patients with CHF and in selected patients of improving their signs and symptoms of CHF.

As several of these studies demonstrated, digoxin tends to be given in situations where the signs and symptoms of CHF may be due to other conditions. Digoxin tends to be continued, however, without critical assessment of its initial efficacy or of the benefit of continuing it. In addition, these studies show that in a large proportion of patients with unequivocal CHF which is improved hemodynamically by digoxin, it is not possible to demonstrate improvement in signs or symptoms of CHF. The low therapeutic index for digoxin, especially in

the elderly, means that we probably need to change recommended usage patterns currently in the package insert and that the optimum use of digoxin involves periodically reassessing the benefits from the continuing use of digoxin. If there is a question regarding the use of digoxin for CHF in a particular patient a careful trial of withdrawal should be attempted if it can be accomplished safely by insuring that patients are well informed and are followed closely.

It is clear that the introduction of new agents with effects on other parts of the cardiovascular system, kidneys and central nervous system as well as drugs with positive inotropic effects will lead to continuing assessment of the role of digoxin in treating CHF. It is not clear however, that the long-term risk benefit ratios of digoxin versus alternative treatment with diuretics alone or a combination of digoxin and diuretics has been adequately assessed.

VENTRICULAR RATE CONTROL

There are three primary studies demonstrating the effectiveness of digoxin to control ventricular rate in patients with atrial fibrillation.

1. Gold, H.; Cattell, M.; Greiner, T.; Hanlon, L. W.; Kwit, N. T.; Modell, W.; Cotlove, E.; Benton, J.; Otto, H. L.: Clinical pharmacology of digoxin. J. Pharmacol Exp. Ther. 109:45, 1953.

This is an open-label, baseline-controlled study of 17 patients, 11 females and 6 males, ranging in age from 37-73 years (mean 55 years) with atrial fibrillation and varying degrees of CHF. The cardiac diagnoses was rheumatic valvular in 8 patients, arteriosclerotic heart disease in 4 and hypertensive heart disease in 5. The patients were placed at bedrest and their ventricular rates counted and recorded several times per day for several days until the rates remained fairly constant. With few exceptions, only patients with rapid ventricular rates, 100/min, were included. Patients were then given digoxin 1.2 mg intravenously or orally and ventricular rate monitored to determine the time of maximal drug effect and duration of effect. One-half of the patients received digoxin IV then orally with the sequence reversed in the other half. When the ventricular rate returned to control levels, the other dosage form was administered.

In another phase of the study, 30 patients with atrial fibrillation and ventricular rates exceeding 100/min on no digoxin were placed on randomly varied doses of digxoin for 4 week periods to determine the effects of maintenance doses on ventricular rates. The doses utilized were 250, 500, 750, 1000 and 1500 ug per day. The patients' ventricular rates were counted at weekly intervals after sitting for 30 mins,. and the means of the weekly rates calculated. At the end of 4 weeks, the patients were placed on another dose of digoxin and this sequence repeated.

The acute study (see figure 1, page 43) demonstrated that the effect of 1.2 mg of digoxin IV appears more rapidly than 1.2 mg given orally. The ventricular rate fell from @ 108 to 80 in 15 minutes and under 70 within the first hour following I.V. administration. By contrast it took 5 hours to reduce the ventricular rate to under 80 and the rate never fell below 70. Interestingly enough the peak effect from both routes of administration occurred at about 7 hours. Based upon the ventricular rate response to the different oral digoxin doses, the authors conclude that only 65% of an oral dose is absorbed into the systemic circulation. Studies done 20 years later with the radioimmune assay for digoxin confirm this conclusion and the sensitivity and accuracy of the ventricular rate response in patients with auricular fibrillation as a bioassay for digoxin.

Digoxin was effective, on a chronic basis, in controlling ventricular rate in the 30 patients studied. Utilizing doses ranging from 250-1500 ug/day, a dose-response curve was constructed (see figure 4, page 43). Using as an end-point, ventricular rate below 85/minute to demonstrate effectiveness, a 250 ug/day dose controlled ventricular rate in 25% of the patients, 500 ug/day controlled 50% of the patients, 750 ug/day was effective in 75% but an increase to 1500 ug/day only controlled another 10% (see figure 5). Doses of 250-750 ug/day resulted in toxicity in 4% of the patients whereas a further increase caused a dose related increase in toxicity (nausea and/or vomiting) as can also be seen in figure 5, page 43, with a 75% incidence of toxic effects at the 1500 ug/day dose).

This study adequately demonstrates the effectiveness of digoxin in controlling ventricular rates in patients with atrial fibrillation both on an acute and a chronic basis. Although patients in the acute phase had varying degrees of heart failure, not described, keeping them at bedrest for several days prior to the study helped to avoid the confounding effects of increased ventricular rate secondary to CHF as diuresis and lessening of failure symptoms were apt to occur in this period. Also, the fact that stabilizing the ventricular rates was an objective of the control period probably adequately controlled for the problem of an independent effect of CHF on ventricular rates. Further support of digoxin's effectiveness was demonstrated by the maintenance study in which a dose related decrease of ventricular rate occurred. As the ventricular rate was counted weekly for 4 weeks on each dose for each patient, the results provide conclusive evidence of ~~a negative chronotropic effect~~ effect on A-V conduction. Thus, this study is adequate and well controlled and demonstrates effectiveness of digoxin to control ventricular rates in patients with atrial fibrillation.

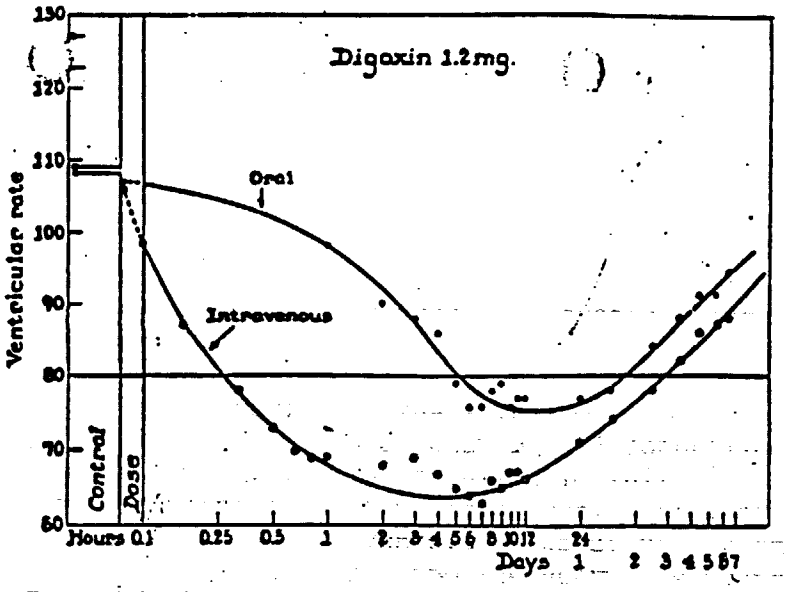


FIG. 1. Curve of development and disappearance of digoxin action in patients with auricular fibrillation.

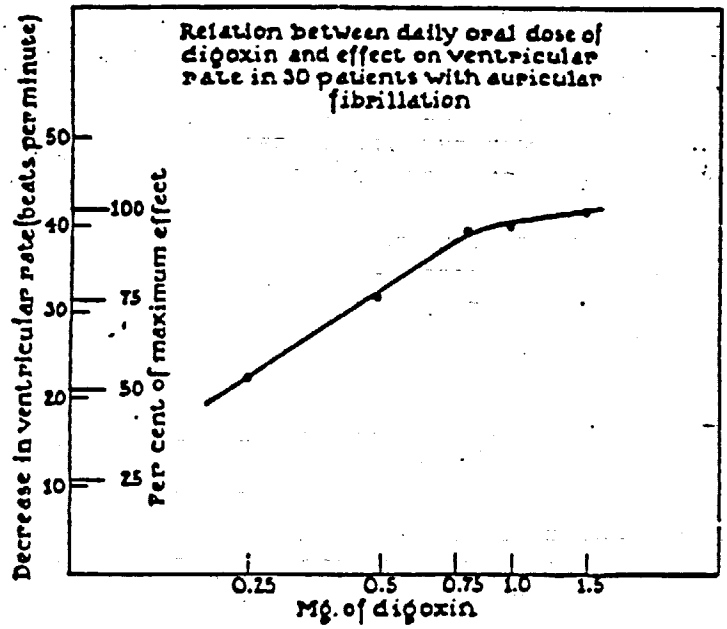
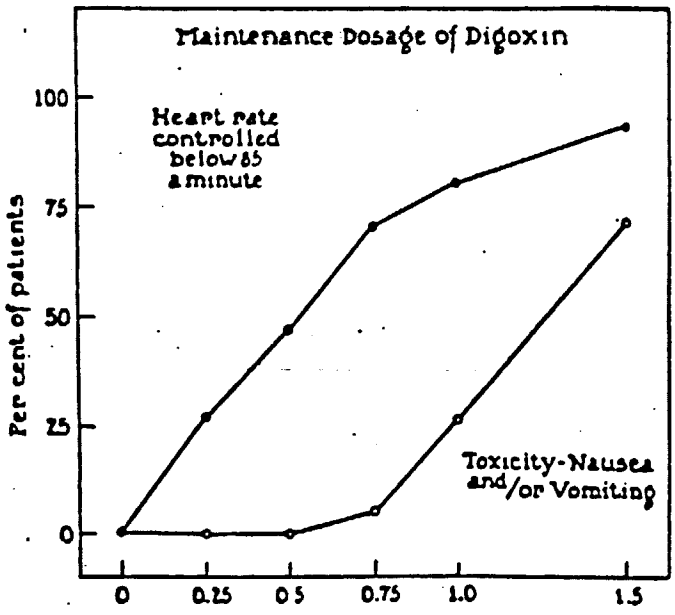


FIG. 4. Dosage-response curve for digoxin. Note that doubling the dose from 0.25 to 0.5 mgm. (condition in which heart rate is fairly rapid) causes a 50 per cent further slowing of the rate, while doubling the dose from 0.75 to 1.5 mgm. (condition in which heart rate is fairly slow) results in negligible further slowing.



2. Redfors, A. The effect of different digoxin doses on subjective symptoms and physical working capacity in patients with atrial fibrillation. Acta Med. Scand. 190:307, 1971.

Redfors, A. Digoxin dosage and ventricular rate at rest and exercise in patients with atrial fibrillation. Acta Med. Scand. 190:321, 1971.

These two reports are of different aspects of a single-blind, baseline controlled study in which 14 patients, 9 males and 5 females, with atrial fibrillation (AF) were used to evaluate the effects of increasing digoxin dosage on ventricular rate. 7/14 had rheumatic heart disease (RHD) and 7/14 had other, not well described, causes for AF. The mean age was 54.9 years (range 32-68 years) and weight was 75.9 ± 11.1 Kg for all 14 patients. The patients with RHD were somewhat younger and weighed less than those without RHD (51.7 vs 58.1 years and 66.4 ± 3.9 vs 85.3 ± 6.8 Kg, respectively). Six additional patients, 3 with RHD and 3 with idiopathic AF, with similar ages and weights as the major group were used as "parallel" controls. However, there is no evidence that patients were randomly assigned to the treatment or control group and a paucity of evidence that they were demographically comparable or were treated the same otherwise. The control group had been receiving digoxin 375 ug by mouth daily for at least 14 days (mean 11 months). 3/14 in the treatment group had not received digitalis prior to the trial but 11/14 had been receiving digoxin in unchanged doses for at least 14 days (mean 10 mos.) prior the study.

Placebo tablets were not used in this study and in patients already digitalized digoxin was not stopped completely. In an effort to reduce bias, different colours of digoxin tablets were utilized and patients were not informed of their exact dosage although they were aware of the general design of the study which was to "optimize" their dosage by first lowering it and then raising it while evaluating their response by different tests ("new and older"). Control patients were told the same thing, but unbeknownst to them they were left on their previous dose although different colored tablets were substituted every 2 weeks. No diuretics were used concomitantly. Eight patients were treated with anticoagulants.

The control group was maintained on 375 ug/day throughout the trial using blinded tablets in order to determine if any findings of the study could be related to familiarity with the trial or to training effects. The treatment group had their digoxin dose reduced to or started at 125 ug daily. The doses of digoxin were systemically increased at 14 day intervals to 250, 375, 500, 750 and 1000 ug daily or until manifestations of digoxin toxicity occurred. Toxicity was diagnosed when GI, cardiac or other signs/symptoms developed and then disappeared when the dosage was reduced. At baseline, with the

patients on a stable digoxin dose, or not on digoxin for the 3 undigitalized patients, a history, physical and x-ray examination, routine laboratory screen, ECG at rest and exercise, phonocardiography, ultrasoundcardiography and 8-10 hour Holter monitor were obtained. On the 14th day of each dosage, repeat examination and testing was performed. An, 8-10 hour Holter monitor was obtained on the 13th day. The exercise test utilized a bicycle ergometer, patient sitting, with the workload changed every 6 minutes. The workloads for women were 100, 200, 300, 400 kpm/min and 150, 300, 450, 600 kpm/min for men.

After 14 days of 125 ug daily, the resting ventricular rates, in the 3 previously undigitalized patients, were reduced by 12 beats/min. At this dosage level the mean resting ventricular rate for the 14 patients was 78/min. When the dosage was increased to 250, 375 and 500 ug daily, the mean ventricular rate further decreased to 69, 65 and 60 beats/min. The 7 patients who tolerated higher dosages demonstrated further reductions in ventricular rate. (see Fig. 2, page 46). An "optimal" dose was determined for each patient based on symptoms, physical work capacity and the toxic dose. The mean "optimal" dose for the 14 patients was 440 ug/day (range 250-750 ug/day). This dose resulted in a mean ventricular rate of 61/min (range 47-75/min). As expected, there was considerable variability between patients for "optimal" dose and resultant ventricular rate.

There was a significant decrease in ventricular rate on excercise with each dosage level increase. (see Fig. 5, page 46).

Again, the ventricular rates were variable between patients at each dosage level. Each patient had their own characteristic rate throughout (e.g. those with high rate maintained a high rate even though it was significantly reduced and those with a low rate correspondingly retained the low rate). The dose response curves during exercise demonstrated a positive relationship between dose and reduction of ventricular rate with the effect most pronounced at medium work loads. (see Fig. 6, page 46).

An interesting contrast to the CHF studies is seen in this study in that subjective improvement in dyspnea and fatigue in patients with auricular fibrillation seemed proportionally greater and a more consistent finding. Exercise tolerance also was consistently improved in these patients as compared to only about half the patients with CHF in the previous studies. The lack of rigorous blinding casts some doubts on these observations, but the author's description of his attempts to deal with that source of bias are fairly reassurring. In addition the study by Arnold, et al, of patients with CHF was unblinded and only 5/9 patients experienced symptomatic improvement on digoxin.

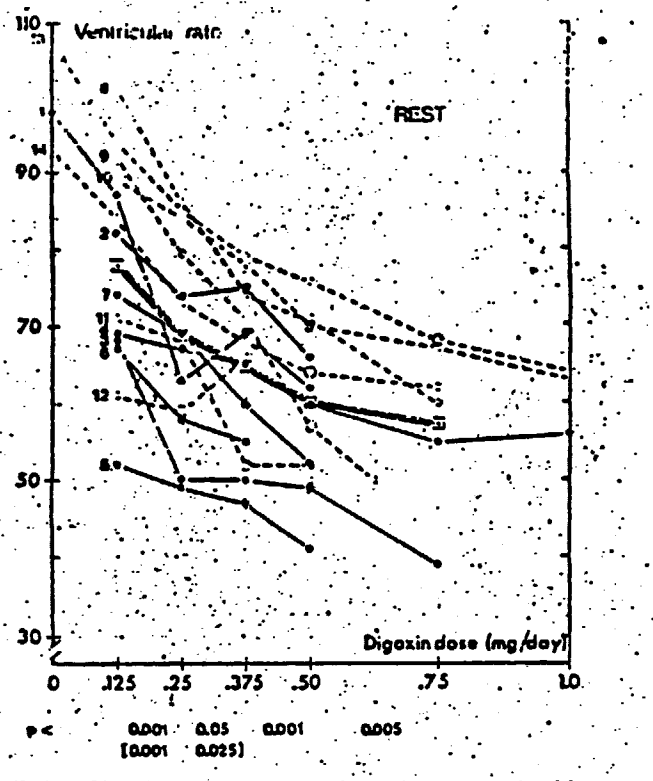


Fig. 2. Ventricular rate at rest in patients treated with increasing digoxin doses. Figures at beginning of the curves denote patient numbers; p = significance of the differences between adjacent examinations; the significances when patient 12 is excluded from the calculations are shown in brackets. ●—● patients with RHD; ○--○ patients without RHD; ⊡—⊡ mean of all patients; ⊙ or ○ = ventricular rate at "optimal" doses.

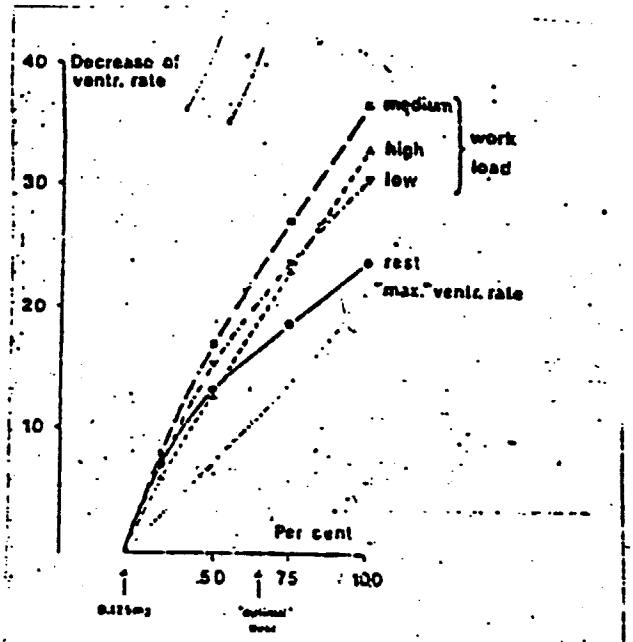


Fig. 6. Decrease of ventricular rate at rest and exercise at increasing digoxin doses expressed as percentage of the toxic doses. Mean values of 13 patients. (Patient 12 excluded.)

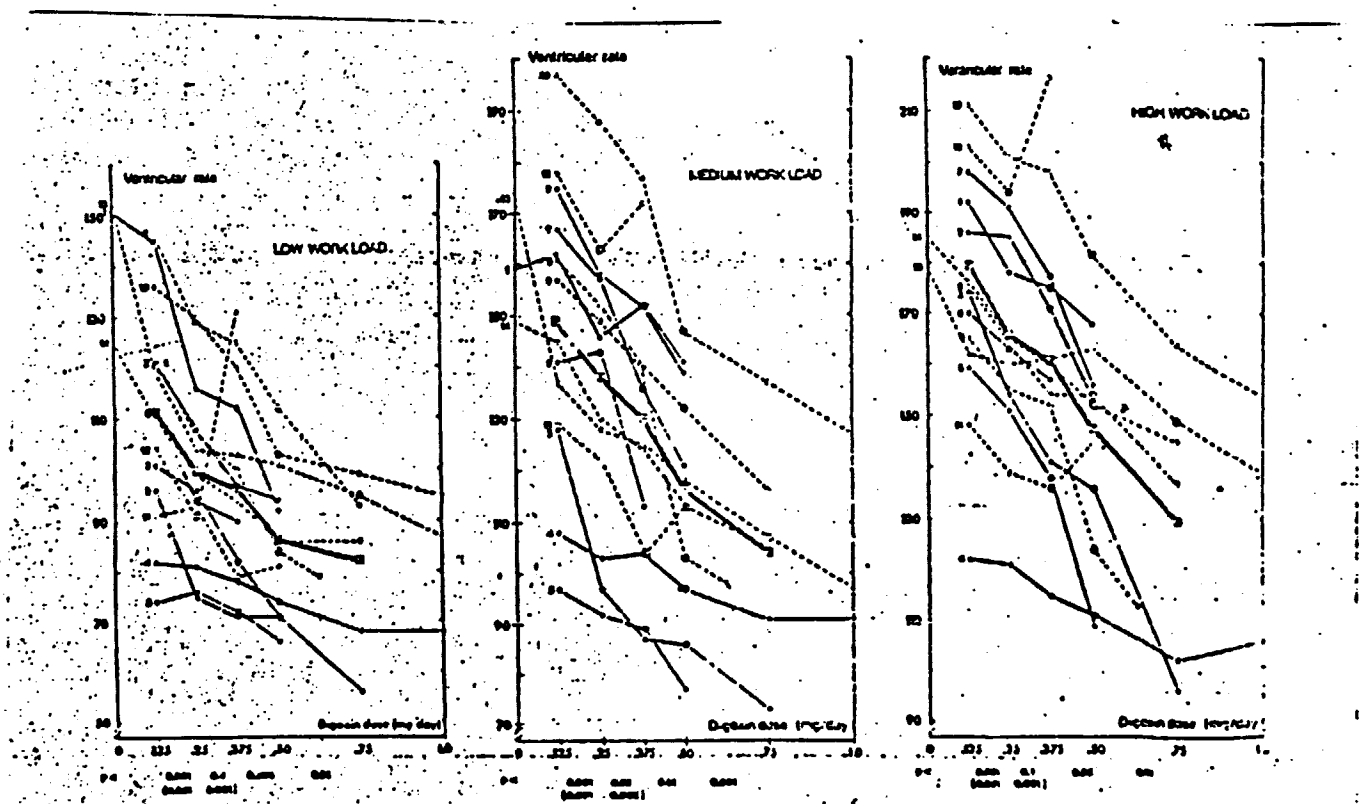


Fig. 5. Ventricular rate at low, medium and high work load = 200–300, 300–450 kpm/min. High work load = 300–

This study provides evidence that digoxin is effective in controlling ventricular rate, subjective symptoms and exercise tolerance in patients with atrial fibrillation. These effects were noted in all dosages employed at rest and with exercise. The control patients did not demonstrate similar findings throughout the trial and were tested identically to the test group. This lends support to the conclusion that the results were not due to training, familiarity with the study or some other artefact introduced by the study. This study did not attempt to directly assess the control of ventricular rate with chronic maintenance treatment. The study, however, by design did evaluate in each patient in the trial for at least 2 months the effects of increasing doses of digoxin. Ventricular rate, symptoms and exercise tolerance were continually reduced with each dosing increase. This is taken as adequate evidence of the continued effectiveness of chronically administered digoxin in controlling auricular fibrillation.

3. Wang, R.; Camin, J.; Ward, D.; Washington, H. and Martin, A. Treatment of chronic auricular fibrillation in the elderly, assessed by ambulatory electrocardiographic monitoring. J. Am. Geriat. Soc. 28:529, 1980

This is an unblinded, placebo (100 mg vitamin C/day), pindolol 5 mg t.i.d., verapamil 40 mg t.i.d., digoxin 1.0 mg loading dose followed by 125 mcg/day, and digoxin 125 mcg/day plus pindolol 50 mg t.i.d. treatment comparison. Ten elderly patients entered the study (63-85 years of age, mean 73 years); 8 completed it (5 men and 3 women)(1 withdrawal for intolerance to pindolol and 1 to verapamil). All of the patients had chronic atrial fibrillation. None had significant valvular heart disease. All had normal thyroid function tests. They had normal serum urea nitrogens. Seven were receiving digoxin and 1 oxprenolol at the time they were selected for the study.

Drug administration was for 1 week each in the fixed sequence outlined above. Preceeding the placebo period was 1 week of no treatment. There was no other washout period built into the study. Blood levels of pindolol and digoxin were measured on the last day of the 3 treatment periods during which they were administered. They were pindolol 5.6 ± 4.2 (S.D.) ng/ml when given alone and 9.0 ± 8.1 ng/ml when given with digoxin. Digoxin levels were 1.7 ± 0.52 nmol/l at the end of the 1st week (given alone) and 1.01 ± 0.54 nmol/l one week later when given with pindolol. Patient compliance was assessed by pill counts.

Five 24 hour continuous ECG tape recordings were made (1 each on the last day of each treatment period). The recordings were started at 10 a.m. and analysis of the recordings was made on 3 - 5 hour periods from each 24 hours record: the period 10 a.m. to 3 p.m. during which the subjects followed a standardized (supervised) activity schedule;

the period 3 p.m. to 8 p.m. during which activity was not controlled and the period from 12 midnight to 5 a.m. while the patients were asleep. Maximum and minimum heart rates were obtained for each period from a calibrated avionics trend recording. The average heart rate and ectopic counts were obtained from the Pathfinder counter system. ANOVA was used to evaluate recording period, treatment period and patient effects.

In this comparison digoxin did very well. Maximum, minimum and average heart rates were significantly lower on digoxin than on placebo or verapamil. There was a trend for lower rates with digoxin alone than with pindol (except for maximum rate)(no differences were statistically significant) and for the combination of digoxin and pindolol than with either drug alone (all rates were lower on the combination)(3 out of the 9 possible comparisons reached statistical significance). Pindolol was also effective in reducing all three rate assessments when compared to placebo and verapamil. The ventricular ectopic rate on all treatments was not significantly different. The ANOVA showed that the standardized activity period (10 a.m. to 3 p.m.) produced the most pronounced effects on maximum, minimum and average heart rates. No statistically significant drug effects could be demonstrated during the sleep period (12 M to 5 a.m.) although the trends were still apparent.

This study demonstrates that oral digoxin and pindolol are effective for controlling the ventricular rate in patients with A-F, but that oral verapamil at 40 mg t.i.d. is no better than placebo. ~~Although~~ The study has several limitations; i.e. only 8 patients completed the 5 treatments; the treatments were each only 1 week in duration; there were no washout periods between treatments; and the drugs were given in a fixed sequence. It also had several off setting strengths; i.e., the efficacy variable (HR) was reasonably objective; one of the evaluation periods (10 a.m. - 3 p.m.) was standardized, and there were both placebo ~~negative~~ and positive control drugs for comparison. Although under the conditions of the study, one can not assume steady state conditions were reached on any treatment or that any conclusions about relative efficacy can be made. The study does offer substantial evidence of the effectiveness of digoxin in reducing the ventricular rate of patients in auricular fibrillation.

The preceeding 3 studies do not assess the effectiveness of digoxin in other supraventricular tachyarrythmias having rapid ventricular response rates (e.g. atrial flutter, paroxysmal atrial tachycardia). There is little reason to suspect a difference in responsiveness to digoxin in these settings which can be considered in a sense variants of auricular fibrillation in which the auricular rate is slower with different degrees of A-V block. As such the data on auticular fibrillation is considered to also provide evidence of effectiveness for these indications.

There is an additional study which deals with the use of digoxin in paroxysmal supraventricular re-entrant tachycardia.

Wellens, H. J. J.; Dilren, D. R.; Liem, K. L. and Lie, K. I. Effect of digitalis in patients with paroxysmal atrioventricular nodal tachycardia. Circ. 52:779, 1975.

This study was an investigation of the effect of intraatrial injection of ouabain and oral digoxin on AV conduction, VA conduction and the ability of programmed electrical stimulation to initiate supraventricular tachycardia in 15 patients suffering from recurrent attacks of paroxysmal atrial tachycardia. Two of the 15 patients had an accessory pathway of conduction from the ventricle to the atrium during tachycardia. In the remaining 13 the re-entry circuit from ventricle to atrium was through the A-V node.

During sinus rhythm and tachycardia 12 patients showed a normal QRS, two showed complete right bundle branch block and one complete left bundle branch block. None of the patients showed electrocardiographic evidence of the Wolff-Parkinson-White syndrome. Eleven patients were female and four male. Their ages ranged from 11 to 73 years.

After obtaining informed consent, four catheters were passed through the femoral veins using the Seldinger technique. Two bipolar catheters were postioned high on the lateral wall of the right atrium. One was used for stimulation, the other for recording an intra-atrial electrogram. A tripolar catheter was placed in the region of the bundle of His to record a His bundle electrogram. The fourth (bipolar) catheter was positioned in the apex of the right ventricle and used for ventricular stimulation. In five patients a patent foramen ovale permitted recording of a left atrial electrogram. With help of the single test stimulus method during right atrial stimulation the functional and effective refractory period of the A-V node, the effective refractory period of the atrium and the zone of premature beat intervals resulting in atrial echoes or sustained tachycardia were carefully determined. Thereafter, using a single test stimulus method the right ventricle was paced up to its effective refractory period. The refractory period and pattern of V-A conduction were registered. Both atrial and ventricular pacing were done at rates just above the spontaneous sinus rate. Following these measurements digitalis was administered as ouabain in a dosage that ranged from 0.75 to 1.25 mg according to body weight. The drug was given directly into the right atrium through the catheter used for recording the atrial electrogram. During the hour following termination of the intraatrial injection of ouabain the same stimulation program was repeated at least four times using identical basic cycle lengths and test stimulus intervals. In seven patients the stimulation procedure was repeated three to six weeks later, after taking oral digoxin in the interim. In these patients the digoxin levels at the time of the second catheterization varied from 1.1 to 2.4 ng/ml. In all seven patients the same basic pacing intervals were used as during their first study. Care was taken to place the stimulating and recording electrodes as nearly as possible in the same positions during the first and second catheterization to minimize the effect of varied approaches to the A-V node on A-V nodal function.

All data obtained during the stimulation studies were recorded on tape (Ampex FR 1300) and directly registered on an eight channel Elema Mangograf recorder. Leads I, II, III, V_1, V_6 the intracavitary right atrial lead, a left atrial lead, if available, and the His bundle lead were all recorded simultaneously. For recording the His bundle electrogram an Elema EMT 12 was used.

The experiment was unblinded. The findings before ouabain served as a control for the findings in the hour after its injections. These findings served as the control for the oral digoxin findings 3-6 weeks later. Because of the nature of the measurements, blinding during the trial is not necessary to avoid bias. However, interpretation and particularly measurements of the eight channel tracings should ideally be blinded to avoid bias. This is not discussed in this paper. The fact that the digoxin measurements required recatheterization and repositioning of the electrodes is a potential problem which the authors discuss reassurringly, but without data comparing complexes recorded on both occassions. Clinical information about the 15 patients is not presented including what happened during the 3-6 weeks of digoxin treatment.

The results of the study show that digitalis (both preparation) slowed A→V conduction and increased the node's refractory period in all patients.

The effect on V→A conduction was more complex because patient's V-A conduction patterns prior to ouabain were different. There were 5 patterns observed before ouabain which did not respond identically to ouabain. Overall though 9 patients showed no change (less than 10 msec) in V-A conduction time and/or refractory period. Six patients showed increases greater than 10 msec (20-110) in the refractory period accompanied by increased conduction times where they could be measured. Similar changes were found after digoxin in 6 of the 7 patients. In the seventh patient who had shown no change in the effective refractory period after ouabain there was a 50 msec - lenthening observed on digoxin. Prior to ouabain tachycardia could be initiated by a single properly timed atrial premature beat in all patients. Following ouabain, 4 patterns of response were observed, all but 1 are theoretically desirable. In 7 patients it was not possible to initiate tachycardia by single atrial stimuli. In the other eight patients there was a consistent shift in the time interval where tachycardia could be initiated to later in the cycle between auricular beats. In 5 patients the time interval of sensitivity was shortened; in 1 it was unchanged, and in 1 it was lengthened (the undesirable response). After digoxin, essentially similar results were seen in the 7 patients in their patterns of response, with 1 patient having less shortening of the tachycardia induction interval on digoxin than on ouabain (100 msec control, 20 msec on ouabain, 50

msec on digoxin). This study confirms the effects of digitalis on the AV node (studies follow) and extends the electrophysiological observations to patients with paroxysmal supraventricular tachycardia. The study demonstrates the effects on the node could be beneficial to such patients, not only for terminating attacks, but also for prevention of tachycardia. In 12 out of 15 patients tachycardia could either no longer be induced (7) or the inteval during which premature beats could initiate the arrhythmia shortened considerably (5). The study does not directly address the efficacy of digoxin in terminating or preventing these arrhythmias for which digitalis has been used for years; however, it is taken as substantial evidence of effectiveness because it so nicely bridges the gap between clinical experience and the experimental electrophysiology in animals and man. The electrophysiologic studies which follow and this study clearly support and to a large extent explain why digoxin has been useful and particularly why it has only been useful in some patients.

The following 5 studies with the authors' abstracts offer confirmatory evidence to support the specific findings of the previous paper. None were designed to prove the effectiveness of digoxin in treating auricular tachyarrhythmias, but rather to understand the effects of digoxin in conduction or to understand the pathophysiology of supraventricular tachyarrhythmias and the pharmacology of their treatment which would explain its effectiveness. The 3rd and 4th papers do not contain data on digoxin. The last reference is an abstract of a paper presented at the 1962 Am. Heart Ass. annual meeting.

1. Kosowsky, B. D.; Haft, J. I.; Lau, S. H.; Stein, E.; and Damato, A. N. The effects of digitalis on atrioventricular conduction in man. Am. Heart J. 75:736, 1968.

The effects of acute digitalization on atrioventricular conduction were studied in 11 normal subjects. P-R intervals were compared during normal sinus rhythm and at several identical heart rates produced by right atrial pacing before and after the intravenous administration of a therapeutic dose of ouabain (0.5 to 0.75 mg). Digitalis produced a consistent decrease in the sinus heart rate with a mean decrease of 8 beats per minute. Because of this change in heart rate, the effect of digitalis on the P-R interval during sinus rhythm was variable. However, comparisons of P-R intervals at identical heart rates revealed a consistent prolongation in A-V conduction time following digitalis, with a mean increase of 27 msec. or 11 per cent. This effect was not abolished by prior atropinization. There were no premature ventricular contractions, T-wave inversions, changes in the QRS or ST segments, nor any subjective signs of digitalis toxicity. Thus a therapeutic dose of digitalis can be shown to prolong the A-V conduction time in the absence of any signs of digitalis intoxication.

2. Przybyla, A. C.; Paulay, K. L.; Stein, E.; and Damato, A. N. Effects of Digoxin on Atrioventricular Conduction Patterns in Man. A. J. Cardiol. 33:344, 1974.

Digoxin was acutely administered to 17 patients, and its effects on atrioventricular (A-V) conduction were assessed. In the control state, before administration of digoxin, progresssively premature atrial depolarization showed conduction delay and block confined solely to the A-V node in eight patients and to both the A-V node and the more distal His-Purkinje tissue in nine patients. His-Purkinje conduction delay was manifested on the surface electrocardiogram by ventricular aberration. After administration of digoxin, an early atrial premature impulse either was blocked in the A-V node or reached the distal intraventricular conduction system so late that block or conduction delay below the His bundle was reduced or no longer occurred. Ventricular aberration on the surface electrocardiogram was thus reduced or eliminated. These effects of digoxin on A-V conduction were due to its effect on the A-V node of slowing conduction of a premature impulse. Such action on the A-V node may abolish aberrant ventricular conduction in atrial fibrillation.

3. Spurrell, R. A. J.; Krikler, D. M.; and Sowton, E. Concealed Bypasses of the Atrioventricular Node in Patients with Paroxysmal Supraventricular Tachycardia Revealed by Intracardiac Electrical Stimulation and Verapamil. Am. J. Cardiol. 33:590, 1974.

Thirteen patients with paroxysmal supraventricular tachycardia were studied with use of His bundle electrograms and programmed intracardiac stimulation. No patient had evidence of either the Wolff-Parkinson-White or Lown-Ganong-Levine syndrome. During ventricular pacing at a rate of 90 to 180 beats/min retrograde conduction time increased by an average of 80 msec in eight patients; in the remaining five patients the average increase was only 9 msec. The tachycardia was terminated in all 13 patients after intravenous administration of verapamil, 10 mg. This drug acts predominantly on the atrioventricular (A-V) node, and during termination of an A-V nodal reciprocal tachycardia both the antegrade and retrograde conduction times would be expected to be prolonged. During termination of the tachycardia antegrade conduction was prolonged by an average of 43 msec and retrograde conduction by an average of 79 msec in eight patients. However, in five patients antegrade conduction was prolonged by an average of 101 msec and retrograde conduction by an average of only 3 msec. The minimal effect of this drug on retrograde conduction and the minimal increase in retrograde conduction during ventricular pacing in these five patients is strong evidence for the presence of an A-V nodal bypass that was not apparent from the surface electrocardiogram. The potential hazards should atrial fibrillation occur and allow rapid antegrade conduction in an A-V nodal bypass are discussed.

4. Wit, L and Cranefield, P. F. Effect of Verapamil on the Sinoatrial and Atrioventricular Nodes of the Rabbit and Mechanism by Which It Arrests Reentrant Atrioventricular Nodal Tachycardia. Cir. Res. 35:413, 1974.

The effects of verapamil, an antiarrhythmic drug that apparently blocks slow inward currents, were studied on the isolated, superfused sinoatrial (SA) and atrioventricular (AV) nodes of the rabbit heart with intracellular microelectrodes. Verapamil decreased the rate of spontaneous impulse initiation by the SA node. This effect could be overcome with epinephrine. Concomitantly, verapamil decreased the amplitude of SA node action potentials without reducing maximum diastolic potential. The peak of the action potential fell well short of reversal after exposure to the drug. Verapamil had similar effects on the action potentials of the upper and middle AV nodal regions, reducing action potential amplitude so that the overshoot vanished without significantly reducing maximum diastolic potential. Action potentials of fibers in the lower region of the AV node were not affected as greatly. Verapamil slowed conduction of atrial impulses through the AV node; such slowing increased when the atrial rate increased. Verapamil also prolonged the effective refractory period of the AV node, thus slowing or blocking conduction of premature impulses. Verapamil prevented AV nodal reentry and initiation of atrial tachycardia by causing premature impulses to block rather than to conduct with the delay needed to initiate reentry. Verapamil had no effect on the rate of depolarization action, potential amplitude, or maximum diastolic potential of atrial of His bundle fibers. The results are consistent with the hypotheses that fibers in the SA and AV nodes show slow response activity, that the slow response plays a crucial role in causing certain cardiac arrhythmias, and that drugs that block the slow response are therefore antiarrhythmic.

5. Fowler, N. O. and Gueron, M. Conversion of Atrial Flutter with Digoxin Alone. Circ. 26:716, 1962.

It is not widely recognized that digitalis alone is effective in converting atrial flutter to sinus rhythm. The following report demonstrates that digitalis in large doses usually produces sinus rhythm in patients with atrial flutter.

Thirty-one consecutive patients with atrial flutter were treated. Their ages were from 28 to 80 years. Hypertension, coronary artery disease, corpulmonale, acute pericarditis, rheumatic heart disease, lupus erythematosus and congenital heart disease were represented. Four had no evidence of organic heart disease.

Ten patients were receiving digitalis when the diagnosis of atrial flutter was made. These patients received 0.5 mg digoxin orally every 8 hours for 5 days; then 0.25 mg digoxin every 6 hours. When atrial fibrillation or sinus rhythm occcurred, digoxin ws reduced to 0.25 mg twice daily. Patients not already receiving digitalis were given 1 mg of digoxin initially.

Sinus rhythm was achieved in 28 of the 31 patients. Two of the 3 failures expired within 2 hours after receiving very little digoxin. With digoxin alone, 13 patients developed sinus rhythm in 2 to 18 days. After treatment for 1 to 14 days atrial fibrillation developed in the other 15 patients. Of these, only 1 required quinidine to achieve sinus rhythm. In no patient was digoxin discontinued. Digitalis intoxication of mild degree developed in only 2 instances.

The duration of atrial flutter before treatment was unknown in these patients. The efficacy of digitalis in long-established atrial flutter is not proved by this study.

CONCLUSIONS:

The data presented in the four primary studies and the supporting electrophysiologic studies provide substantial evidence that digoxin is effective in controlling the ventricular rate in patients with atrial fibrillation by its basic effects on conduction and refractriness of cardiac tissue and paroxysmal atrial tachycardia.

Although the substantial evidence for effectiveness of digoxin in auricular fibrillation meets FDA's requirements for (2 or more) adequate and well-controlled human studies, the clinical data in man for auricular flutter and paroxysmal auricular tachycardia do not meet that standard per se. In this reviewer's opinion, the evidence for effectiveness is substantial for the reasons pointed out in the review. If the Bureau Director concurs, he may wish to consider waiving the requirement for 2 adequate and well-controlled studies in this instance in approving these latter two indications rather than to run the risk of other sponsors attempting to use digoxin as a precedant for seeking approval on the basis of less than 2 adequate and well-controlled studies in other "similar" cases.

RECOMMENDATIONS

1. Lanoxicaps be approved for use in the treatment of patients with congestive heart failure when its positive inotropic action is judged clinically to ameliorate signs and/or symptoms of failure and for use in controlling the ventricular rate in patients with supraventricular tachycardias (atrial fibrillation, atrial flutter and paroxysmal atrial tachycardias).

2. That the sponsor be requested (but not required) to do as a phase IV study a long term follow-up of patients with congestive heart failure initially equally well-maintained symptomatically on diuretics or digoxin or the combination. This probably represents a subpopulation of about 1/2 the patients on digoxin for congestive heart failure. Such patients selected by open titration and then randomly assigned to blinded treatment with either drug alone or the combination would allow a long term risk/benefit assessment of these alternative treatments. Because of the large number of people who eventually die on long term diuretic and digoxin treatment this is an important experiment from a public health standpoint. The proposed study would not be easy to do and may even be something more reasonably done by the NIH. The number of patients manageable on digoxin alone may be small enough that the study need only follow 2 groups rather than three.

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