

A STUDY OF PLASMA LEVELS OF DIGOXIN IN THE CAT AFTER ORAL
ADMINISTRATION OF NORMAL AND TOXIC DOSES CORRELATED
WITH CLINICAL AND ELECTROCARDIOGRAPHIC SIGNS

by

DEBORAH FINETTE ERICHSEN

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D.V.M., Kansas State University, 1968

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Approved by:


Major Professor

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ABSTRACT:

Unanesthetized cats of both sexes were given oral digoxin in three different dosage forms (elixir, tablet, and crushed tablet mixed with food). Peak plasma levels of digoxin were highest with the elixir (1.89 ng/ml mean) and lowest with the crushed tablet mixed with food (0.66 ng/ml mean). Males had a significantly higher mean plasma digoxin level than females.

A second group of unanesthetized cats of both sexes were given digoxin elixir orally at therapeutic levels (0.011 mg/kg) once a day for four consecutive days. The cumulative effect of digoxin resulted in 62% increase in the mean peak plasma level and 231% increase in the 24-hour plasma level of digoxin over the four-day period. Males had a significantly higher mean plasma digoxin level than females. No significant changes in the electrocardiograms were recorded.

A third group of unanesthetized cats of both sexes were given a single toxic (0.11 mg/kg) dose of digoxin elixir orally. All cats showed clinical signs of digitalis toxicity (depression, vomiting, salivation, anorexia, etc.) before electrocardiographic changes appeared. Alterations in the electrocardiograms were minimal; the most significant changes were a slight increase in the P-Q interval, an elevated S-T segment, and decreased heart rate. The cats were clinically ill for 48-96 hours. Results indicate a plasma digoxin level of 2.3 ng/ml is not toxic. Males had higher plasma digoxin levels than females.

INTRODUCTION:

Congestive heart failure^{27,29,37} and cardiomyopathy^{28,38,40,41,57,60,61,62} in the cat have been recognized and reported in the literature over the past ten years. A demand for more knowledgeable treatment regimens for feline cardiac diseases has developed with the increased recognition of cardiovascular problems in this species. Ten years ago it was recommended that the use of cardiac glycosides be avoided in the cat if possible.⁶⁶ Although a dosage schedule for digitalization of the cat with congestive heart failure is now accepted (digoxin, 0.002-0.01 mg/lb daily in two equal doses),²⁹ little is known of digoxin plasma levels and its correlation with electrocardiographic or clinical signs of digitalis toxicity in the cat over an extended period of time.

The therapeutic effects of digitalis glycosides in congestive heart failure--increased cardiac output; decreased heart size, venous pressure, and blood volume; diuresis and relief of edema--are due to positive inotropic action.²⁰ A cat with congestive heart failure responds qualitatively to the inotropic action of digitalis in the same manner as man and dog.¹¹ The chronotropic action of digitalis--altered automaticity, excitability, conduction velocity, and refractoriness--¹ is not believed to be due to a direct negative chronotropic action on the sinoatrial node but is probably mediated indirectly through altered autonomic neural control on the heart.⁵⁹ Data from a recent investigation in cats indicates that the neural effects of digoxin result from drug action within the peripheral autonomic nervous system rather than the central nervous system.⁶⁴

Digitalis produces characteristic electrocardiographic changes that are qualitatively similar in various species, including the cat.¹⁰

Changes include diminished amplitude or altered direction of the T wave, depression of the S-T segment, prolonged P-R interval and shortened Q-T interval.²⁰

The lethal effect of digitalis in the cat is due to cardiotoxicity¹¹ which includes arrhythmias such as sinus arrhythmia, paroxysmal tachycardia, atrial or ventricular tachycardia, extrasystoles, second degree A-V block, atrial fibrillation or atrial standstill, ventricular fibrillation and third degree A-V block.²⁰ Studies in the cat have found that the toxic, nonlethal doses of cardiac glycosides cause temporary rather than permanent damage.⁶⁵

The LD₅₀ for intravenous digoxin in the cat is 0.36 mg/kg as compared to 0.60 mg/kg in the dog and <0.15 mg/kg in man.⁴⁵ The LD₅₀ for oral digoxin in aqueous alcohol for the cat has been reported as 0.80 mg/kg.⁵ Species difference in glycoside sensitivity has been suggested to be due to a difference in the responsiveness of digitalis receptors rather than difference in distribution or metabolism.⁴⁷

The extracardiac signs of digitalis toxicity are anorexia, nausea, vomiting, salivation, diarrhea, and abdominal discomfort.²⁰ In the cat the early symptoms of digitalis toxicity are extracardiac, the earliest and most regular being vomition,⁴⁶ along with salivation and retching which are signs connected with vomiting.⁵³ The intravenous emetic dose of digoxin in the cat is 0.11 mg/kg.⁴⁶ The mechanism of digitalis-induced emesis is due to direct action of digitalis on the chemoreceptor trigger zone (CRTZ)¹⁹ located in the area postrema of the medulla.⁴⁶ Diarrhea is believed to be due to the drug's local irritating action on the intestinal tract.⁶⁵

The oral route of administration of digoxin without the loading dose is preferred to the parenteral route in the cat.²⁹ Acidic gastric juice (below pH 3) is capable of hydrolyzing digoxin³² which may be pertinent in the case of slowed gastric emptying. Significantly greater amounts of digoxin are absorbed from the proximal small intestine than the distal segment.²¹ It would appear necessary for the digoxin to be in its most soluble form while in the proximal segment for maximum absorption. Ninety percent⁴³ to 100%³¹ of oral digoxin in aqueous-alcoholic solution is absorbed from the gut. The primary route of transportation appears to be via the portal vein²¹ and the rate of absorption is strongly dependent on portal blood flow.²⁴ The nature of the absorption process is poorly understood. At low substrate concentration there appears to be active transport but at high substrate concentration transport is mainly via passive diffusion.³⁵

Absorbed digoxin is widely distributed throughout the body and rapidly fixed to tissue. The serum level of digoxin is approximately one-fortieth the tissue concentration but appears to be in equilibrium with it.⁴³ Disappearance from tissue parallels the serum disappearance rate in spite of differences in tissue concentration.¹⁴ Digoxin is loosely bound to tissue protein (including myocardial) and is readily reversible.⁴⁵ In the cat the tissue distribution of digoxin in decreasing order of concentration is kidney > liver > heart.⁵³ Myocardial concentration reaches its peak at one hour post-intravenous digoxin in dogs.¹⁴ A partial blood-brain barrier for distribution has been demonstrated.⁴³

Biological half-life, which is a measure of the relative duration of action of pharmacological agents, is not equivalent to duration of

drug action, although the two are directly related. The biological half-life for digoxin in the cat is 27 hours as compared to 44 hours in man and 27 hours in the dog.⁴⁵

Digoxin is 25% bound to plasma protein and the remaining is free in solution in the plasma. The protein bound portion in man is entirely bound to serum albumin.¹⁶ In the cat 18.1% is plasma protein bound as compared to 27.0% in the dog and 17.3% in the rat.³ Large quantities of steroids (cortisol and progesterone) and cholesterol decrease plasma protein binding of digoxin.¹⁶

Digoxin metabolites are digoxigenin, digoxigenin mono-digitoxoside, digoxigenin bis-digitoxoside, dihydrodigoxigenin, and C-3 epidigoxigenin.¹² Digoxigenin mono-digitoxoside and digoxigenin bis-digitoxoside have been found to be cardio-active. Bottcher showed that in cat heart-lung preparations the mono-digitoxoside of digoxigenin was more efficient in its inotropic effect and had a wider therapeutic range (threshold dose vs toxic dose) than the other metabolites.⁹ Lullmann's study in guinea pigs also found the monodigitoxoside of digoxigenin showed the strongest inotropic effect of the digoxin metabolites and the greatest affinity.⁴²

Urinary excretion of the unchanged glycoside makes up 80% of digoxin elimination and is predictably related to creatinine clearance.¹² The kidney can also excrete conjugates of digoxigenin.² Intestinal tissue can metabolically degrade digitalis glycosides.²⁴ In the guinea pig biliary excretion is the source of most, if not all, of the intestinal excretion of digoxin and its metabolites.⁴⁴ Digoxin carried to the liver via the portal vein is excreted in the bile and then reabsorbed and redistributed. Approximately four-fifths of the digoxin excreted in the bile is unchanged.¹⁸ Bisdigitoxoside of digoxigenin is the

predominant metabolite produced from the cat liver³³ and is cardio-active. There are species variabilities in the percent of absorbed dose that is excreted in the bile: cat = 5.2% in 3 hours,³⁴ man = 14.8% in 8 days,⁴⁴ and dog = 15.0% in 4.5 days.³⁰ Lipid solubility, intestinal reabsorption, and recycling through the enterohepatic circulation may account for the cumulative effects of digoxin.⁴⁵

The above information has greatly augmented the understanding of cardiac glycoside metabolism and myocardial activity in the cat but it is somewhat difficult to transfer this data to the clinical situation. The purpose of this study is to correlate various dosage forms of oral digoxin that are used clinically with the blood plasma levels, electrocardiographic changes and clinical signs of digitalis toxicity in the cat.

MATERIALS AND METHODS:

Experiment 1--Six adult, clinically healthy (as determined by observation and physical examination), intact cats (two males and four females) were given three different oral dosage forms of digoxin during separate trials with an interval of two weeks between trials. The cats were housed in separate cages and were given food^a and water ad libitum before, during, and after the trials. Reward^b for good behavior was offered after blood samples were taken. Venepuncture sites were clipped and the cats conditioned to their surroundings prior to the actual trials.

A single dose of digoxin in elixir,^c tablet,^d or crushed tablet (powder)^d mixed with cat food^e was given at one of the three trials at a therapeutic level of 0.011 mg/kg (0.005 mg/lb) based on body weight. Heparinized blood samples were taken at pre, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hour post-dosage intervals and centrifuged. Plasma was withdrawn from the samples and frozen. Plasma was thawed and assayed for digoxin using a radio-immunoassay kit,^f a double antibody assay utilizing a digoxin tyrosine methyl ester derivative iodinated with ¹²⁵I. Plasma digoxin levels determined for each cat during the elixir, tablet, and crushed tablet trials were submitted for statistical analysis.

^aPurina Cat Chow^R, Ralston Purina Co., St. Louis, Mo.

^bTender Vittles^R, Ralston Purina Co., St. Louis, Mo.

^cLanoxin^R Pediatric Elixir, Burroughs Wellcome, Greenville, N.C.

^dLanoxin^R Tablets, Burroughs Wellcome, Greenville, N.C. (date of manufacture unknown)

^ePuss'n Boots^R, Quaker Oats Co., Chicago, Ill.

^fLanoxitest^R, Burroughs Wellcome, Greenville, N.C.

Analysis of variance was run on the data to determine if differences between dosage forms, sexes, and primary and secondary peaks were significant.⁵⁶

Experiment 2--Five adult, clinically healthy, intact cats (two males and three females) were anesthetized^a and indwelling catheters^b were surgically placed in the jugular vein. The chronic catheters were flushed with heparinized saline each day and after each blood sample collection. Electrocardiograms were recorded on a Burdick EK-5 at 25 and 50 mm/second with a 1 mV/cm standard calibration. Bipolar Leads I, II, and III were used to record electrical activity from the heart. Connections for the three bipolar leads were as follows: the grounding electrode was attached to the right stifle in all cases; for Lead I the electrode for the positive terminal was attached to the point of the left elbow, the electrode for the negative terminal was attached to the point of the right elbow; in Lead II the left stifle electrode was the positive terminal and the right elbow electrode was the negative; in Lead III the left stifle electrode was the positive terminal and the left elbow the negative.¹⁵ Copper alligator clips (#60) were used as electrodes. All electrocardiograms were recorded with the cat in sternal recumbancy in a crouched position (Fig. 1). Recordings were made on each cat 2-3 days before the trial was begun to condition the cats to the procedure and the surroundings. At no time during the recording were the cats given a tranquilizer or other CNS depressant.

^a10 mg of Rompun^R, Haver-Lockhart, Shawnee, Ks., and 50 mg of Ketaset^R, Bristol, Syracuse, N.Y.

^b20G X 8" #6976 indwelling radiopaque intravenous catheters, Becton-Dickinson, Rutherford, N.J.



Figure 1. Electrode connections for electrocardiogram recording with the cat in sternal recumbency in a crouched position.

A reward^a was offered at the end of each handling period both before and during the trial sessions. The cats were housed in separate cages and were given food and water ad libitum throughout the trial.

The cats were given a daily oral dose of digoxin elixir^b at a therapeutic level of 0.011 mg/kg body weight (0.005 mg/lb), for four consecutive days. Digoxin was administered orally using the graduated dropper included with the pediatric elixir bottle. The dropper was not calculated for delivery accuracy. Heparinized blood samples were taken at pre-, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 hour post-dosage intervals the first day and at 1, 2, 4, 6, and 24 hour post-dosage intervals the following three days. Electrocardiograms were recorded at pre-, 1, 2, 4, 6, and 24 hour post-dosage intervals all four days. Digoxin levels assayed from the plasma of each cat were submitted for statistical analysis. Analysis of variance was run on the one-hour peak plasma level to determine if differences between peak heights over the four successive days and between sexes were significant.⁵⁶

Experiment 3--Six cats (three males and three females) with chronic indwelling jugular catheters, preconditioned to the surroundings and EKG procedure, were given a single dose of digoxin elixir at a known toxic level determined by previous dose studies in this lab, 0.11 mg/kg (0.05 mg/lb). The elixir was made by dissolving pure powdered digoxin^c in 40% ethyl alcohol to a concentration of 0.5 mg/ml. Heparinized blood samples were taken at pre-, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, and 168 hour post-dosage intervals and at the time of vomiting.

^aTender Vittles^R, Ralston Purina Co., St. Louis, Mo.

^bLanoxin^R Pediatric Elixir, Burroughs Wellcome, Greenville, N.C.

^cSupplied by Burroughs Wellcome, Greenville, N.C.

Electrocardiograms were recorded at pre-, 1, 2, 4, 6, 12, 24, 48, 72, 144, and 168 hour post-dosage intervals and at the time of vomition.

Clinical signs of digitalis toxicity (vomiting, depression, anorexia, salivation, diarrhea) were recorded throughout the trial period.

Digoxin levels determined by plasma assay were submitted for statistical analysis. Analysis of variance was run on the two-hour peak plasma level to determine if the difference between sexes was significant.⁵⁶

RESULTS:

Experiment 1--During separate trials cats in this group received a single dose of digoxin in elixir, tablet, or crushed tablet (powder) form mixed with food. The highest average peak blood level of digoxin was reached with the elixir dosage form--1.89 ng/ml (Table 1). The peak blood level for tablets was 1.22 ng/ml while the crushed tablets mixed with food had the lowest average peak level of 0.66 ng/ml. The peak level using the tablet form was 65% of that reached with the elixir and the peak level reached using the crushed tablets was 35% of the elixir. The difference between the elixir and tablet form had a significance value of $P < 0.10$. The difference between the elixir and crushed tablet mixed with food had a significance value of $P < 0.05$. There was no significant difference between the tablets and crushed tablets as determined by analysis of variance. Each dosage form showed a peak blood level of digoxin an average of one hour following administration of the drug and it was this one hour time interval on which the analysis of variance was determined.

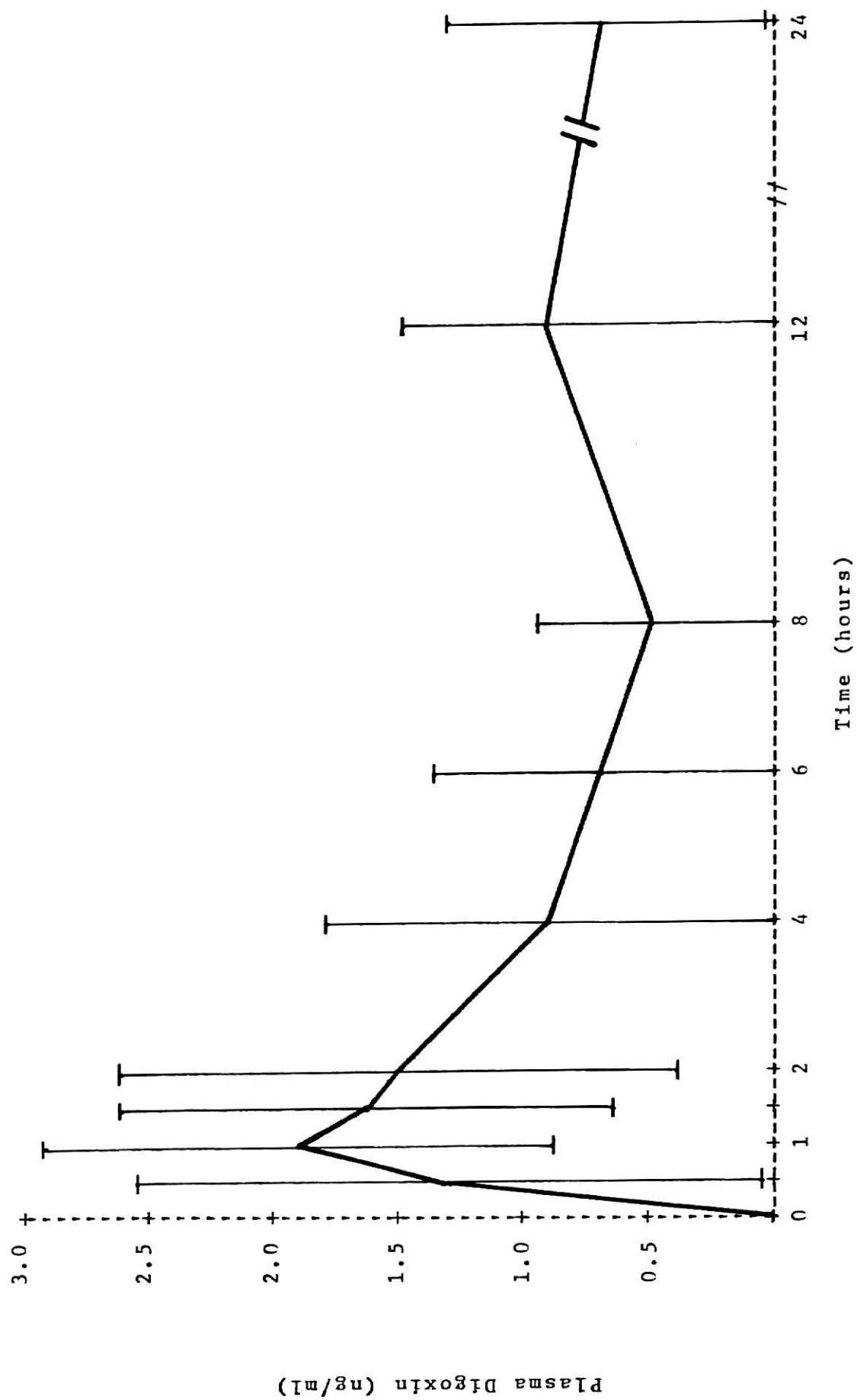
All three dosage forms showed a second peak digoxin level at a varying interval of 1 to 24 hours following the primary peak (Figs. 2-4). This peak was not significant as indicated by analysis of variance; $P > 0.10$ with each dosage form.

The dominant plasma half-time of digoxin for each dosage form was as follows: elixir--21 hours, tablet--25.5 hours, and crushed tablet mixed with food--20.5 hours (Figs. 5-7).

Plasma digoxin levels of the males were averaged and compared with the average female blood levels (Table 1). Results from all three dosage forms showed an initially higher blood level of digoxin in the

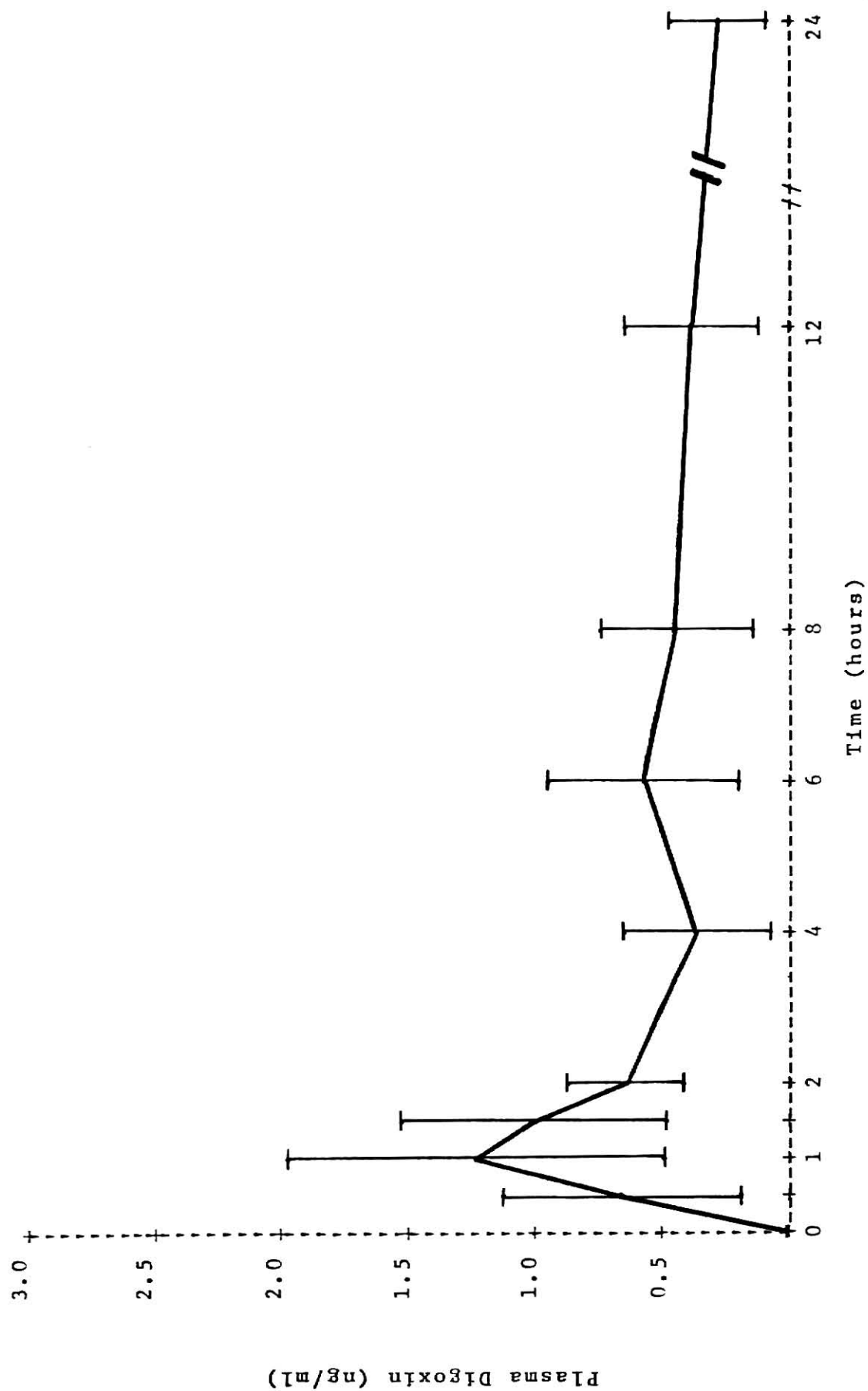
Table 1: Average peak plasma levels of digoxin (ng/ml) of three different oral dosage forms of digoxin. Blood samples were collected 1hour after the therapeutic dose of digoxin was administered (0.011 mg/kg).

	Elixir	Tablets	Crushed Tablets Mixed with Food
Average 6 cats	1.89	1.22	0.66
Average 4 female cats	1.62	0.93	0.51
Average 2 male cats	2.42	1.81	0.96



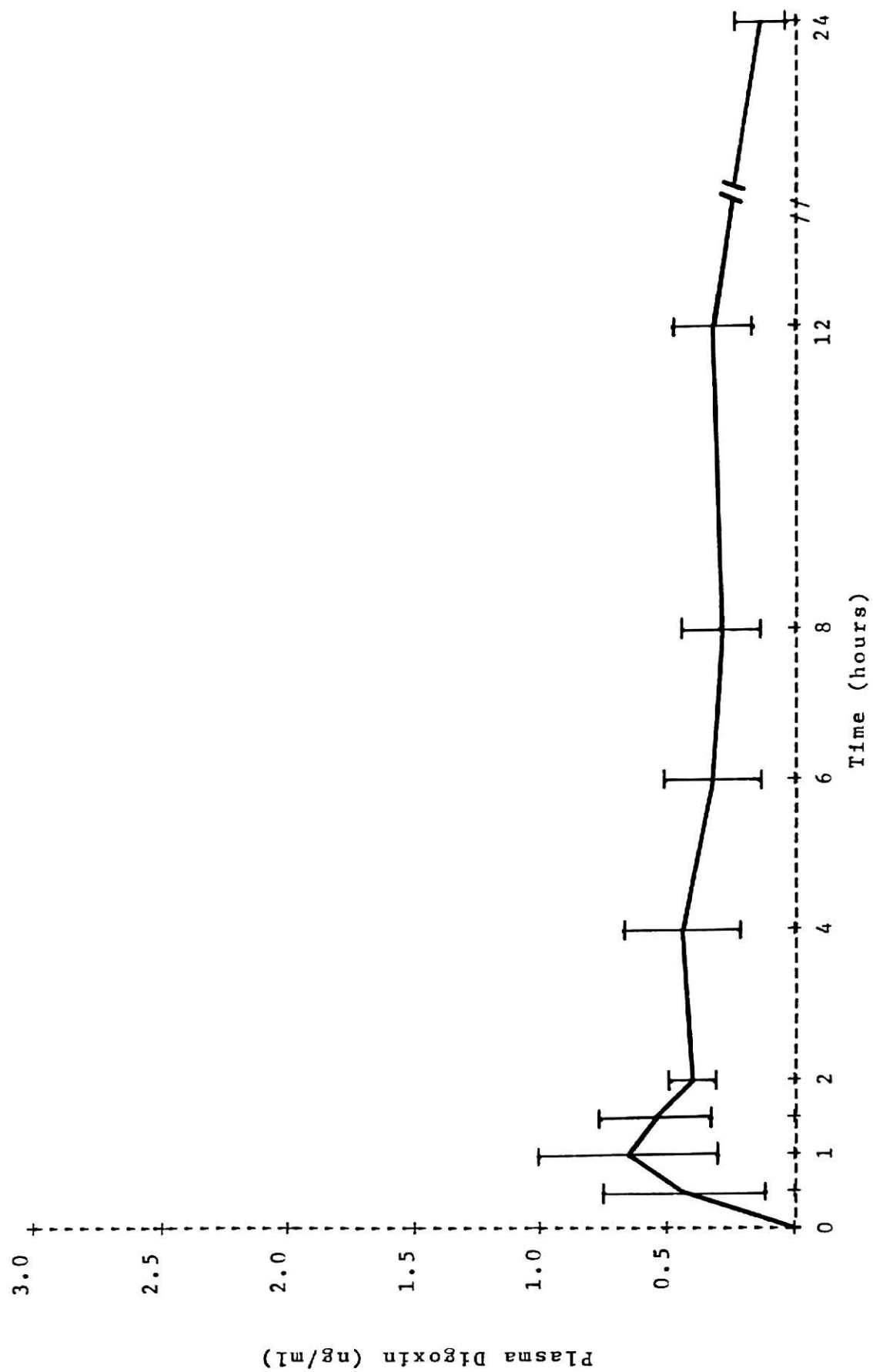
Elixir form: Six cats, $\bar{x}$ and σ

Figure 2



Tablet form: Six cats, $\bar{x}$ and σ

Figure 3



Crushed tablet form mixed with food: Six cats, $\bar{x}$ and σ

Figure 4

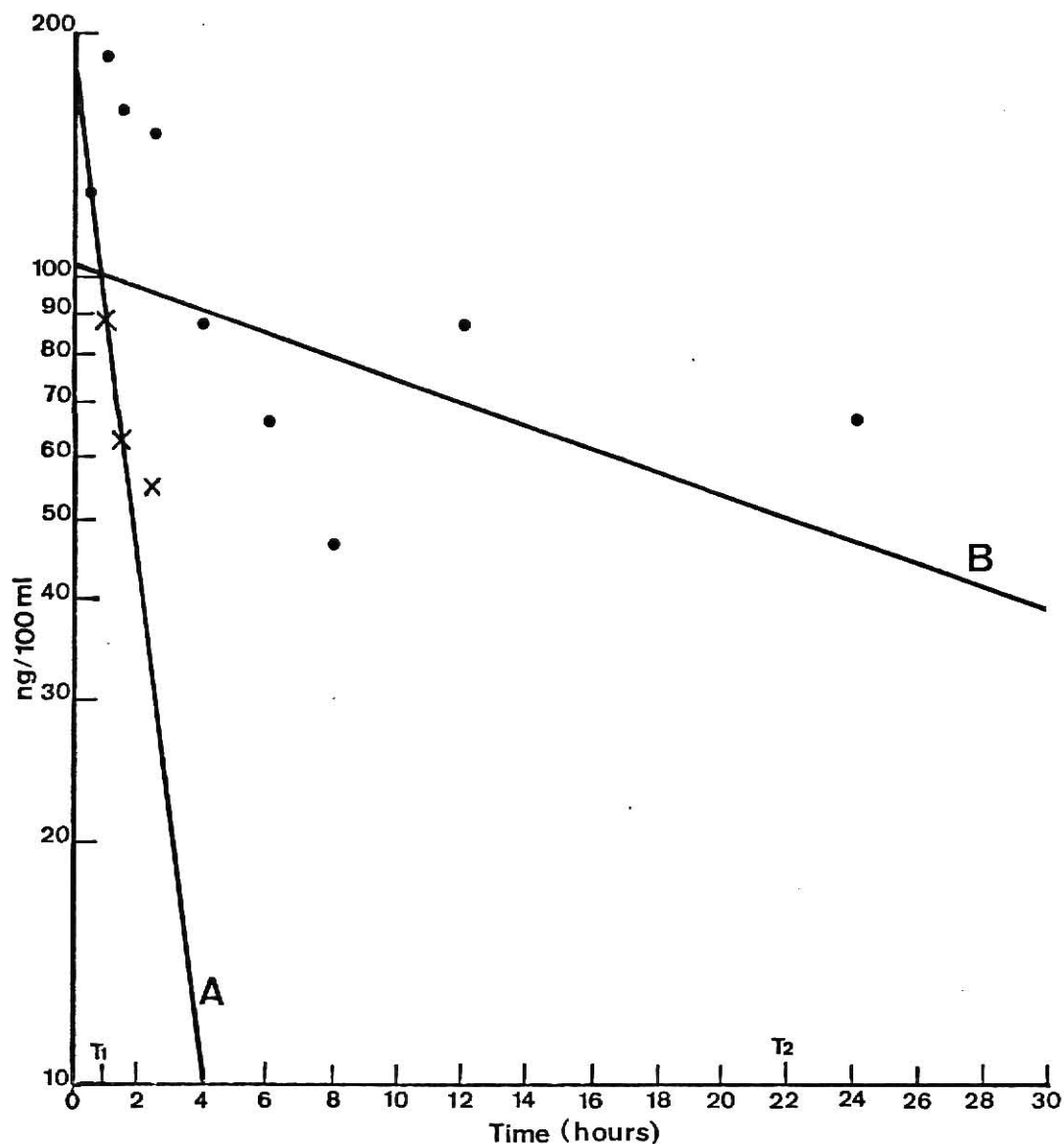


Figure 5 - PLASMA TURNOVER OF DIGOXIN AFTER ORAL ADMINISTRATION OF ELIXIR (AVERAGE SIX CATS). Digoxin concentration in plasma is shown on a semilogarithmic scale on the ordinate; time is shown on the abscissa. Plotted points (•) represent the actual plasma digoxin concentration. Line B represents the best estimated straight line that can be drawn after equilibrium is reached, extrapolated to time zero. This line represents the metabolism and excretion of digoxin. The dominant half-time obtained from line B (21 hours) is the time required for one-half the digoxin originally present to disappear. Line A represents those plasma concentrations of digoxin above line B, minus line B (x); this process eliminates metabolism and excretion of digoxin. Line A thus represents distribution and tissue binding of digoxin and has a half-time of 48 minutes.

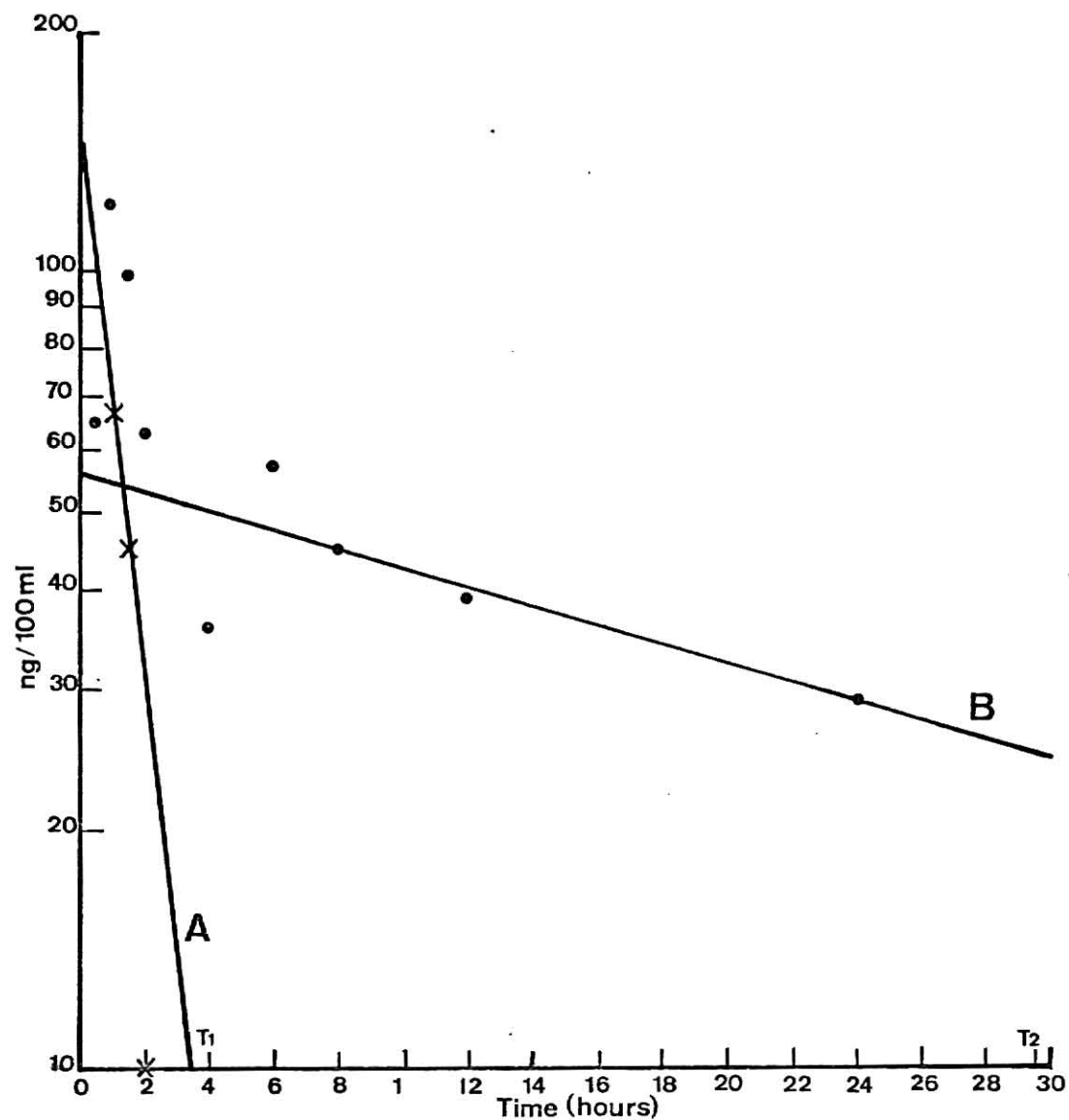


Figure 6 - PLASMA TURNOVER OF DIGOXIN AFTER ORAL ADMINISTRATION OF TABLET (AVERAGE SIX CATS). Digoxin concentration in plasma shown on semilogarithmic scale on the ordinate; time shown on the abscissa. Plotted points (•) represent the actual plasma digoxin concentration. Line B is derived as explained in Figure 5 and represents metabolism and excretion of digoxin. The dominant half-time is 25.5 hours. Line A is derived as before (x) and represents distribution¹² and binding of digoxin to tissue. It has a half-time of 54 minutes.

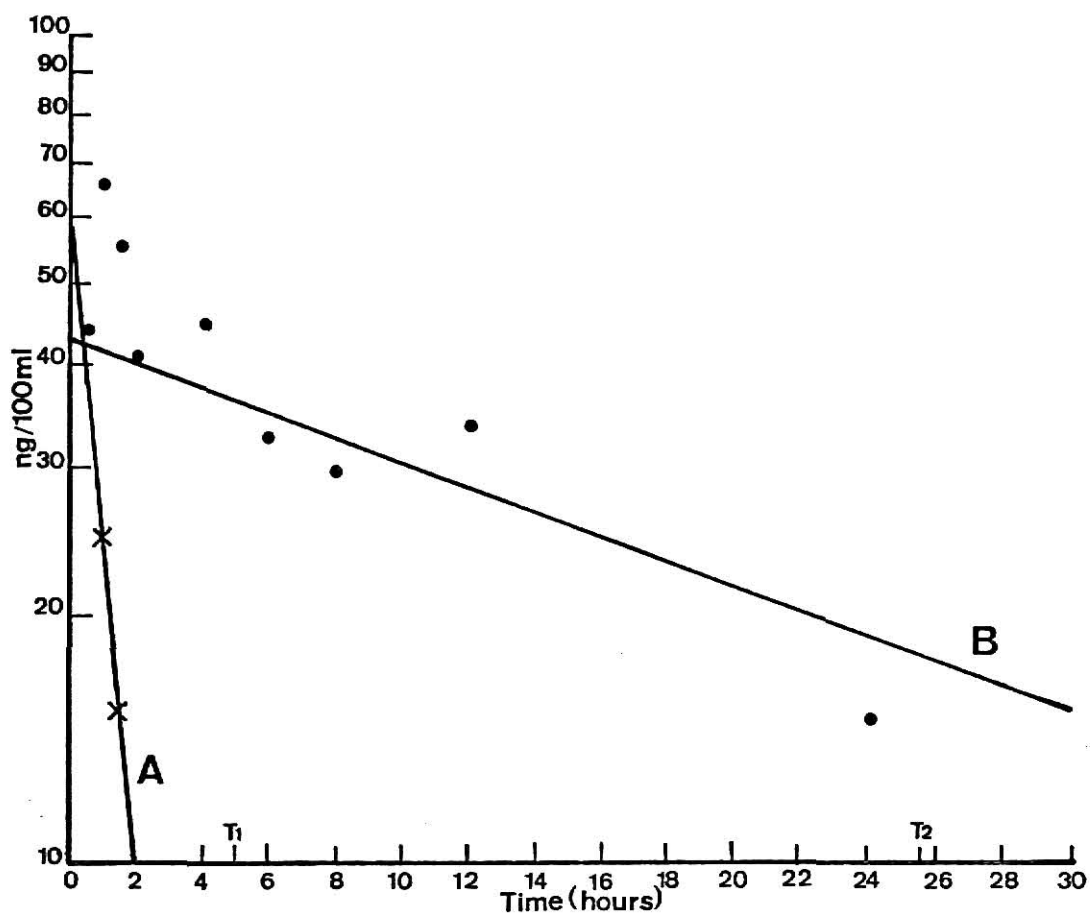


Figure 7 - PLASMA TURNOVER OF DIGOXIN AFTER ORAL ADMINISTRATION OF CRUSHED TABLET MIXED WITH FOOD (AVERAGE SIX CATS). Digoxin concentration is shown on the ordinate on a semilogarithmic scale; time on the abscissa. Plotted points (•) represent the actual plasma digoxin concentration. Line B is derived as in Figures 5 and 6 and represents the metabolism and excretion of digoxin. The dominant half-time is 20.5 hours. Line A is derived as before (x) and represents distribution and tissue binding of digoxin and has a half-time of 48 minutes.¹²

males than the females and the elixir and tablet dosage forms maintained a higher blood level of digoxin in the males than the females (Figs. 8-10). The difference between the males and females had a significance value of $P < 0.10$ as determined by analysis of variance.

Experiment 2--Five cats were given a single therapeutic (0.011 mg/kg) oral dose of digoxin elixir on four consecutive days. The average peak blood level of digoxin on the first day was slightly in excess of 1 ng/ml with an average peaking time of one hour post-dosage. The peak blood levels increased each day with each successive dose so that by day four the average peak blood level was 62% higher than that of the first day (Fig. 11). The heights of the peaks increased in a linear manner over the four days studied. The highest average peak level was 1.96 ng/ml and no clinical or electrocardiographical signs of toxicity occurred in any of the cats. The average 24-hour blood level of digoxin also continued to rise on each successive day so that by day four the 24-hour blood level was 231% greater than that of the 24-hour blood level after the first dose. The dominant half-time of digoxin for the first day of the trial was 20 hours (Fig. 12).

When the average plasma digoxin levels of the male cats were compared to the average female levels, the males had higher peak blood levels (Fig. 13). The difference between the males and females had a significance value of $P < 0.05$ as determined by analysis of variance.

Analysis of the electrocardiograms included heart rhythm and rate; P wave and QRS duration; P-Q and Q-T intervals; P, T, and QRS amplitude and wave forms. Interpretation of the electrocardiograms was based on published data for normal cat electrocardiogram parameters^{7,8,26,48,51,58} and known electrocardiographic alterations due to digitalis

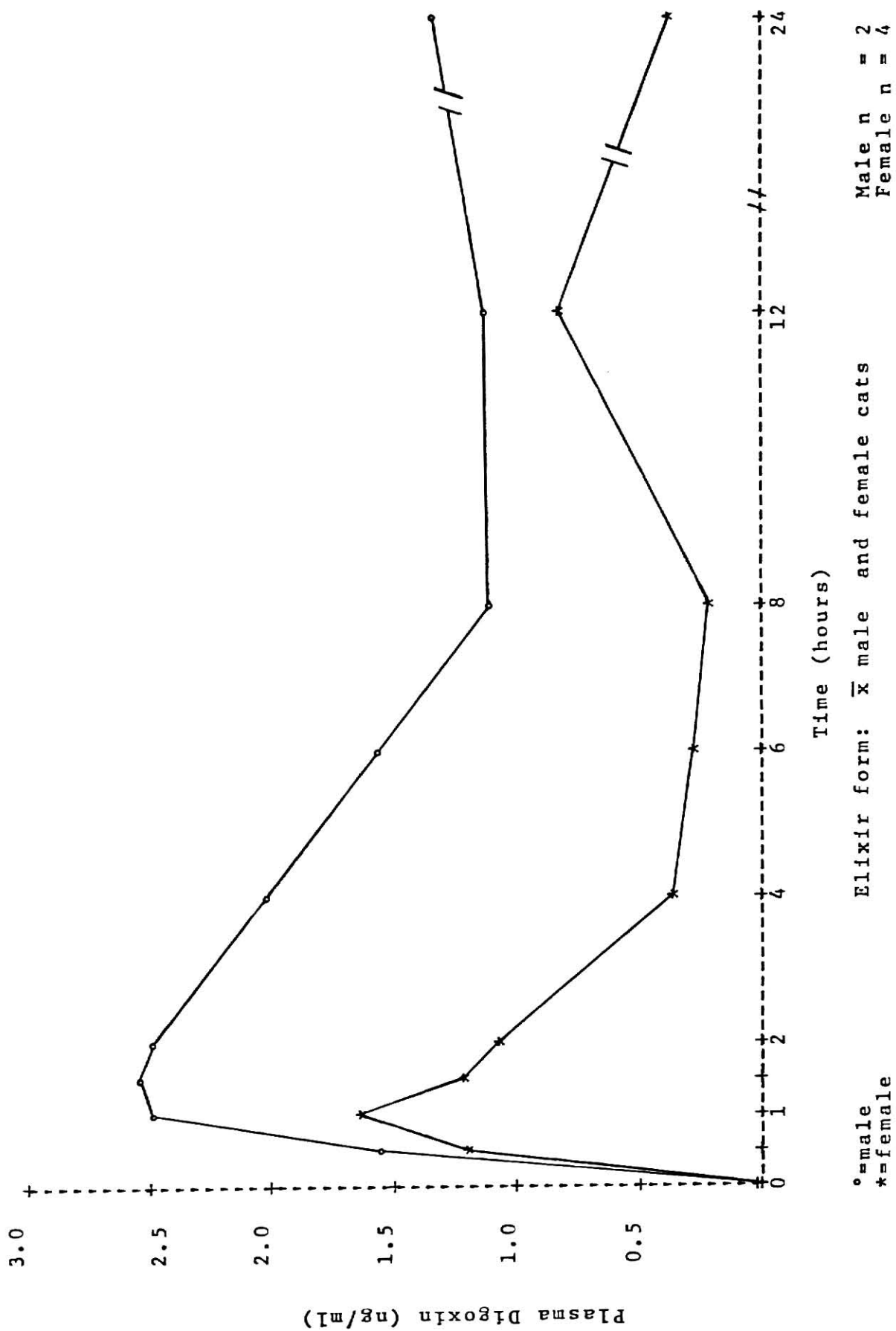
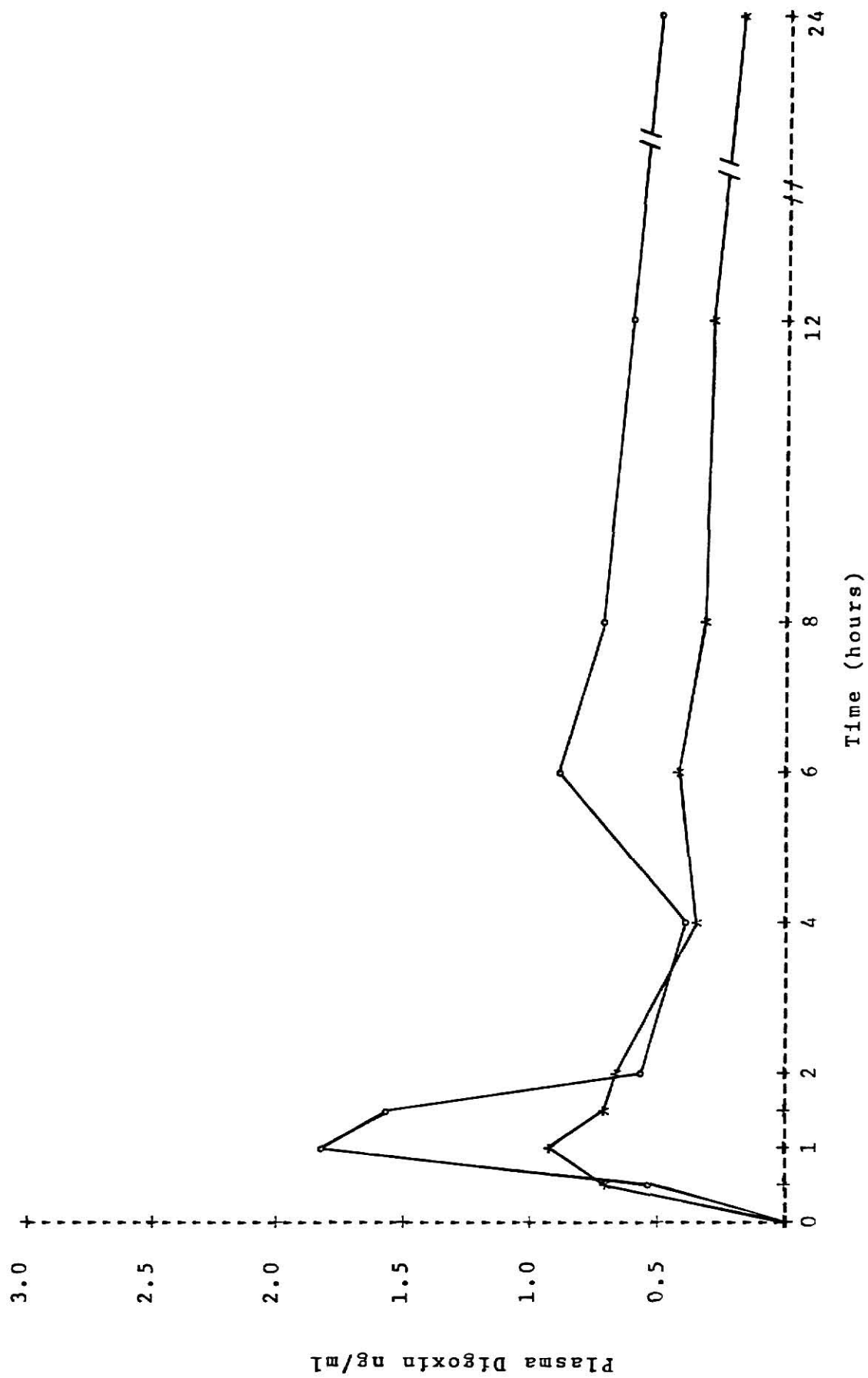


Figure 8

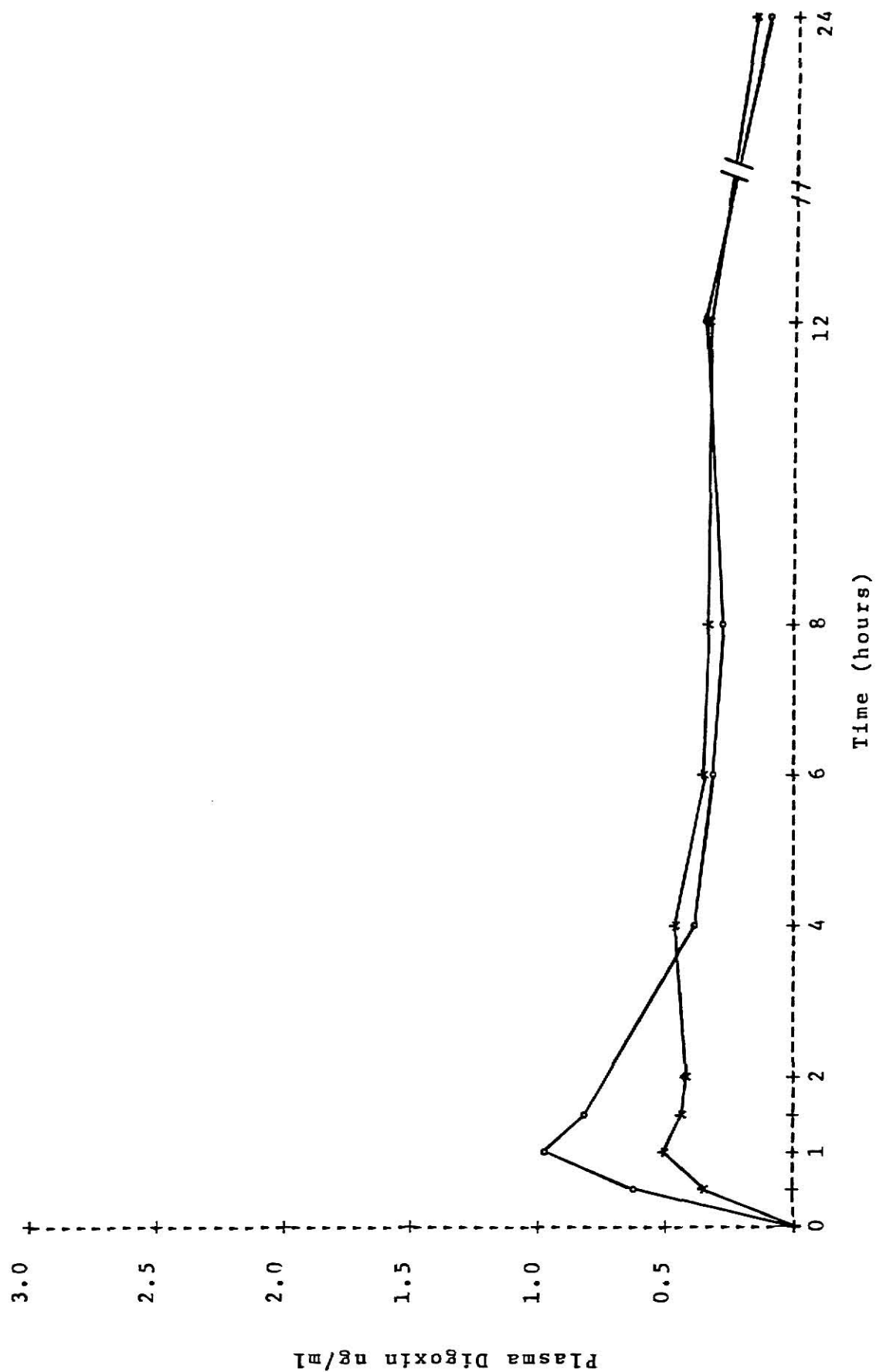


○=male
 * =female

Tablet form: $\bar{x}$ male and female cats

Male n = 2
 Female n = 4

Figure 9

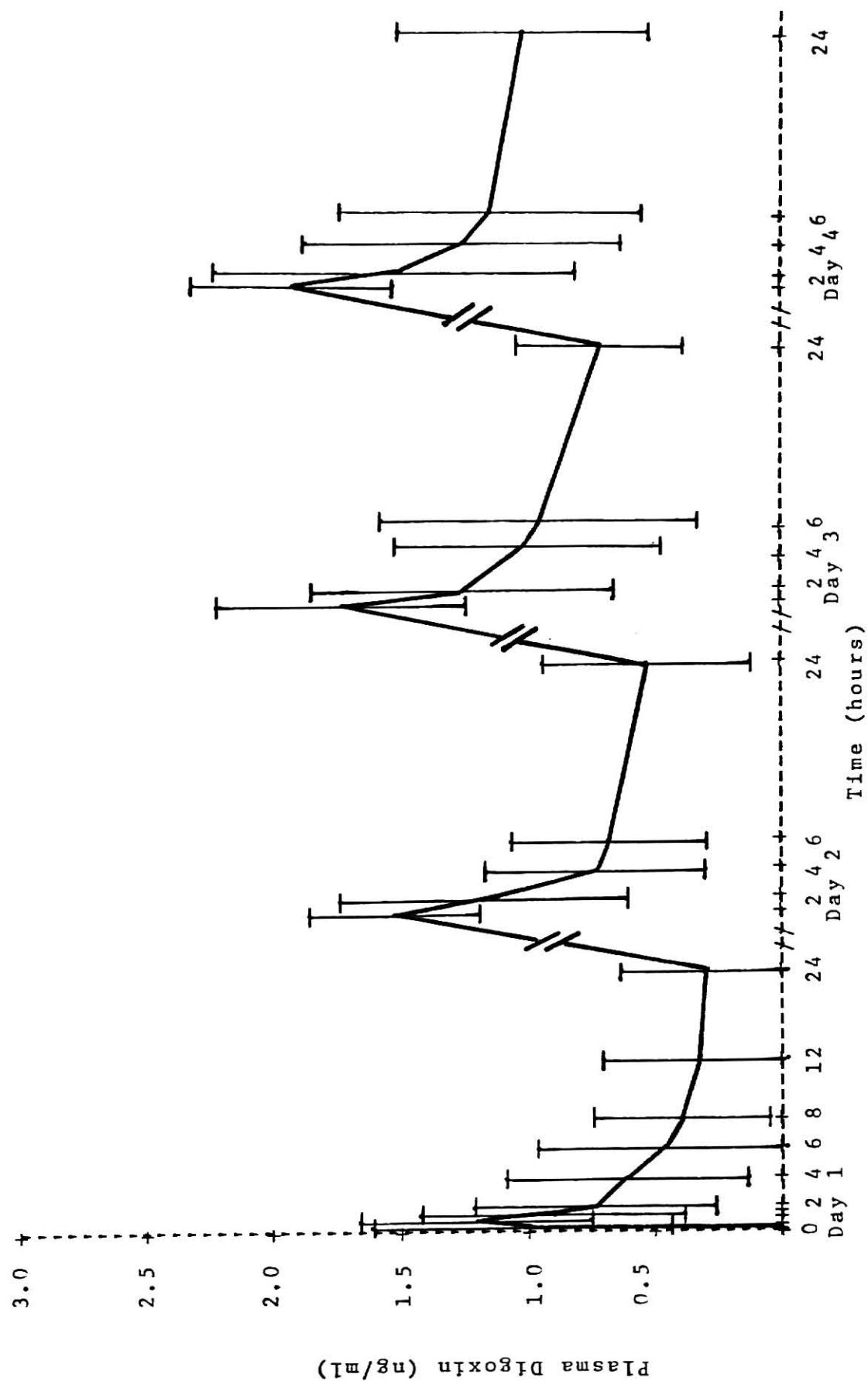


○ = male
 ★ = female

Crushed tablet form mixed with food:
 x male and female cats

Male n = 2
 Female n = 4

Figure 10



Four days at therapeutic dose (0.011 mg/kg): Five cats, $\bar{x}$ and σ

Figure 11

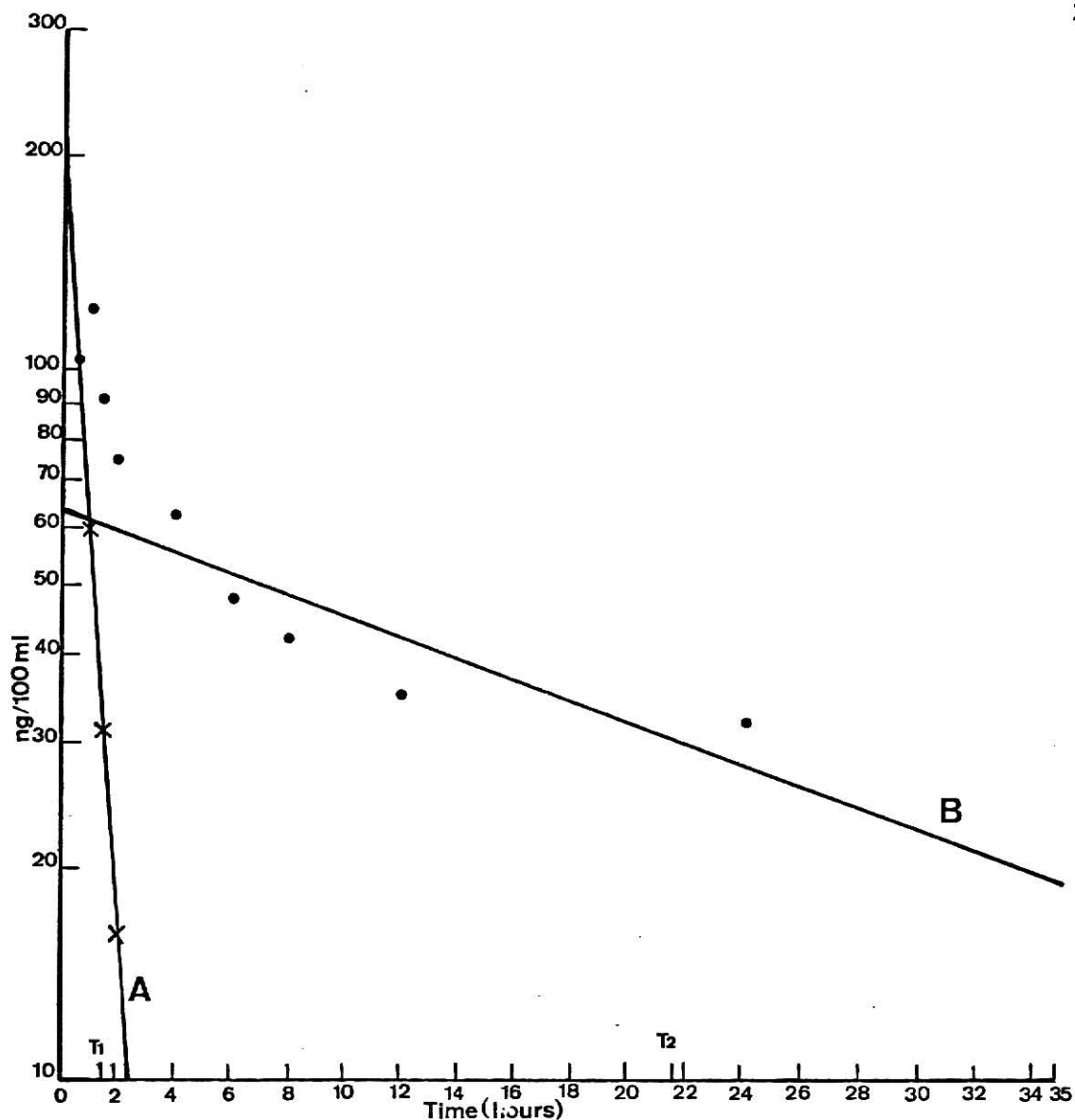
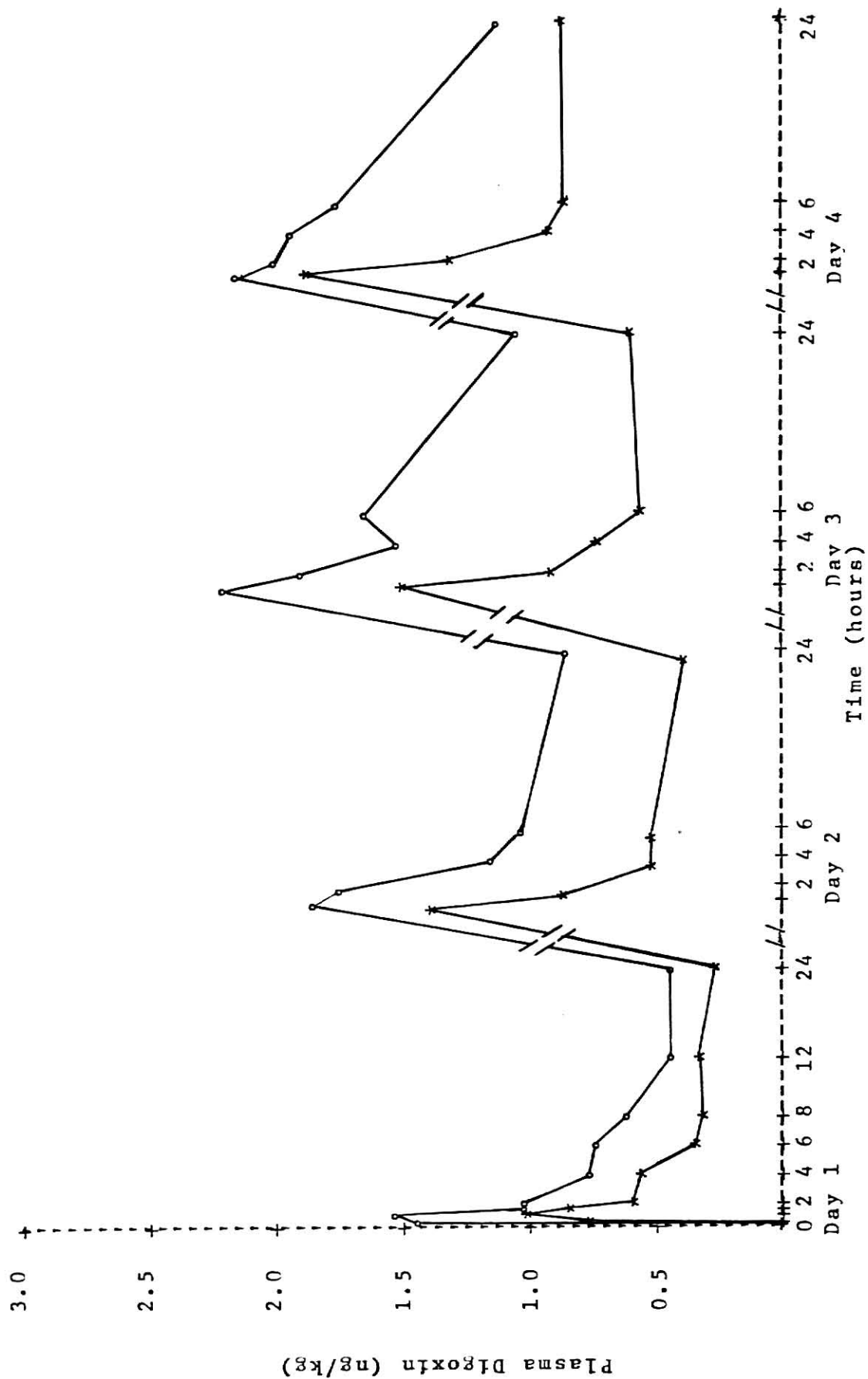


Figure 12 - PLASMA TURNOVER OF DIGOXIN AFTER ORAL ADMINISTRATION OF ELIXIR (FIRST DAY OF FOUR-DAY TRIAL, AVERAGE 5 CATS). Digoxin concentration in plasma shown on semilogarithmic scale on the ordinate; time is shown on the abscissa. Plotted points (•) represent actual plasma digoxin concentration. Line B is derived as explained previously and represents metabolism and excretion of digoxin. The dominant half-time is 20 hours. Line A is derived as before (x) and represents distribution and binding of digoxin to tissue. It has a half-time of 36 minutes.¹²



○ = male
* = female

Four days at therapeutic dose (0.011 mg/kg):
x male and female cats

Male n = 2
Female n = 3

Figure 13

therapy or toxicity.²⁰ Normal ranges accepted for Lead II values are shown in Table 2. No significant differences were seen in any series of electrocardiograms. A normal EKG recorded on the fourth day of the trial is shown in Figure 14. It was noted that occasionally there was a slight increase in the P-Q interval by 0.01-0.02 seconds but this change did not correlate with plasma levels of digoxin for the trial period nor with day to day recordings. Table 3 lists the range of electrocardiographic values for Lead II recorded on all of the cats for the entire pre-trial and four-day trial period.

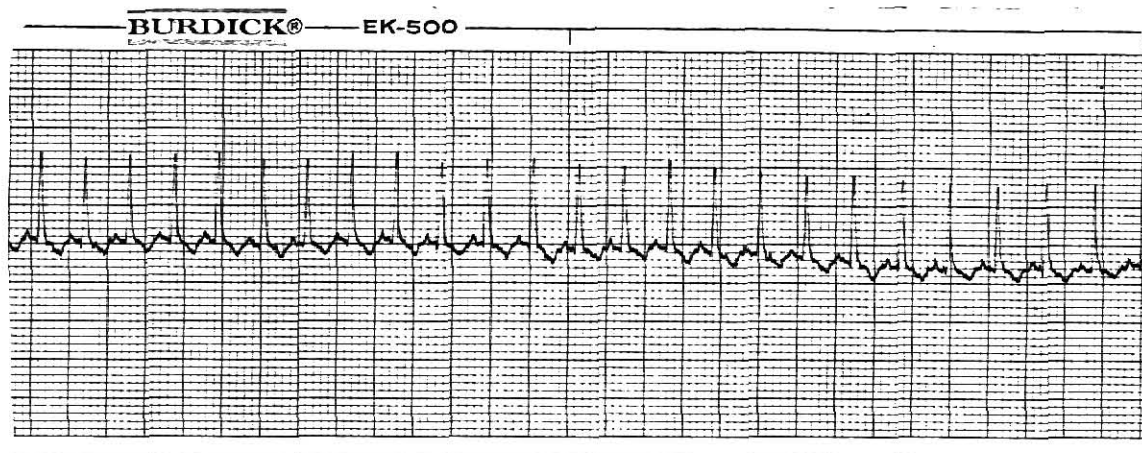
Experiment 3--Six cats were given a single toxic dose (0.11 mg/kg) of digoxin elixir. The average peak plasma level of digoxin was in excess of 7 ng/ml with an average peak time of two hours post-dosage (Fig. 15). Plasma levels were still over 1.3 ng/ml at 168 hours post-dosage. The dominant half-time was 88 hours (Fig. 16). Males showed higher plasma digoxin levels than females (Fig. 17). This difference due to sex was not significant ($P > 0.10$) due to the great variation between individuals of the same sex.

All cats receiving the toxic dose level of digoxin vomited at some time during the trial with an average vomition time of 4.9 hours post-dosage. Two cats out of the six vomited at the time of their peak blood levels of digoxin. The other four cats vomited 1.5-10 hours after peak blood levels. The cats were clinically ill for a period of 48-96 hours after initial vomition by showing signs of depression, vomiting, anorexia, salivation, gagging, and four of the six had diarrhea. None of the cats showed clinical signs of illness prior to initial vomition. By the time the cats had returned to normal clinically, plasma digoxin levels averaged 31% of the mean peak level or 2.3 ng/ml.

Table 2: Normal electrocardiographic ranges for the cat. Lead II.

Heart rate	110-260 beats/min
P wave duration	0.02-0.06 sec.
P-Q interval	0.04-0.12 sec.
QRS duration	0.02-0.06 sec.
Q-T interval	0.08-0.20 sec.
P wave	0.05-0.30 mV
R wave	0.20-1.75 mV

Figure 14: Cat No. 100. Electrocardiogram recorded two hours following oral digoxin (0.011 mg/kg) on the fourth day of a four-day trial.



Lead II, 25 mm/sec, 1 mV/cm

Table 3: Lead II electrocardiographic ranges recorded from five cats given single daily oral doses of digoxin elixir (0.011 mg/kg) for four consecutive days. Twenty-two electrocardiograms were recorded from each cat over the four day period.

Heart rate	130-260 beats/min
P wave duration	0.03-0.05 sec.
P-Q interval	0.07-0.12 sec.
QRS duration	0.02-0.05 sec.
Q-T interval	0.12-0.20 sec.
P wave amplitude	0.08-0.15 mV
R wave amplitude	0.20-1.50 mV
T wave amplitude	0.07-0.35 mV

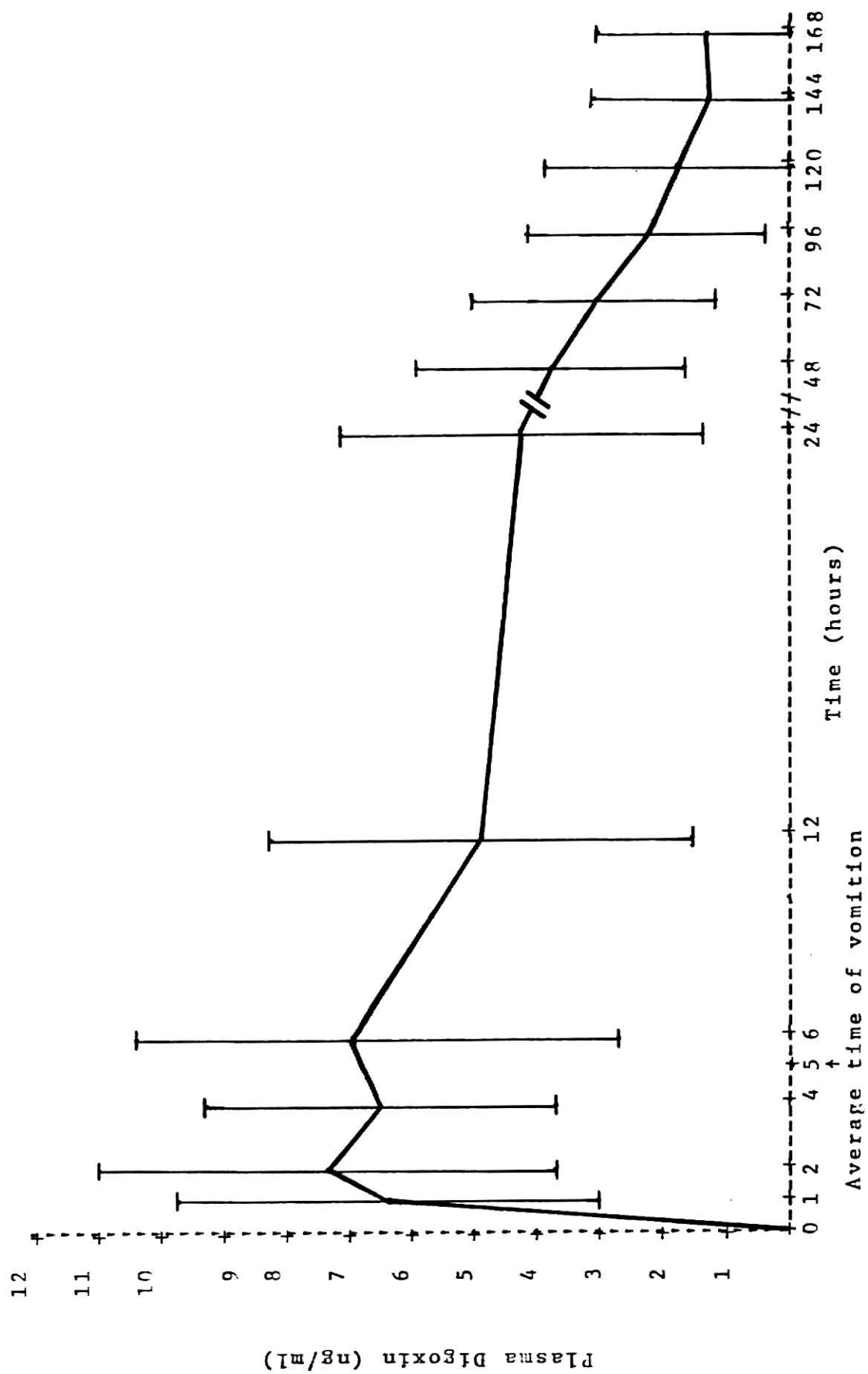


Figure 15

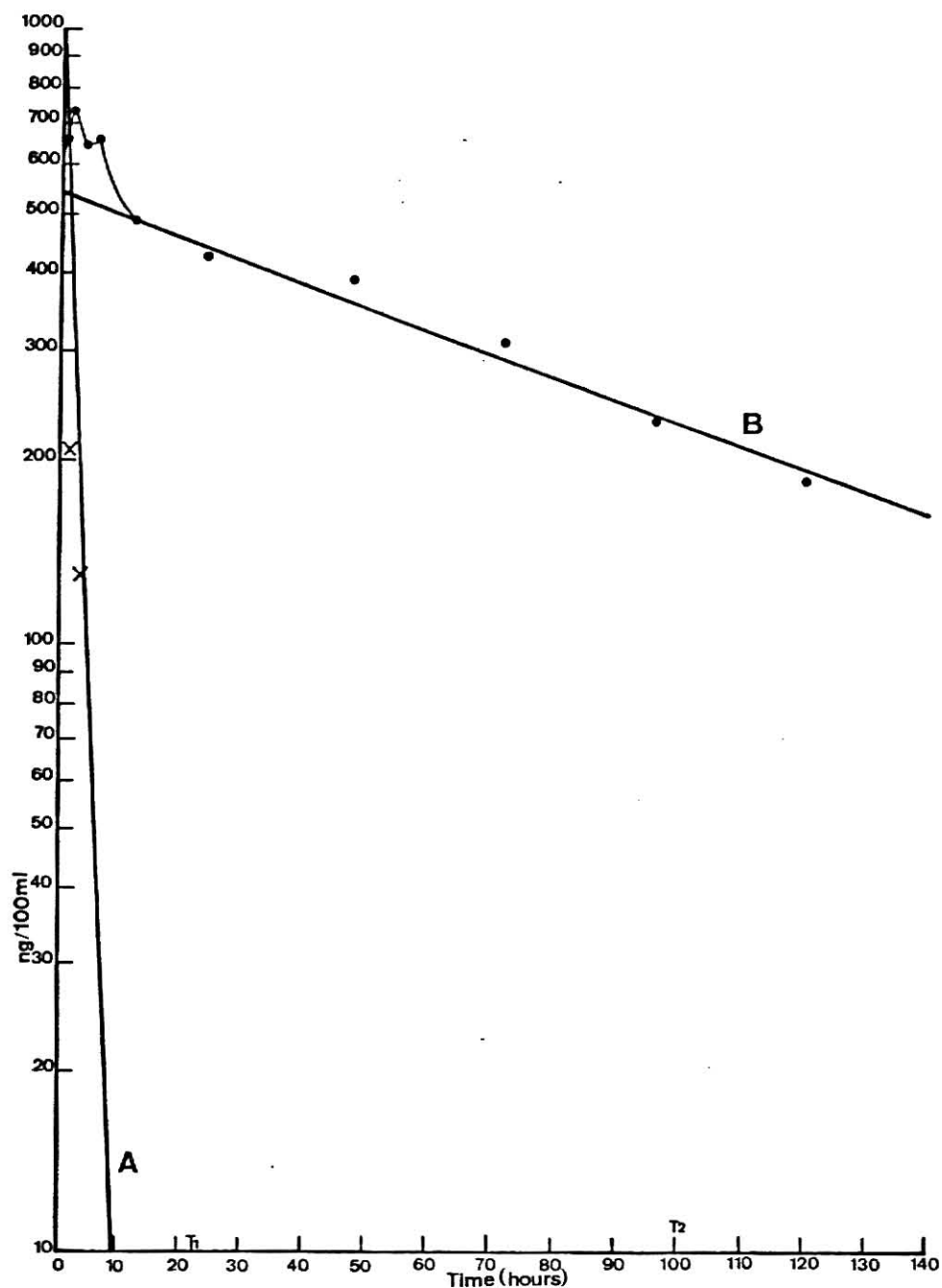


Figure 16 - PLASMA TURNOVER OF DIGOXIN AFTER ORAL ADMINISTRATION OF A TOXIC DOSE OF ELIXIR (AVERAGE SIX CATS). Digoxin concentration in plasma shown on semilogarithmic scale on the ordinate; time shown on the abscissa. Plotted points (•) represent the actual plasma digoxin concentration. Line B is derived as previously explained and represents metabolism and excretion of digoxin. The dominant half-time is 88 hours. Line A is derived as explained (x) and represents distribution and binding of digoxin to tissue. It has a half-time of 90 minutes.¹²

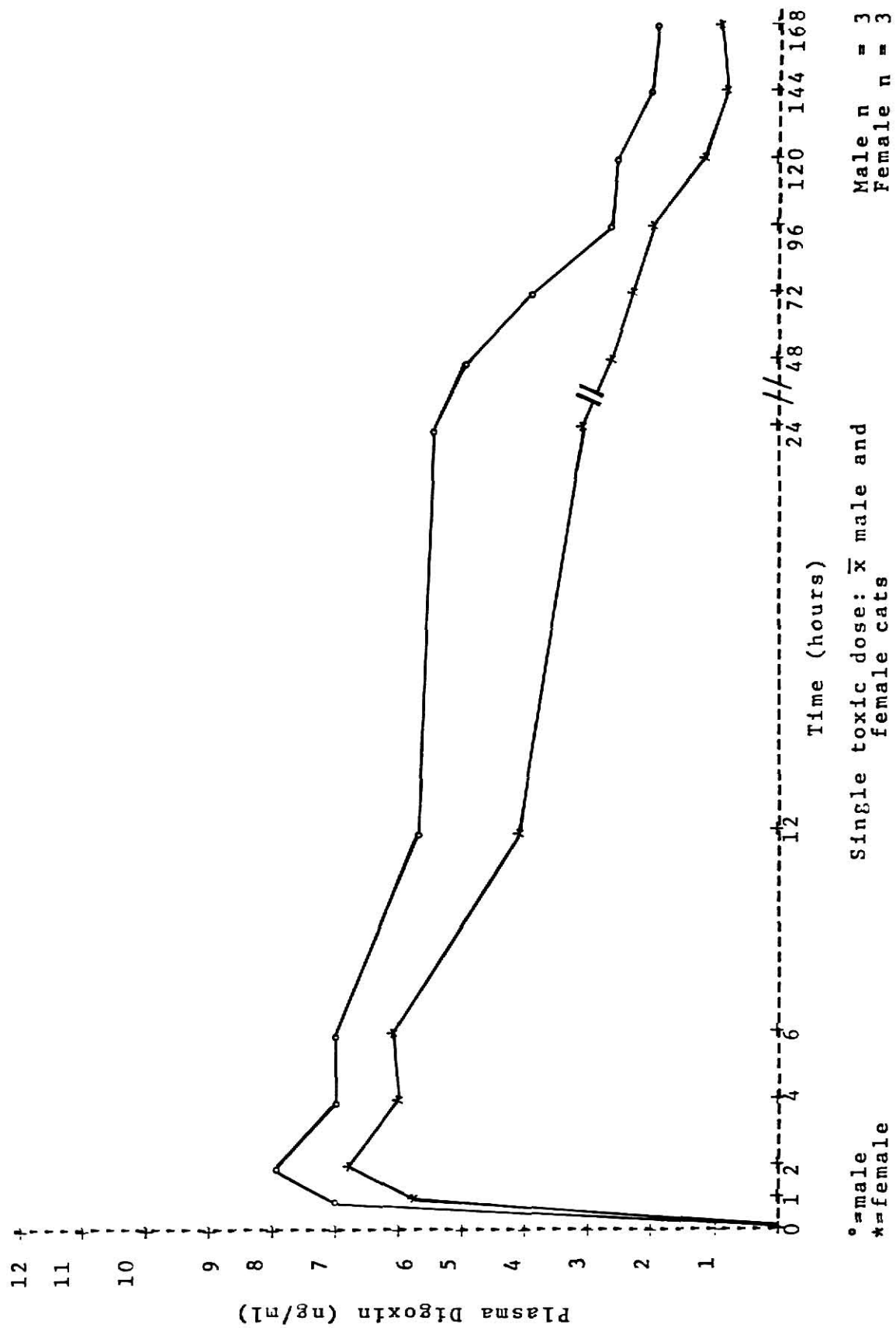
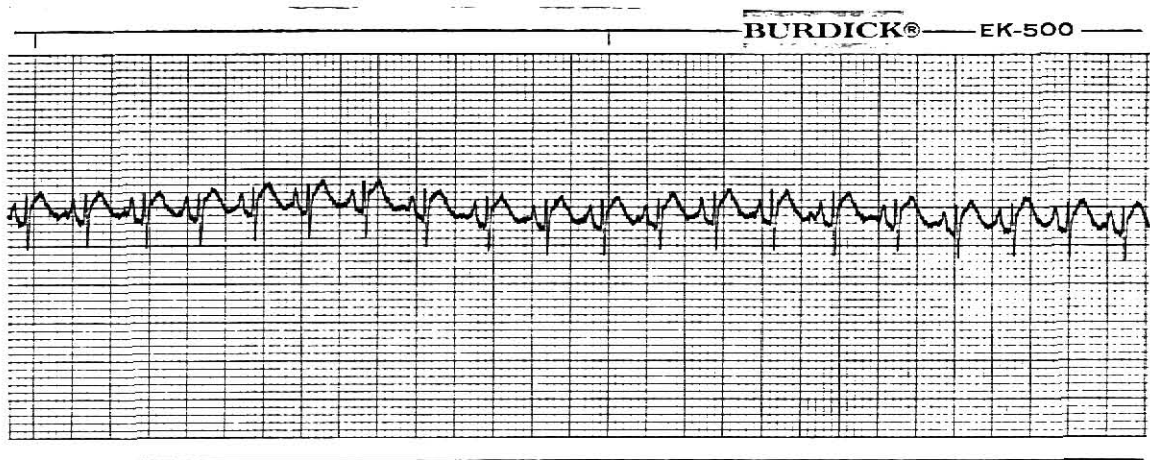


Figure 17

Changes in the electrocardiograms, if any, were slight. Three cats showed an increase in the P-Q intervals with an average increase of 0.026 seconds. One of the cats showed an elevated S-T segment and another showed a decreased heart rate with an elevated S-T segment (Fig. 18). All of the changes seen in the electrocardiograms occurred at the time of vomition or after, with an average time after vomition of 17.7 hours. None of the cats showed electrocardiographic changes before they were clinically ill. Table 4 lists the pre- and post-dosage electrocardiographic values seen in cat No. 44 with the most significant EKG changes noted.

Figure 18: Cat No. 44. Electrocardiogram recorded 72 hours following oral digoxin, 0.11 mg/kg, showing elevated S-T segment.



Lead II, 25 mm/sec, 1 mV/cm.

Table 4: Lead II electrocardiographic values recorded from cat No. 44 that was given a single toxic oral dose of digoxin elixir (0.11 mg/kg).

Hours		Post Dosage	Heart rate (beats/min)	Rhythm	Duration (sec.)				Amplitude (mV)			Interpretation, comments
Date	Post				P wave	P-Q Int.	Q-T Int.	P wave	R wave	T wave		
7/12/76	0	NSR*	200		0.06	0.08	0.04	0.17	0.20	0.50	0.20	WNL ⁺
7/14/76	0	NSR	220		0.06	0.10	0.04	0.16	0.25	0.30	0.20	WNL
7/15/76	0	NSR	210		0.06	0.09	0.04	0.18	0.20	0.30	0.20	WNL
7/16/76	0	NSR	200		0.05	0.09	0.04	0.18	0.20	0.40	0.20	WNL
7/19/76	0	NSR	220		0.05	0.09	0.04	0.18	0.20	0.35	0.15	WNL
7/20/76												Admin. digoxin elixir
7/20/76	1	NSR	220		0.05	0.08	0.04	0.16	0.20	0.30	0.20	WNL
7/20/76	2	NSR	210		0.05	0.08	0.04	0.17	0.20	0.35	0.20	WNL
7/20/76	4	NSR	200		0.05	0.08	0.04	0.17	0.20	0.25	0.20	WNL
7/20/76	6	NSR	180		0.05	0.10	0.04	0.16	0.20	0.25	0.25	WNL
7/20/76	12	NSR	160		0.04	0.09	0.04	0.17	0.15	0.40	0.35	WNL, vomition
7/21/76	24	NSR	140		0.04	0.08	0.04	0.16	0.15	0.40	0.25	WNL, decreased heart r.
7/22/76	48	NSR	180		0.05	0.08	0.04	0.16	0.20	0.30	0.20	WNL
7/23/76	72	NSR	200		0.05	0.08	0.04	0.18	0.20	0.40	0.20	Elevated S-T segment
7/26/76	144	NSR	180		0.05	0.08	0.04	0.16	0.20	0.40	0.20	Slightly elev. S-T seg.
7/27/76	168	NSR	200		0.05	0.08	0.04	0.16	0.20	0.40	0.30	WNL

*Normal Sinus Rhythm

⁺Within Normal Limits

DISCUSSION:

Digoxin is most often administered to the cat via the oral route. Maximum blood levels of digoxin are shown in this study to be reached by using the elixir form, based on the same dosage per pound of body weight (0.011 mg/kg), as compared to the tablet or crushed tablet mixed with food. White demonstrated in cats that digoxin tablets are absorbed very slowly whereas digoxin dissolved in aqueous alcohol is absorbed more completely and uniformly in a shorter time.⁶⁵ Similar results have been reported in man.^{31,36} Because additional time is required to solubilize the solid form in the intestinal tract,⁶⁵ there is insufficient time for all the digoxin to reach the solution state while in the upper part of the intestinal tract where most of digoxin absorption occurs.⁶³ Therefore, the more slowly absorbed preparations have peak levels much lower than those obtained with elixir or aqueous solutions.⁶³ Since the digoxin in the elixir is already in a soluble form, it would be expected to be more readily absorbed than that in tablet formulation.²⁰ The elixir has the added advantage of more accurate dosage based on body weight due to the greater flexibility of the liquid.

Hamlin has shown in the dog that powdered digitoxin is absorbed poorly while tincture of digitoxin is absorbed completely.²⁵ Crushed tablets (powder) mixed with food would have the added disadvantage of increased ingesta bulk causing less contact with absorptive sites in addition to delayed gastric emptying.²⁰ Delayed gastric emptying would subject the digoxin to the hydrolyzing action of acidic gastric juice for a longer period of time,³² decreasing the amount of active digoxin absorbed. The data from Experiment 1 indicates that it would be necessary to double the normal therapeutic dose when using tablets in order

to obtain a similar peak blood level as that reached with the elixir. However, this conclusion is based on the information derived from the tablet formulation used in this lab, the date of manufacture being unknown. It has been shown that some digoxin tablets manufactured after 1972 have a significantly greater bioavailability with twice the absorption rate as the pre-1972 tablets.¹⁷

The dominant half-times for digoxin at the therapeutic dose level were as follows: 21 hours for the elixir form, 25.5 hours for the tablet form, 20.5 hours for the crushed tablet form mixed with food, and 20 hours for day 1 of the four-day trial. These similar half-times, which represent the metabolism and excretion of digoxin, along with the similar half-times taken from the early portion of the plasma disappearance curve which represent distribution and tissue binding,¹² indicate that the variation in digoxin plasma levels is due to differences in bioavailability and intestinal absorption of the various forms. These half-times compare favorably with other studies. The dominant half-time for man given digoxin elixir orally is 31.3 hours while the plasma half-time derived from the early portion of the curve is 50 minutes.¹² In the dog given digoxin intravenously, the initial half-time is 30 minutes and the dominant half-time is 23 hours.¹⁴

The data from all three experiments indicates there is a different effect on plasma digoxin levels due to sex. Male cats show higher peak plasma levels than female cats. The protective effect of estrogen against digitalis toxicity has been documented.^{22,49} The protective effect of nonestrogenic steroids has also been reported.^{22,54,55} Female dogs given a single toxic dose of digoxin exhibit a greater delay in the onset of arrhythmia than do male dogs.²³ Another study utilizing

castrated bitches with and without estrogen replacement and dogs in natural estrus indicated that estrogenic hormones exert a protective action against the toxic effects of digoxin on the myocardium.²³ An increased resistance to the cardiotoxic effects of cardiac glycosides has been shown to occur in women.⁵⁰ Rodensky showed that female rabbits require a longer period of time to succumb to the cardiotoxic effects of continuous intravenous infusion of digoxin than do male rabbits.⁴⁹ The exact mechanism of action of this protective effect is still unknown.

The secondary increase in plasma digoxin seen in the plasma concentration curves would indicate a storage of digoxin with a subsequent release at a later time. Although the secondary increase was not statistically significant in this study, bile cycling of digoxin in man can cause secondary peaks in plasma concentration curves when the patients eat soon after an oral dose.¹⁷ Due to the experimental protocol of providing food to the cats ad libitum, the post-dosage feeding time is not known and, therefore, cannot be correlated with the secondary plasma peak. Studies involving the biliary excretion of digoxin and other digitalis glycosides have been numerous.^{13,24,30,34,44,52} Digoxin is absorbed from the gut, transported via the portal vein to the liver, some is excreted in the bile principally in its original form, most is reabsorbed from the gut and redistributed. The percent of absorbed dose that is excreted in the bile shows some species variability; the cat has been shown to excrete 5.2% of the absorbed dose in three hours³⁴ as compared to 14.8% in eight days in man.⁴⁴ The long dominant half-time seen in the toxicity study (Experiment 3) suggests augmented biliary recycling due to the high digoxin levels and, therefore, slowed excretion of digoxin.

Biliary recycling is thought to have an effect on the cumulative levels of digoxin.⁴⁵ These cumulative levels from a daily dose schedule are apparent from the four-day daily dose trial (Experiment 2). In man digitalis poisoning is usually due to the cumulative effect of maintenance doses taken over relatively long periods of time²⁰ and toxicity is considered to be present when digoxin plasma levels are above 4 ng/ml.⁶ The increasing daily blood digoxin levels seen over the four-day period with the same daily oral dose would indicate a potential toxicity problem even though the administered dose is unchanged and within the therapeutic range. The toxicity study (Experiment 3) shows that the clinical signs of toxicity appear in the cat before any electrocardiographic changes occur, making early detection of digitalis toxicity easier for both the client and the practitioner. Adjustments can be made in the dosage schedule before serious arrhythmias occur. This study indicates a plasma digoxin level of 2.3 ng/ml is not toxic. It has been recommended that after the development of toxic signs, the next two doses of digoxin should be withheld⁴ and then resumed at a reduced dosage level.

From this study it can be concluded that the highest therapeutic levels of plasma digoxin can be obtained with the elixir form, along with added ease and accuracy of administration. Both practitioner and client should be aware of the cumulative effect of digoxin from daily maintenance doses which may lead to digitalis toxicity. Fortunately, extracardiac signs of toxicity appear initially, allowing early removal of the drug before serious cardiac arrhythmias occur. The significant difference in plasma digoxin levels between male and female cats indicates toms and neuters would be more susceptible to digitalis toxicity than intact queens.

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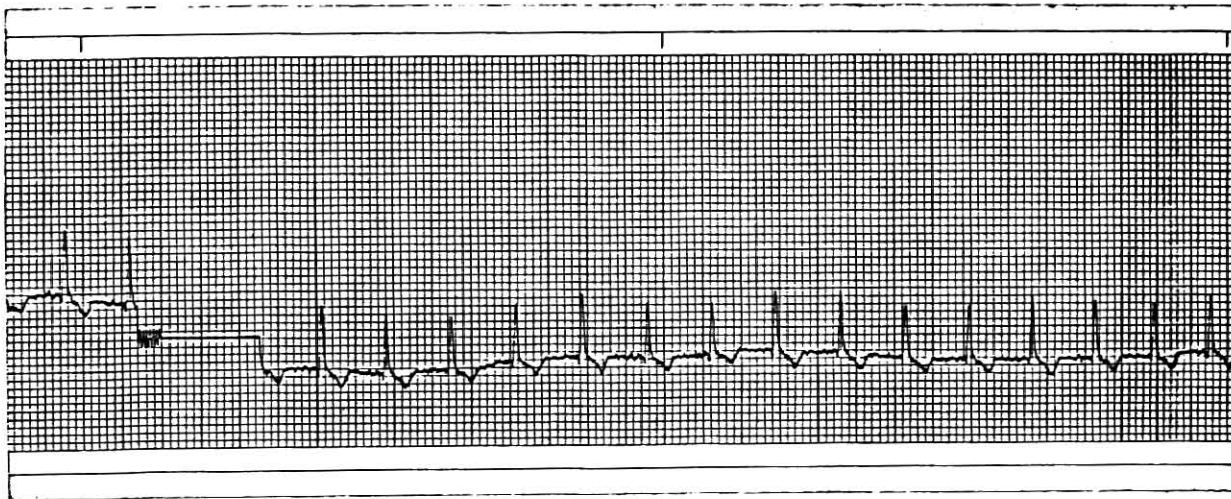
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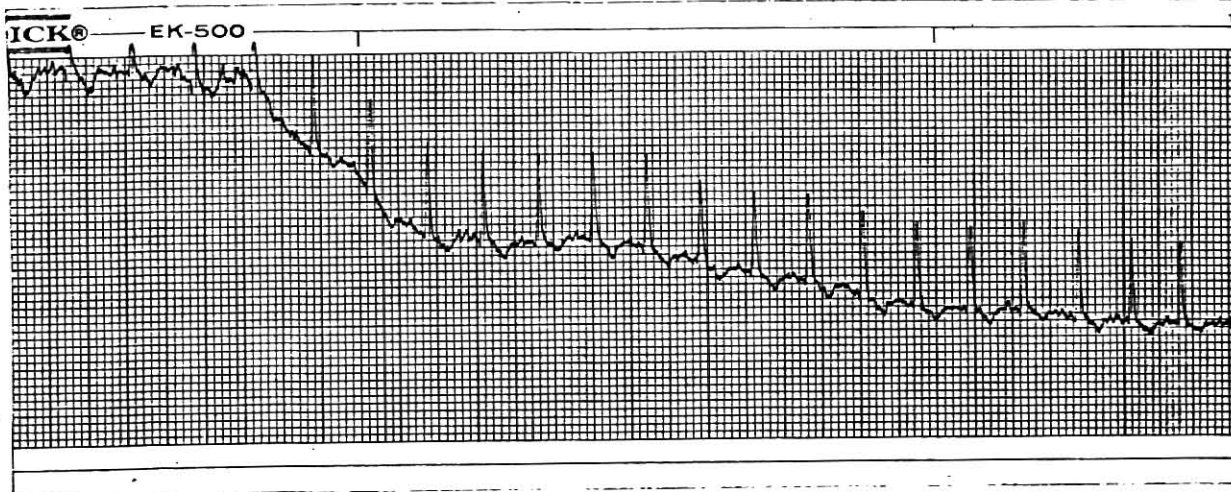
APPENDICES

#100 "Patience" 6/18/76 Pre-digoxin (0.005 mg/lb.), Day 0

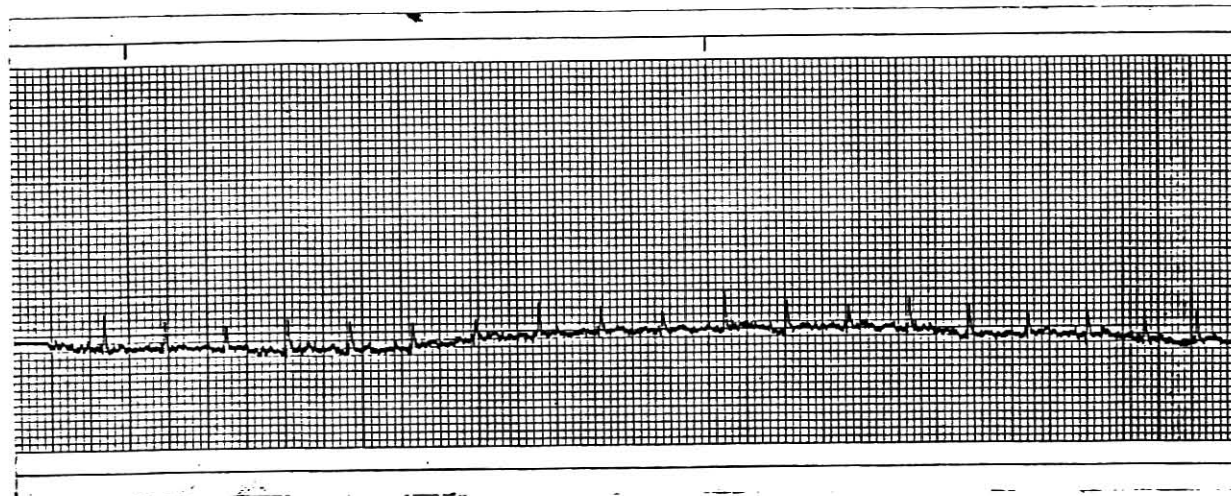
Interpretation Within normal limits



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-18-76 Trial 0.011 mg/kg; Pre D; Day 0

RHYTHM Normal Sinus Rhythm

RATE 190

P wave duration: 0.03 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.14 sec. - Lead II

Maximum Voltage

P wave .1 mV, Lead II

R wave 1.1 mV, Lead II

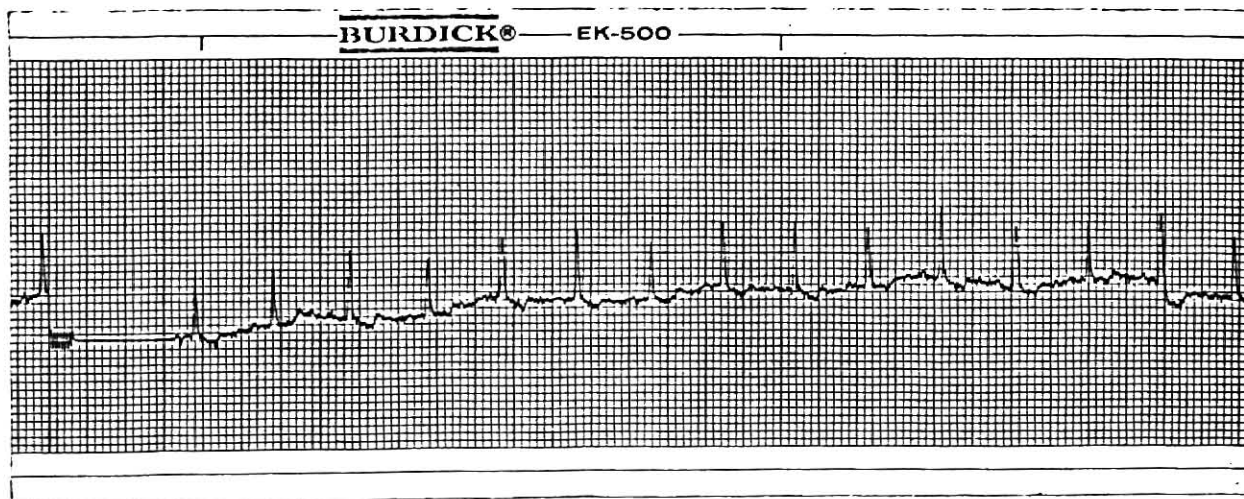
T wave .15 mV, Lead II

REMARKS:

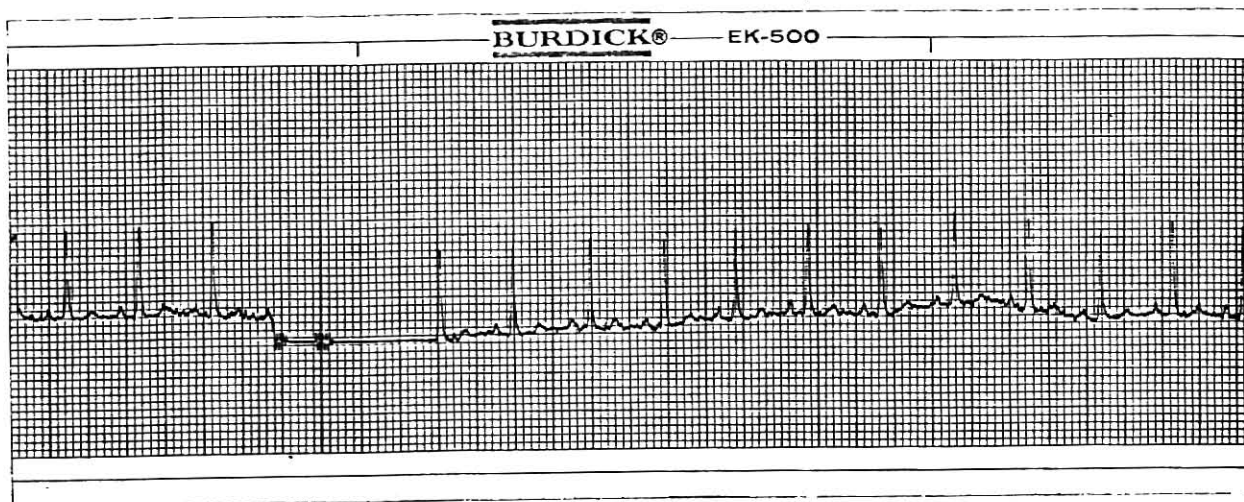
INTERPRETATION: Within normal limits

#100 "Patience" 6/21/76 Pre-digoxin (0.005 mg/lb.), Day 1

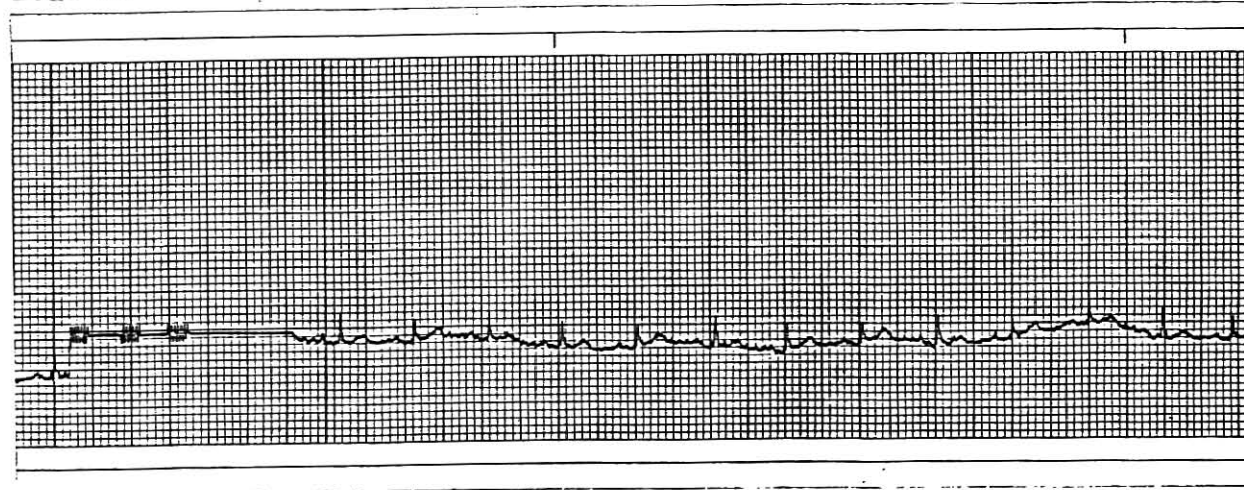
Interpretation Within normal limits



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-21-76 Trial 0.011 mg/kg; Pre D; Day 1

RHYTHM Normal Sinus Rhythm

RATE 150

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.20 sec. - Lead II

Maximum Voltage

P wave .15 mV, Lead II

R wave 1.15 mV, Lead II

T wave .15 mV, Lead II

REMARKS:

INTERPRETATION: Within normal limits

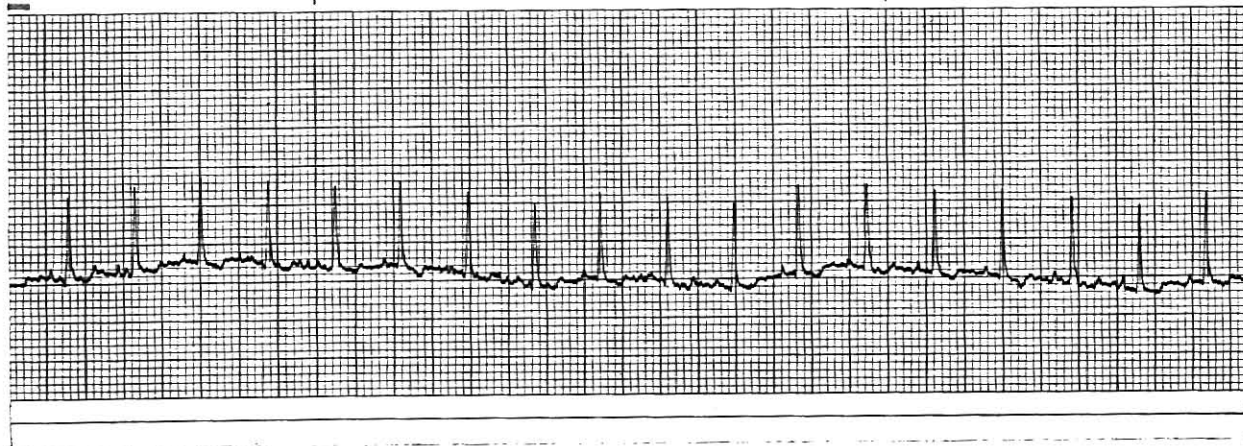
#100 "Patience" 6/21/76 1 hour post-digoxin (0.005 mg/lb.), Day 1

Interpretation WNL



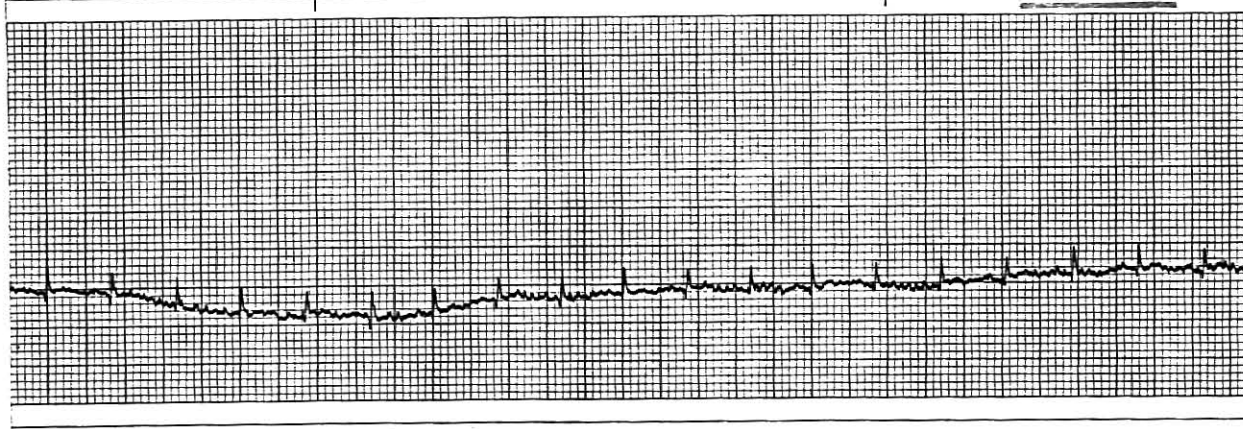
Lead I

K® — EK-500



Lead II

BURDICK®



Lead III

Cat #100, "Patience" Date 6-21-76 Trial 0.011 mg/kg; 1 hr PD; Day 1

RHYTHM Normal Sinus Rhythm

RATE 160

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.10 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .12 mV, Lead II

R wave 1.2 mV, Lead II

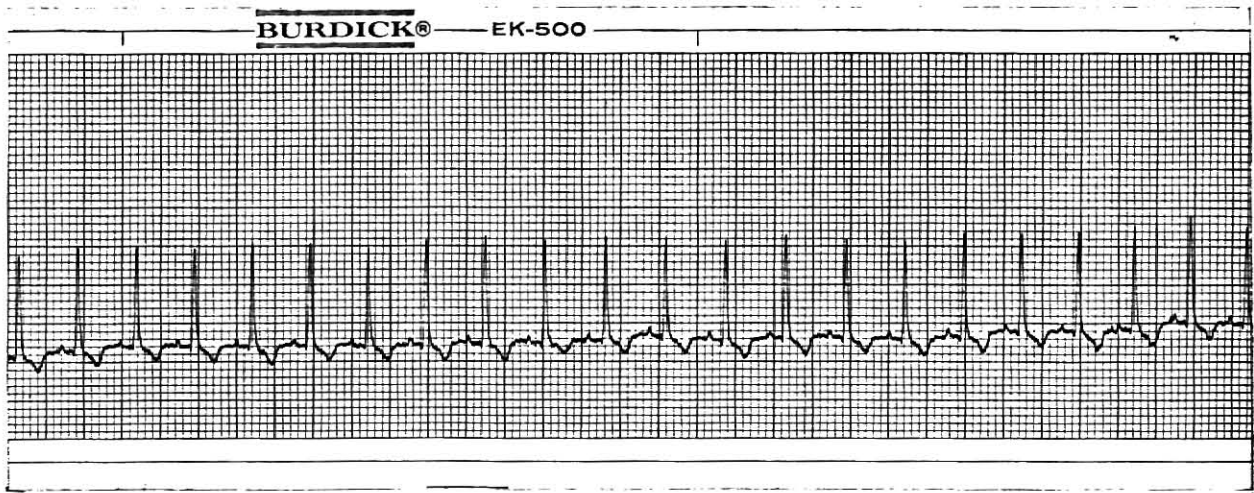
T wave .1 mV, Lead II

REMARKS: Slight increase in P-Q interval

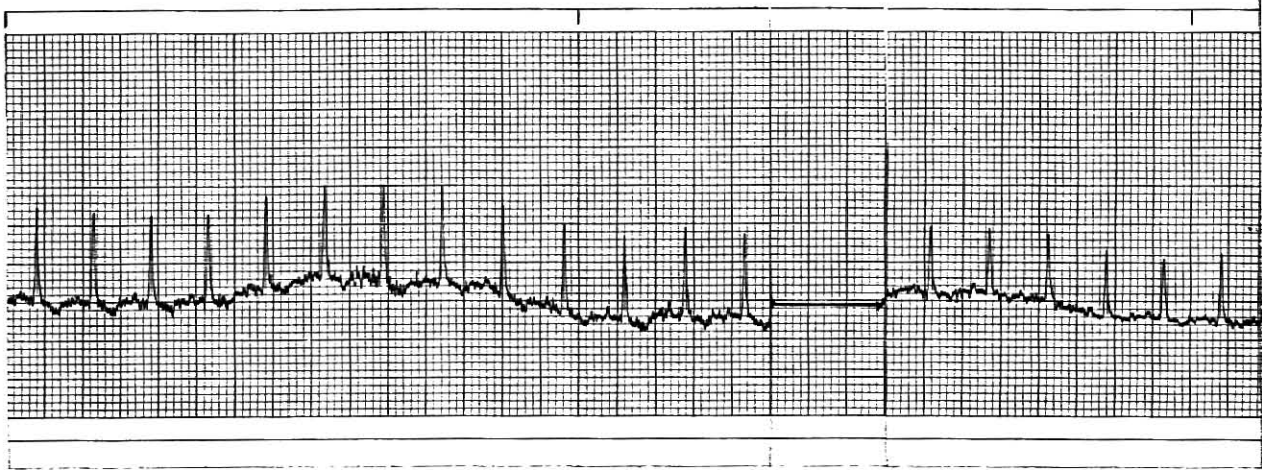
INTERPRETATION: Within normal limits

#100 "Patience" 6/21/76 2 hour post-digoxin (0.005 mg/lb.), Day 1

Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-21-76 Trial 0.011 mg/kg; 2 hr PD; Day 1

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.04 sec. - Lead I

P-Q interval: 0.08 sec. - Lead I

QRS duration: 0.04 sec. - Lead I

Q-T interval: 0.16 sec. - Lead I

Maximum Voltage

P wave .12 mV, Lead I

R wave 1.25 mV, Lead I

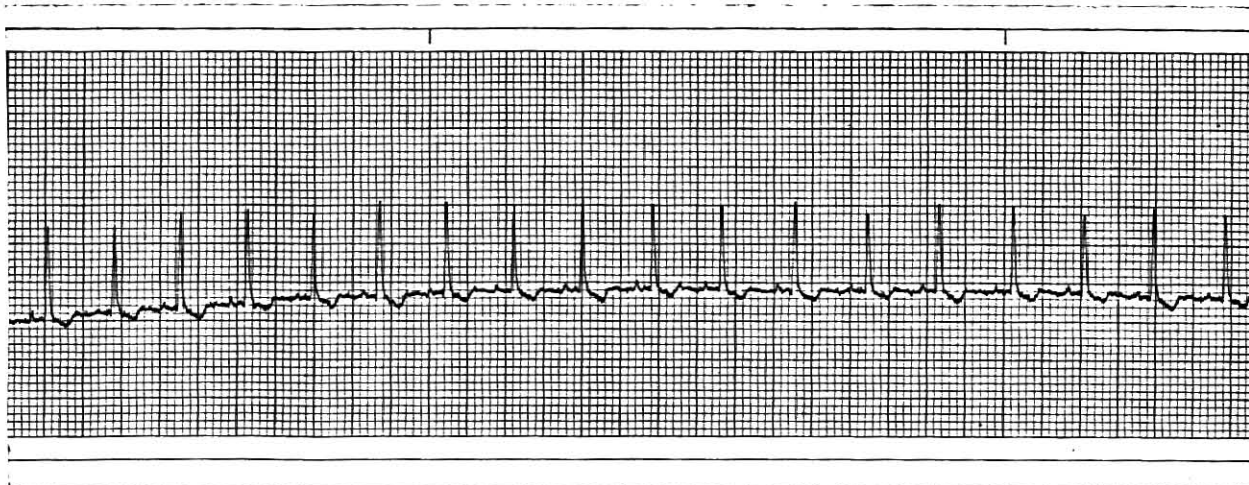
T wave .15 mV, Lead I

REMARKS:

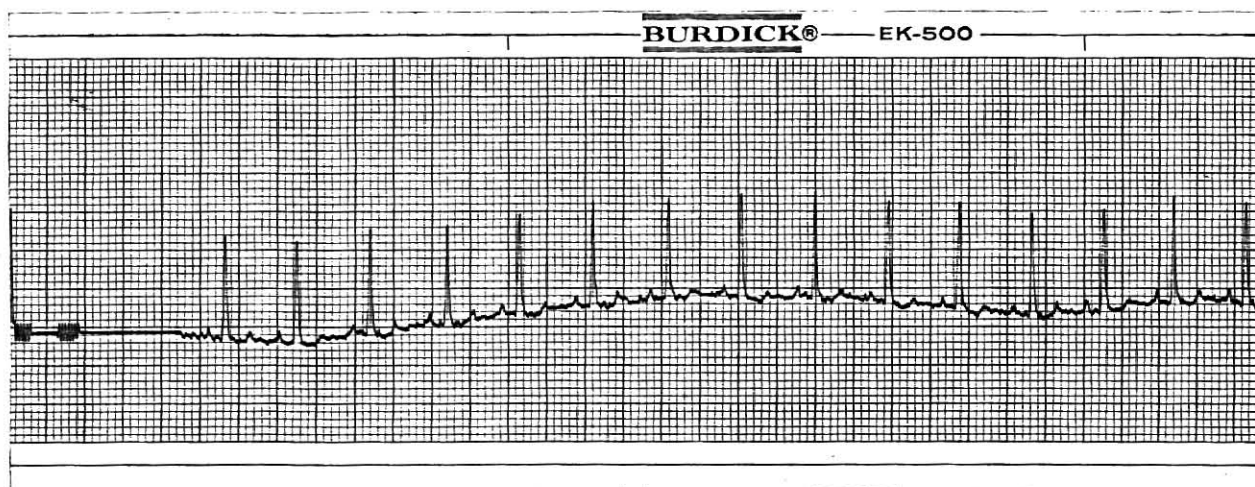
INTERPRETATION: Within normal limits

#100 "Patience" 6/21/76 4 hour post-digoxin (0.005 mg/lb.), Day 1

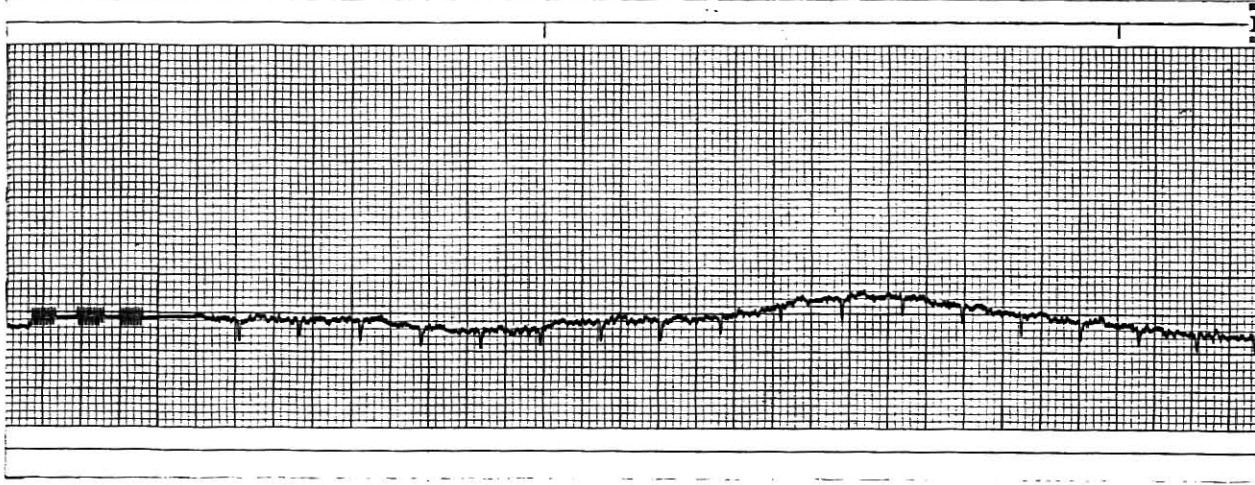
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-21-76 Trial 0.011 mg/kg; 4 hr PD; Day 1

RHYTHM Normal Sinus Rhythm

RATE 160

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.18 sec. - Lead II

Maximum Voltage

P wave .12 mV, Lead II

R wave 1.4 mV, Lead II

T wave .15 mV, Lead II

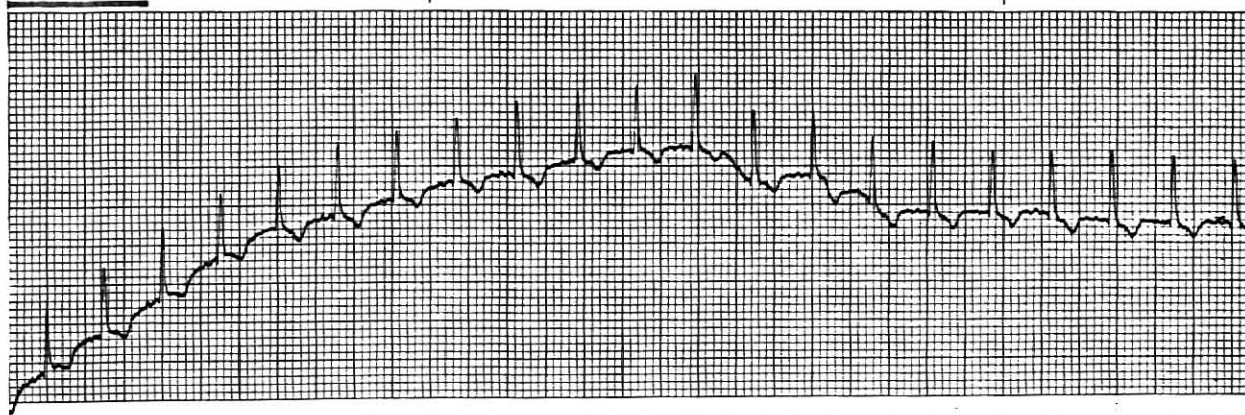
REMARKS:

INTERPRETATION: Within normal limits

#100 "Patience" 6/21/76 6 hour post-digoxin (0.005 mg/lb.), Day 1

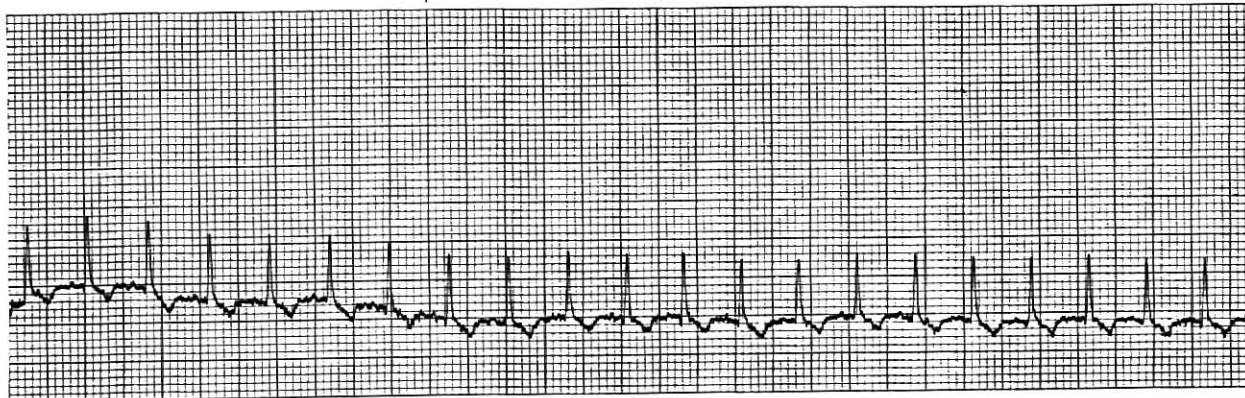
Interpretation WNL

BURDICK® — EK-500



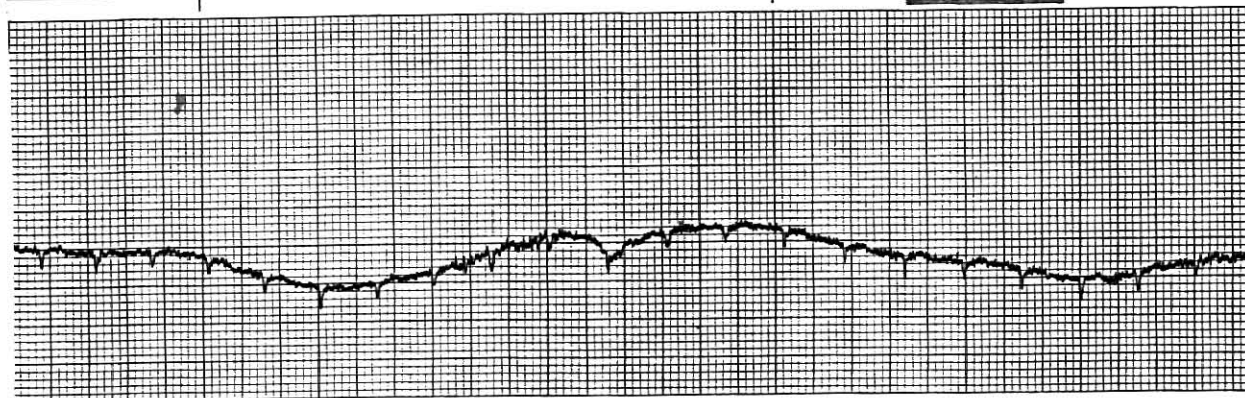
Lead I

BURDICK®



Lead II

BURDICK® — EK-500



Lead III

Cat #100, "Patience" Date 6-21-76 Trial 0.011 mg/kg; 6 hr PD; Day 1

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .1 mV, Lead II

R wave .9 mV, Lead II

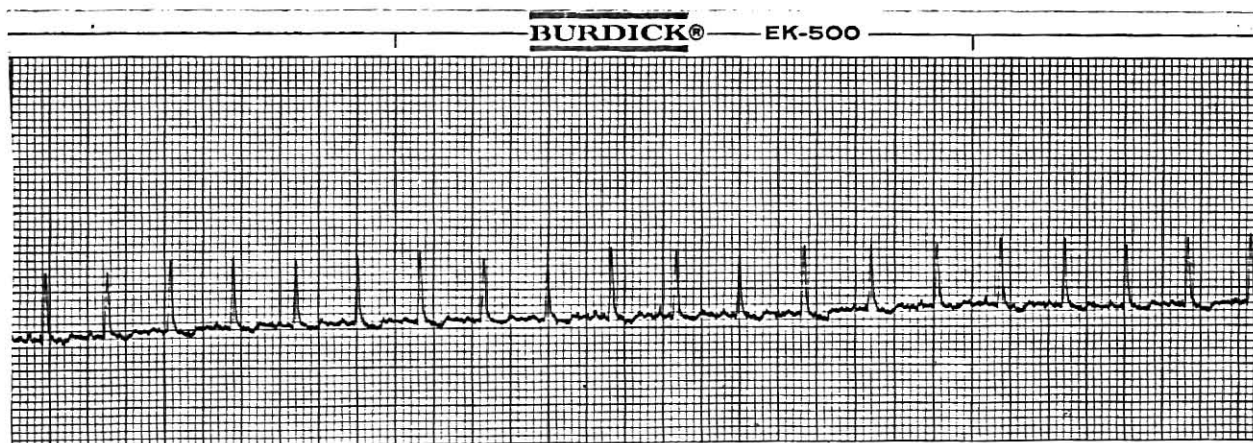
T wave .2 mV, Lead II

REMARKS:

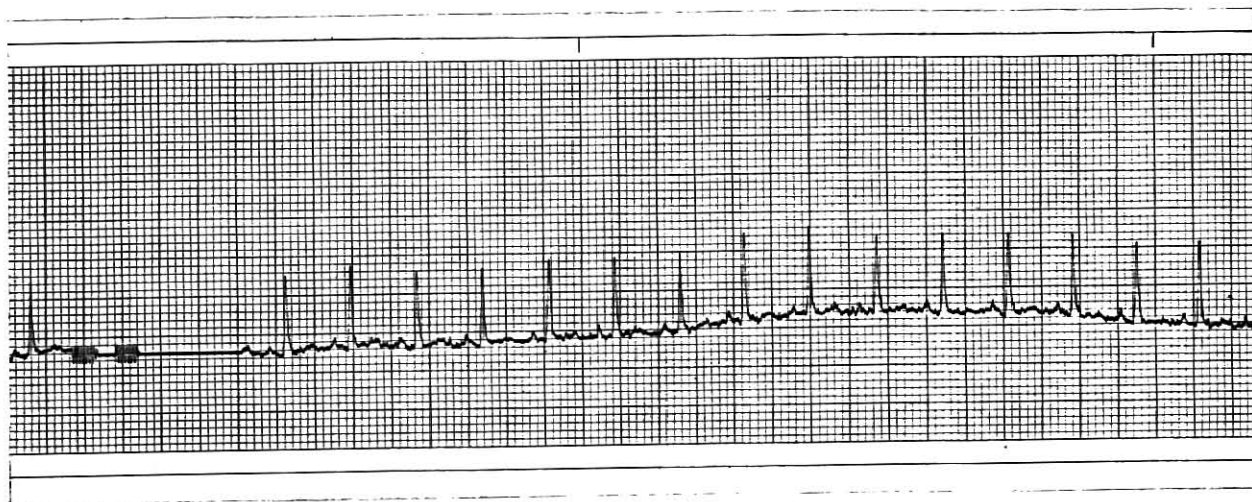
INTERPRETATION: Within normal limits

#100 "Patience" 6/22/76 24 hour post-digoxin (0.005 mg/lb.), Day 1

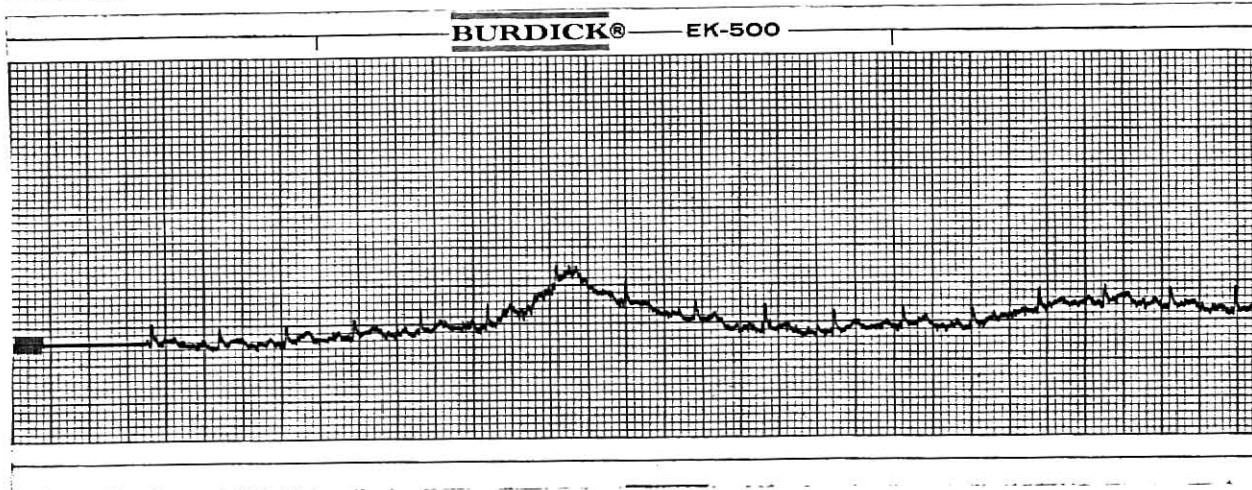
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-22-76 Trial 0.011 mg/kg; 24 hr PD; Day 1

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.06 sec. - Lead II

Q-T interval: 0.18 sec. - Lead II

Maximum Voltage

P wave .15 mV, Lead II

R wave 1.1 mV, Lead II

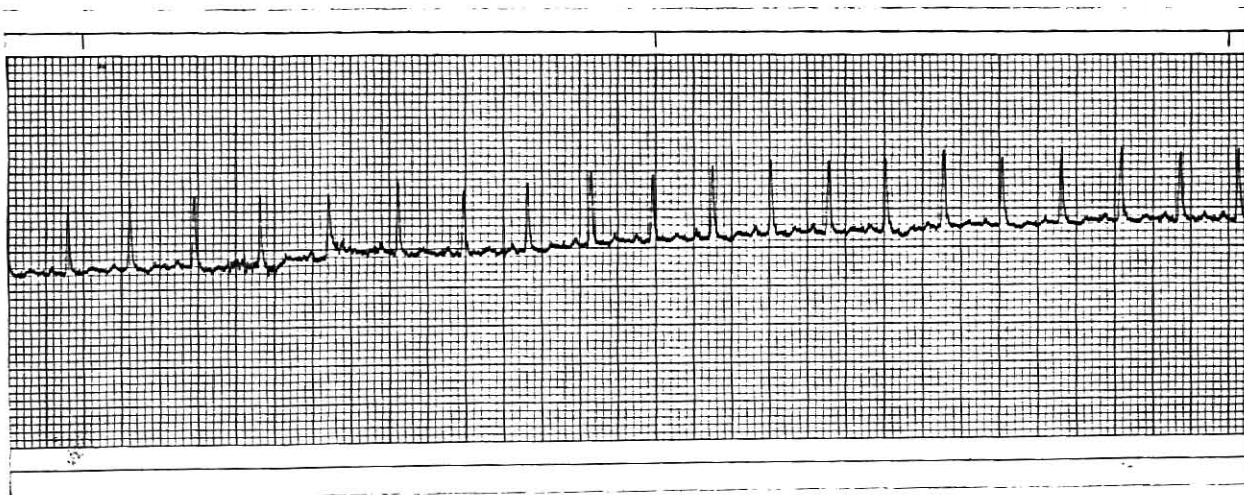
T wave .1 mV, Lead II

REMARKS: _____

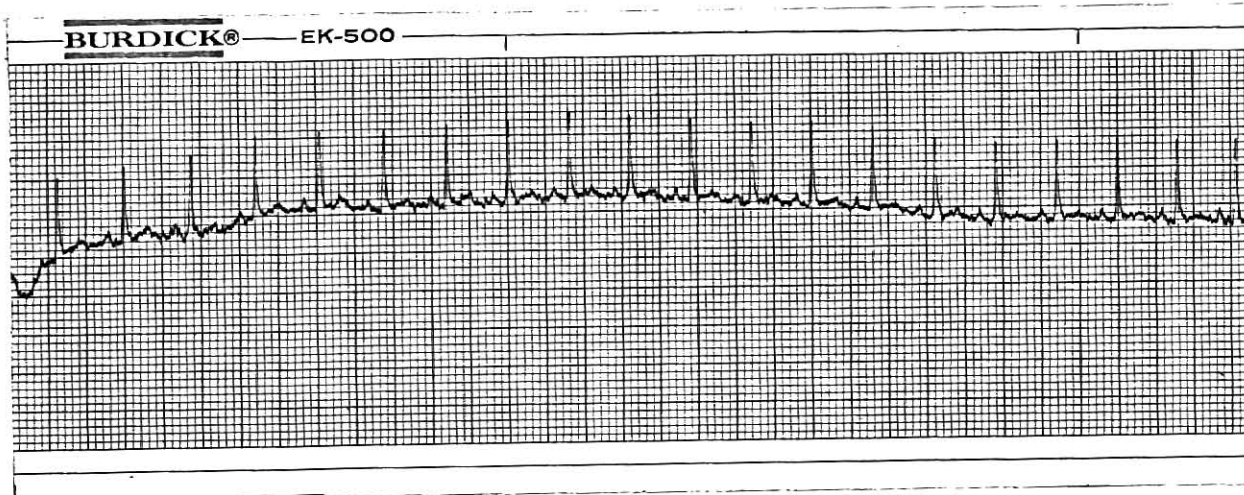
INTERPRETATION: Within normal limits

#100 "Patience" 6/22/76 1 hour post-digoxin (0.005 mg/lb.), Day 2

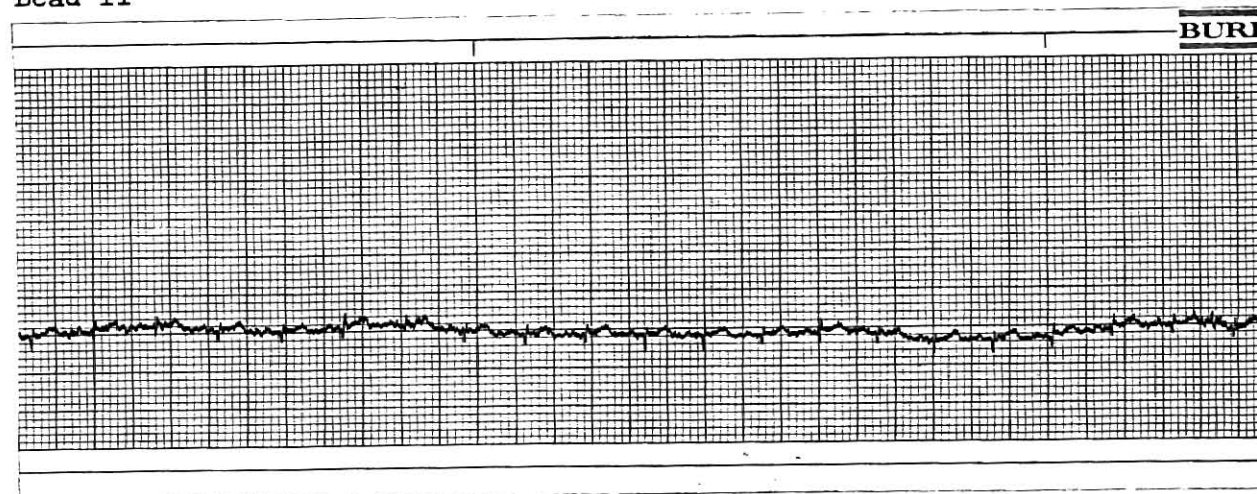
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-22-76 Trial 0.011 mg/kg; 1 hr PD; Day 2

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.18 sec. - Lead II

Maximum Voltage

P wave .15 mV, Lead II

R wave 1.1 mV, Lead II

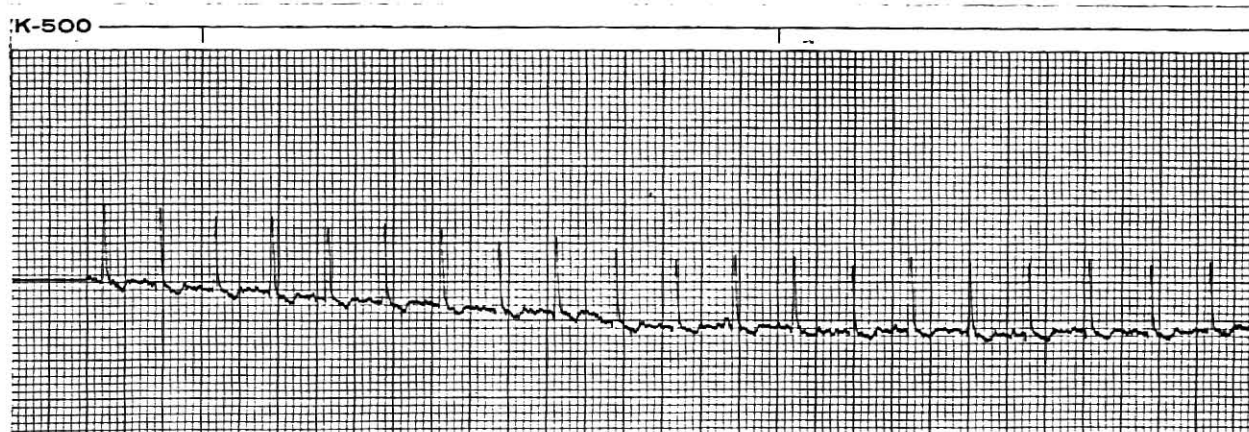
T wave .15 mV, Lead II

REMARKS:

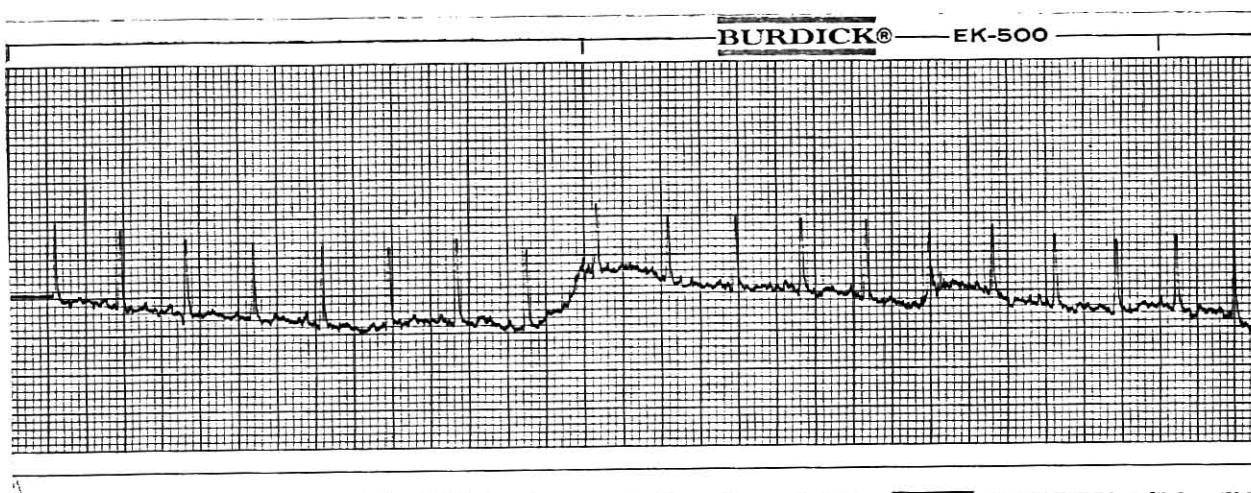
INTERPRETATION: Within normal limits

#100 "Patience" 6/22/76 2 hour post-digoxin (0.005 mg/lb.), Day 2

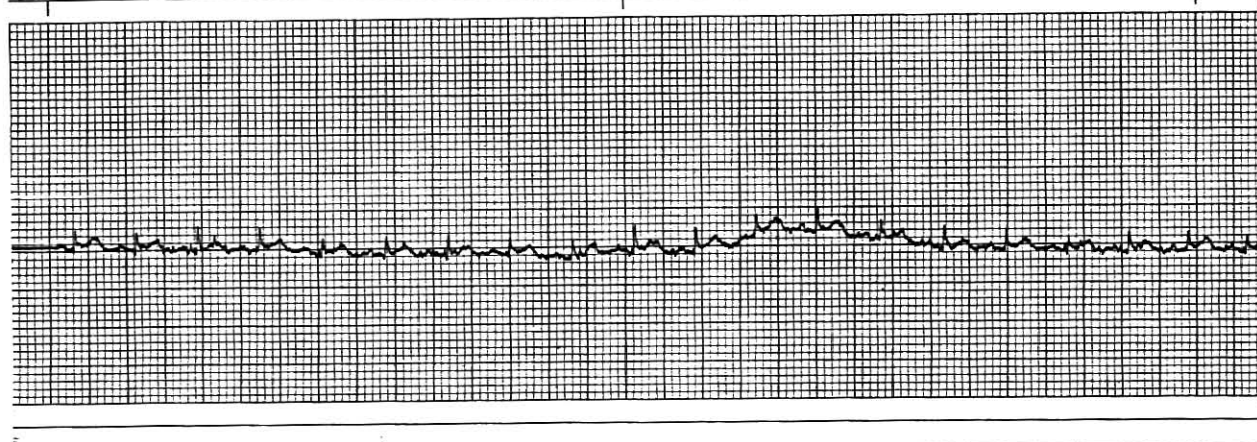
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-22-76 Trial 0.011 mg/kg; 2 hr PD; Day 2

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead I

Maximum Voltage

P wave .15 mV, Lead II

R wave .9 mV, Lead II

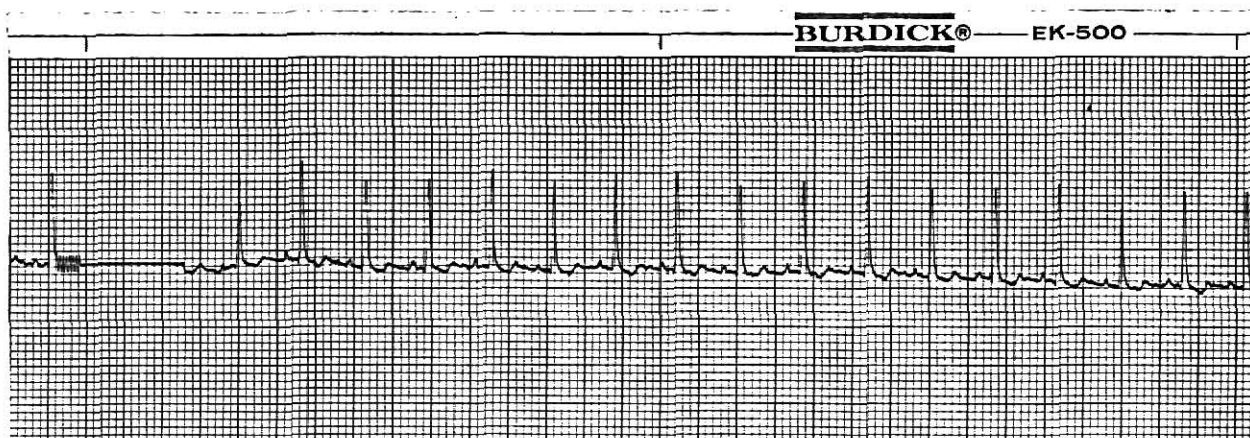
T wave .12 mV, Lead II

REMARKS:

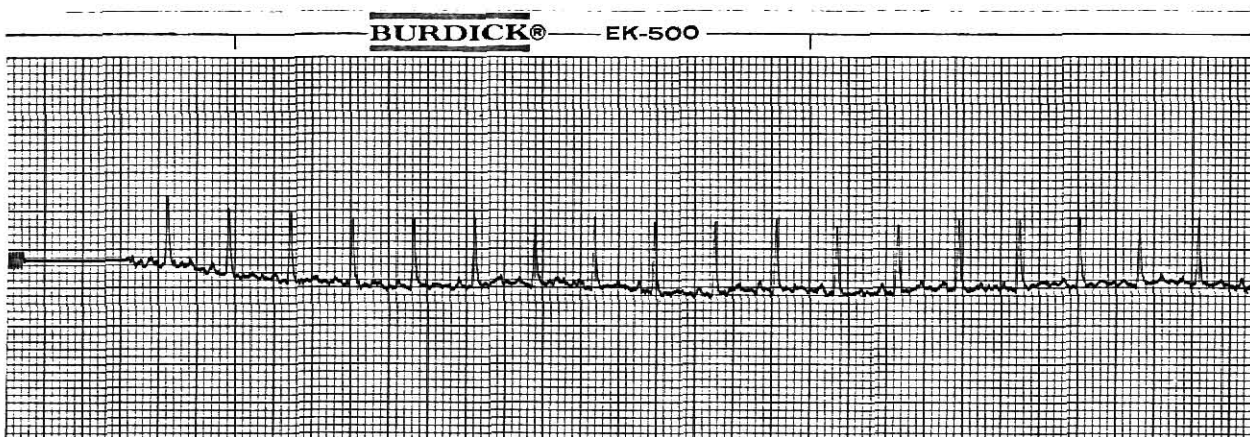
INTERPRETATION: Within normal limits

#100 "Patience" 6/22/76 4 hour post-digoxin (0.005 mg/lb.), Day 2

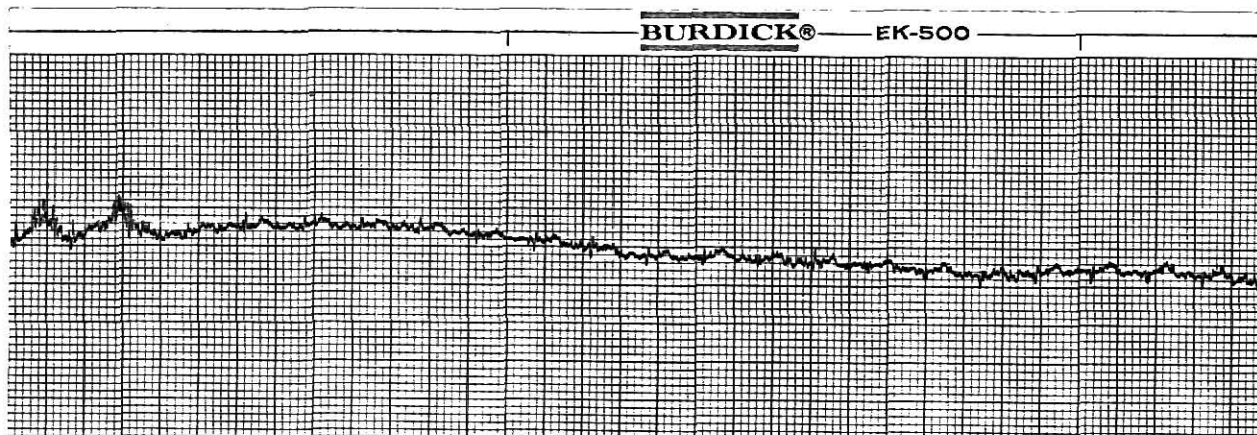
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-22-76 Trial 0.011 mg/kg; 4 hr PD; Day 2

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead I

P-Q interval: 0.08 sec. - Lead I

QRS duration: 0.04 sec. - Lead I

Q-T interval: 0.14 sec. - Lead I

Maximum Voltage

P wave .1 mV, Lead I

R wave 1.2 mV, Lead I

T wave .15 mV, Lead I

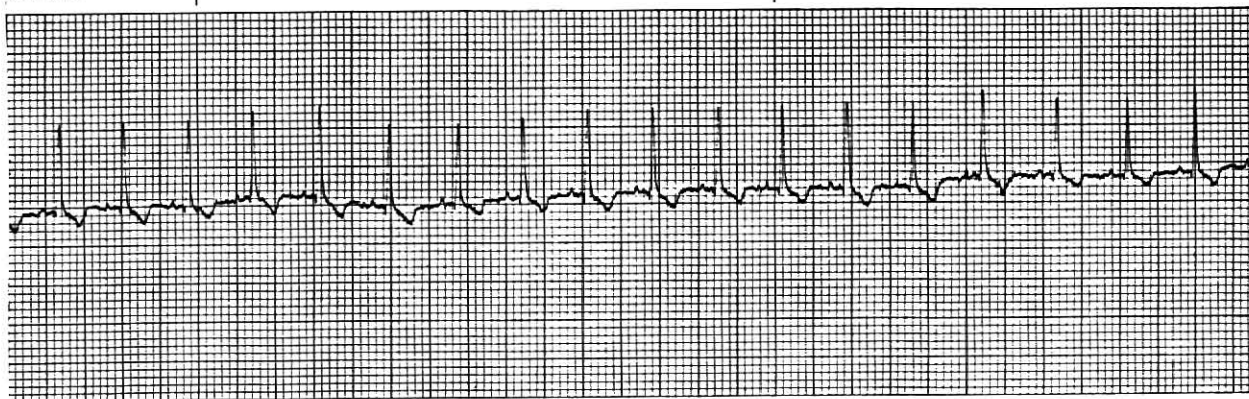
REMARKS: _____

INTERPRETATION: Within normal limits

#100 "Patience" 6/22/76 6 hour post-digoxin (0.005 mg/lb.), Day 2

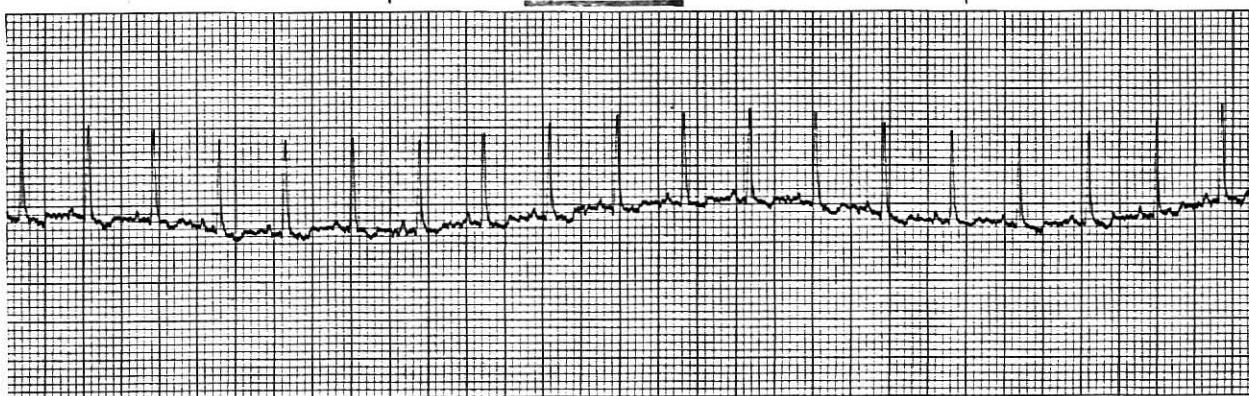
Interpretation WNL

K-500

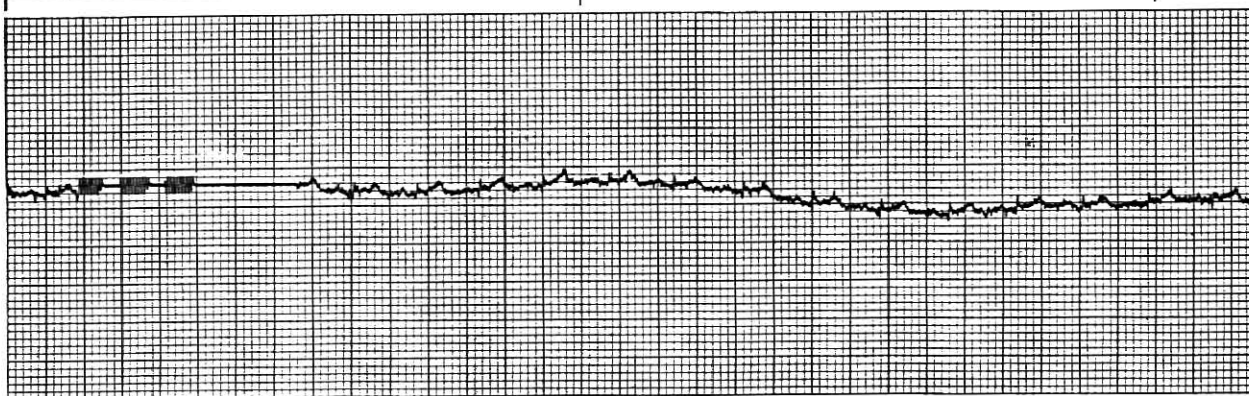


Lead I

BURDICK® EK-500



Lead II



Lead III

Cat #100, "Patience" Date 6-22-76 Trial 0.011 mg/kg; 6 hr PD; Day 2

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .12 mV, Lead II

R wave 1.2 mV, Lead II

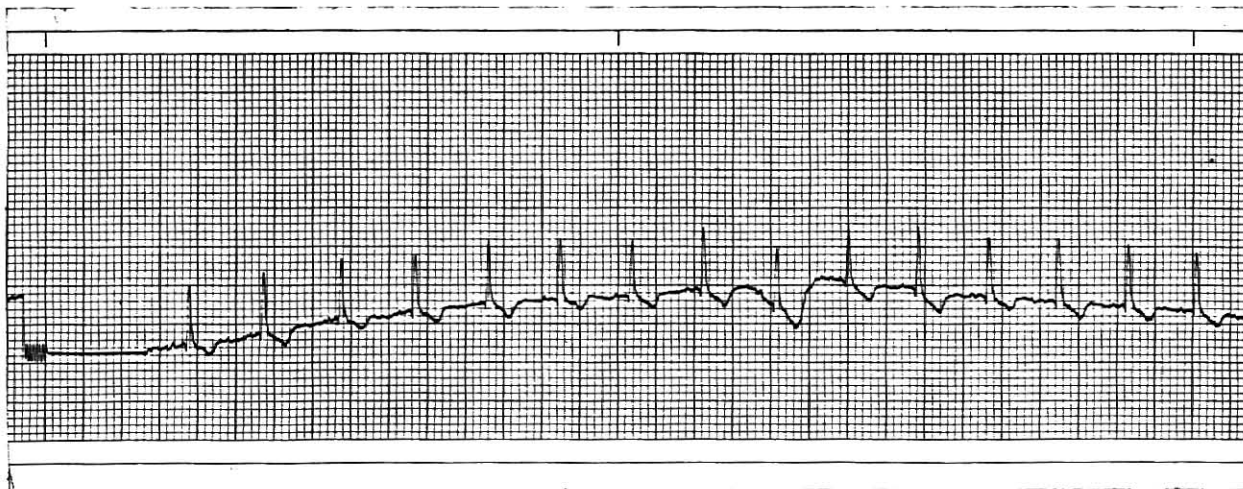
T wave .1 mV, Lead II

REMARKS:

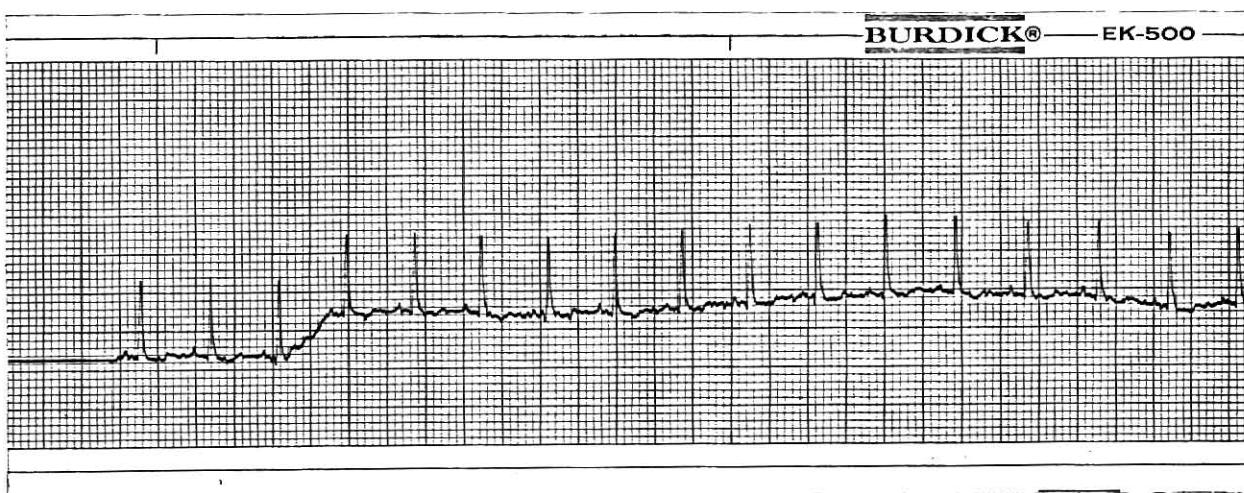
INTERPRETATION: Within normal limits

#100 "Patience" 6/23/76 24 hour post-digoxin (0.005 mg/lb.), Day 2

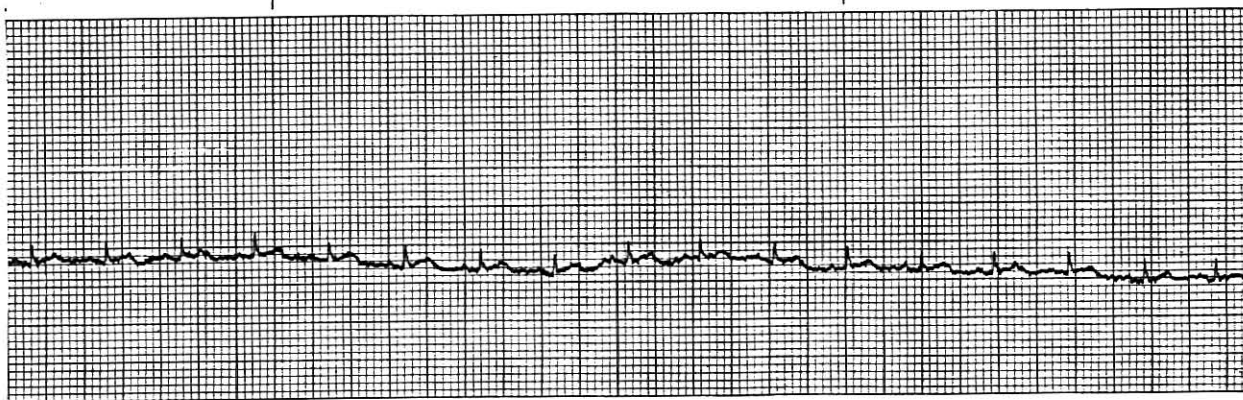
Interpretation _____



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-23-76 Trial 0.011 mg/kg; 24 hr PD; Day 2

RHYTHM Normal Sinus Rhythm

RATE 160

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .12 mV, Lead II

R wave 1.0 mV, Lead II

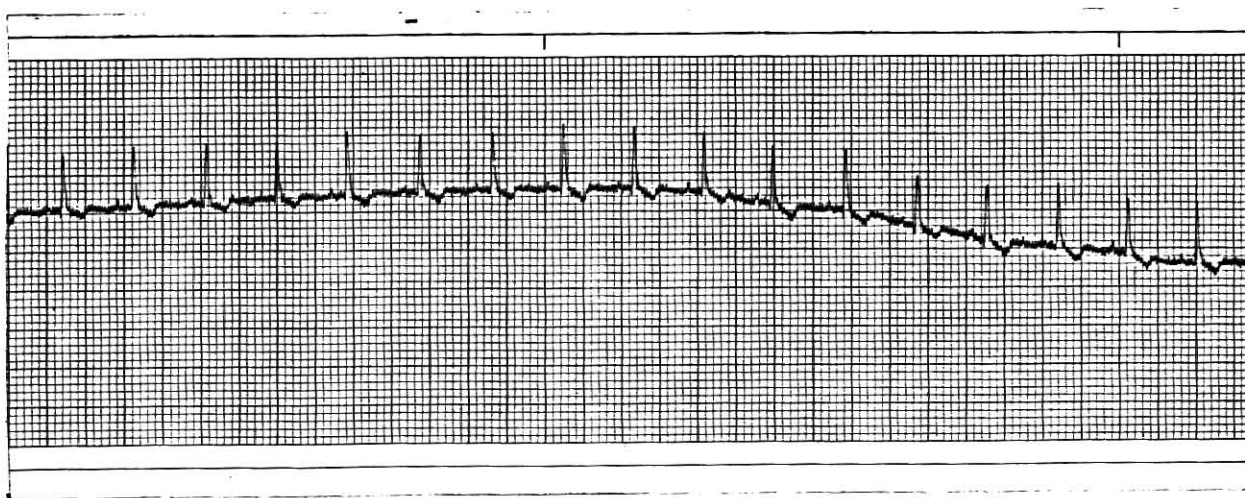
T wave .1 mV, Lead II

REMARKS: Depressed ST segment - head I?

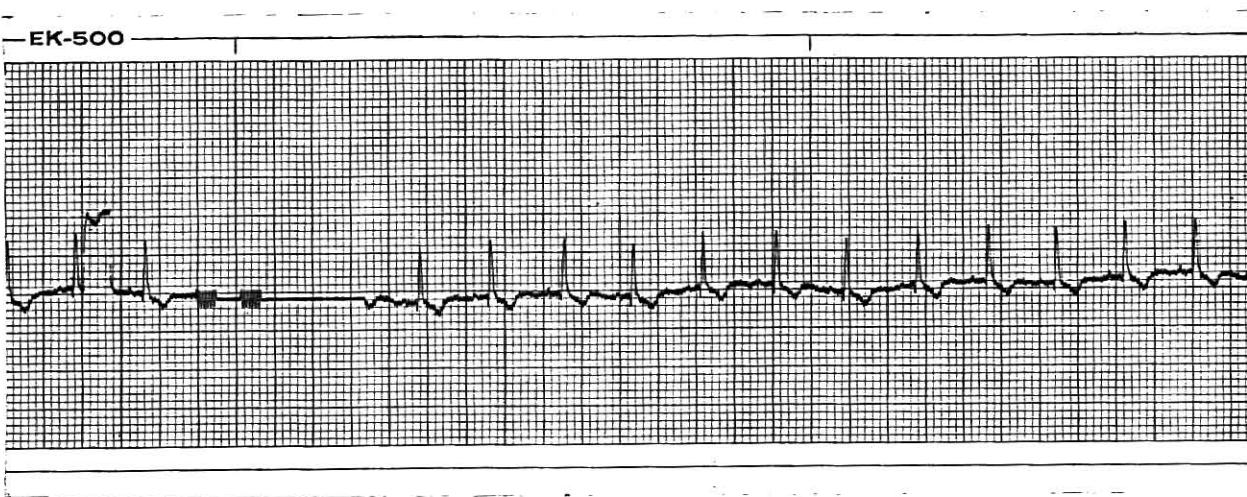
INTERPRETATION: Within normal limits

#100 "Patience" 6/23/76 1 hour post-digoxin (0.005 mg/lb.), Day 3

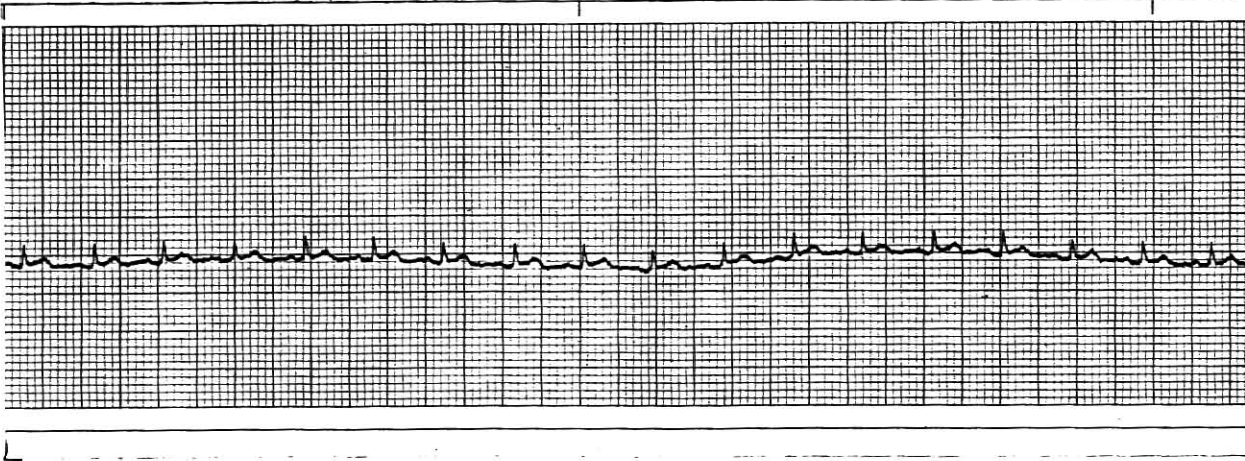
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-23-76 Trial 0.011 mg/kg; 1 hr PD; Day 3

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .1 mV, Lead II

R wave .8 mV, Lead II

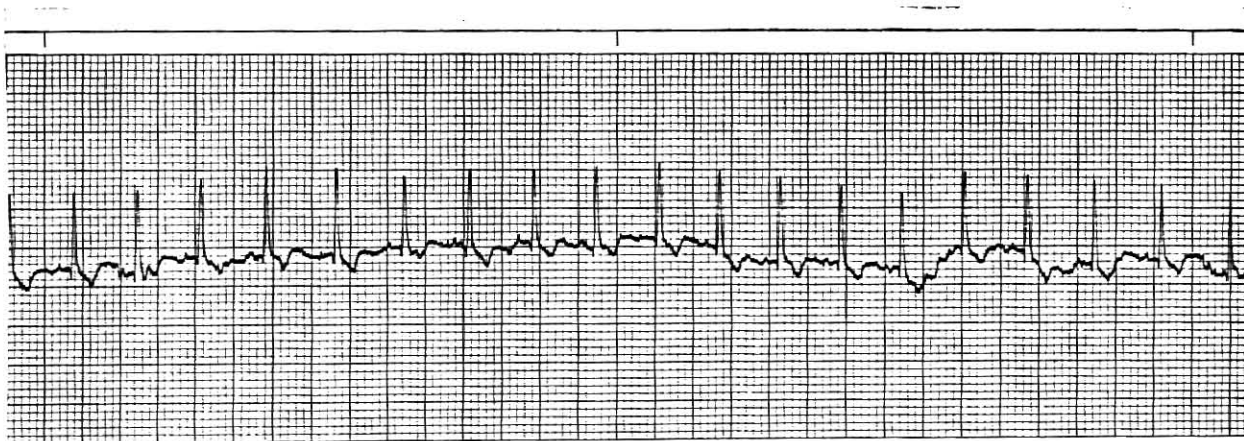
T wave .13 mV, Lead II

REMARKS:

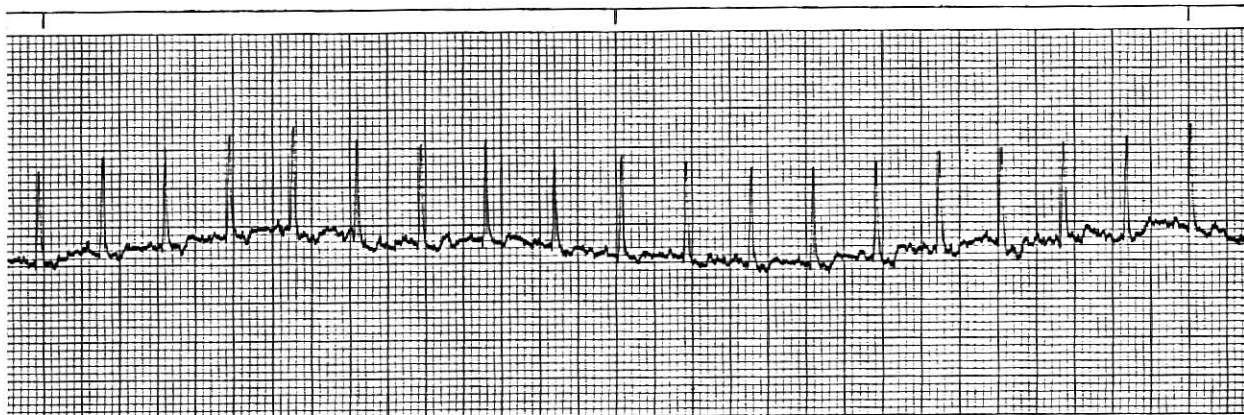
INTERPRETATION: Within normal limits

#100 "Patience" 6/23/76 2 hour post-digoxin (0.005 mg/lb.), Day 3

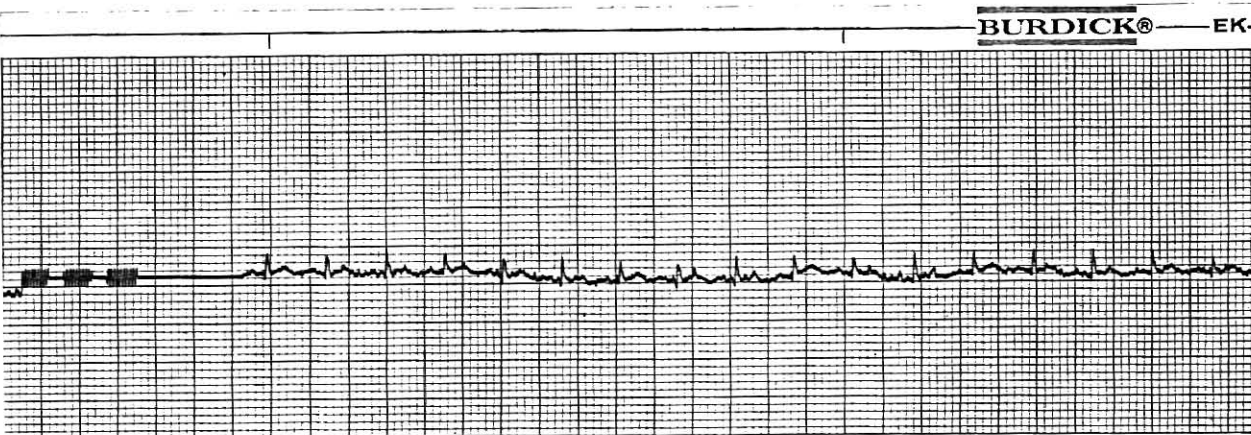
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-23-76 Trial 0.011 mg/kg; 2 hr PD; Day 3RHYTHM Normal Sinus RhythmRATE 170P wave duration: 0.04 sec. - Lead IIP-Q interval: 0.08 sec. - Lead IIQRS duration: 0.05 sec. - Lead IIQ-T interval: 0.14 sec. - Lead II

Maximum Voltage

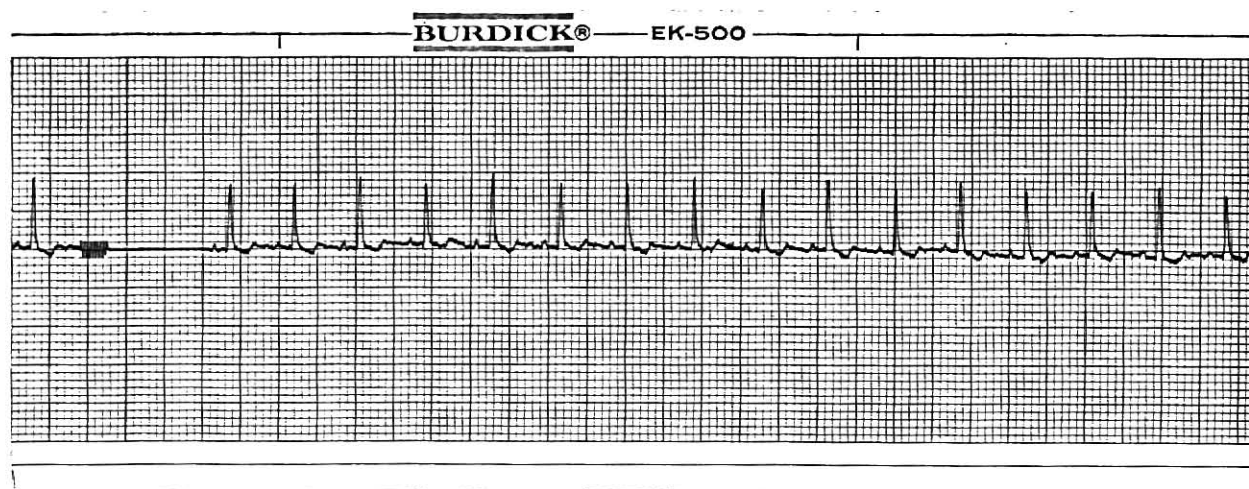
P wave .1 mV, Lead IIR wave 1.4 mV, Lead IIT wave .1 mV, Lead II

REMARKS: _____

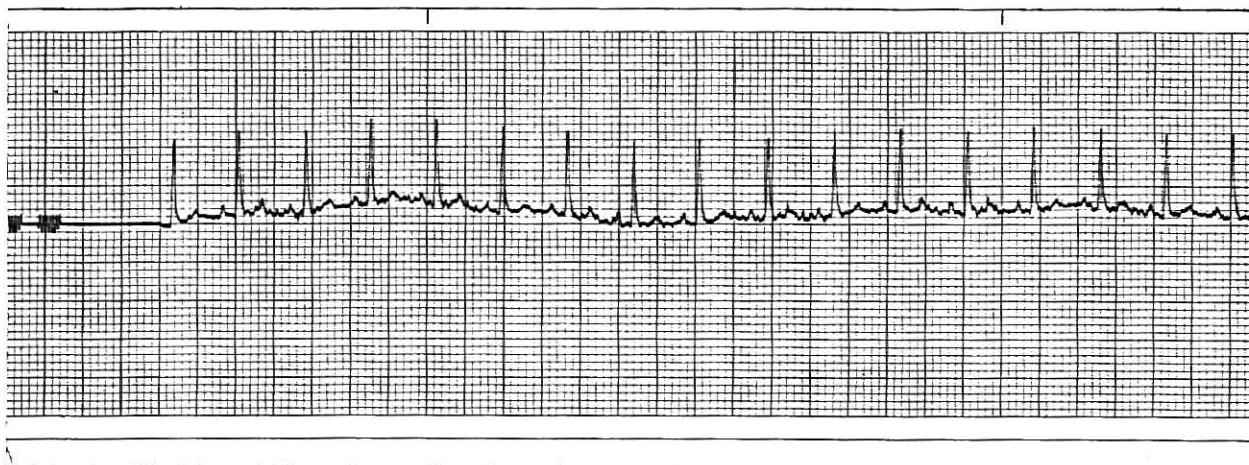
INTERPRETATION: Within normal limits

#100 "Patience" 6/23/76 4 hour post-digoxin (0.005 mg/lb.), Day 3

Interpretation WNL

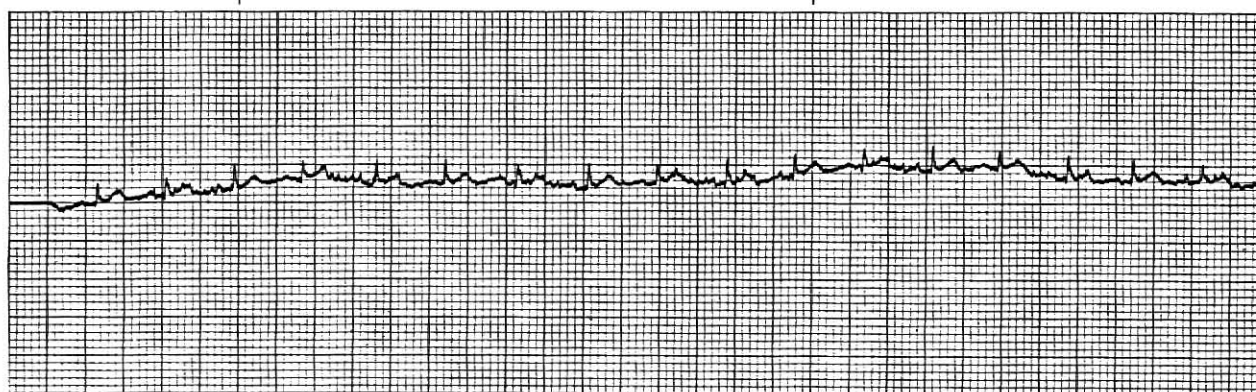


Lead I



Lead II

EK-500



Lead III

Cat #100, "Patience" Date 6-23-76 Trial 0.011 mg/kg; 4 hr PD; Day 3

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .13 mV, Lead II

R wave 1.05 mV, Lead II

T wave .1 mV, Lead II

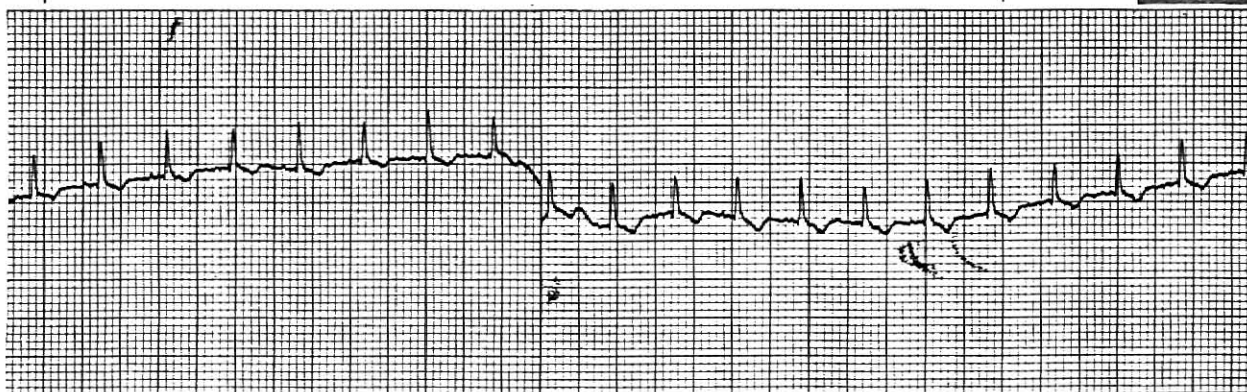
REMARKS: _____

INTERPRETATION: Within normal limits

#100 "Patience" 6/23/76 6 hour post-digoxin (0.005 mg/lb.), Day 3

Interpretation WNL

BURDICK

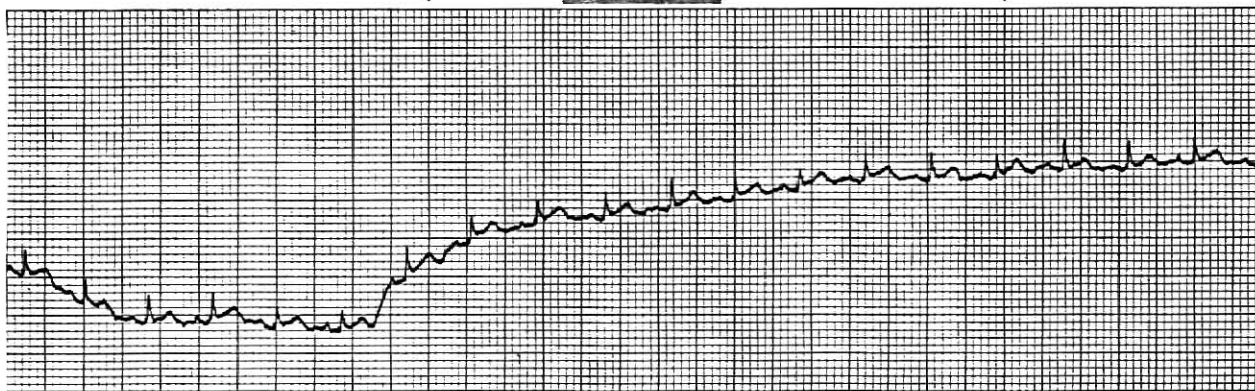


Lead I



Lead II

BURDICK® EK-500



Lead III

Cat #100, "Patience" Date 6-23-76 Trial 0.011 mg/kg; 6 hr PD; Day 3

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .1 mV, Lead II

R wave .8 mV, Lead II

T wave .1 mV, Lead II

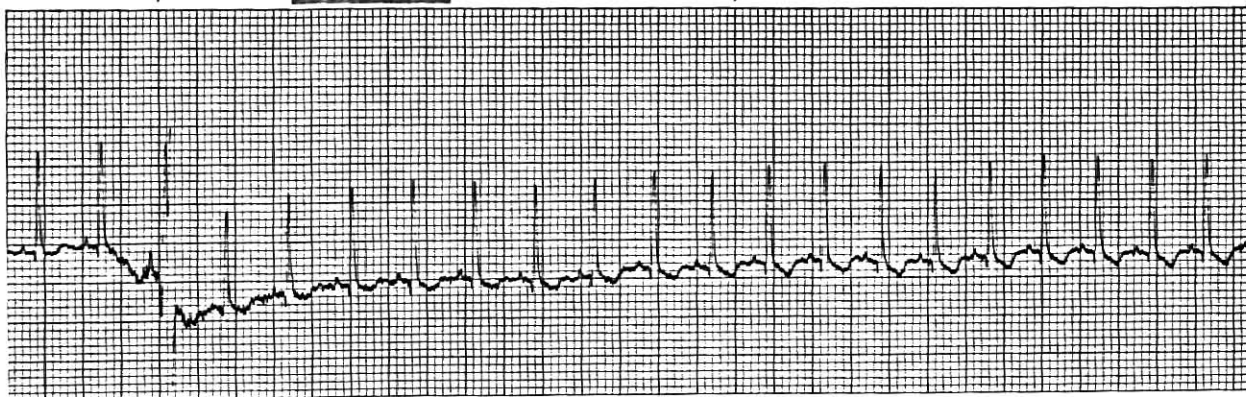
REMARKS: _____

INTERPRETATION: Within normal limits

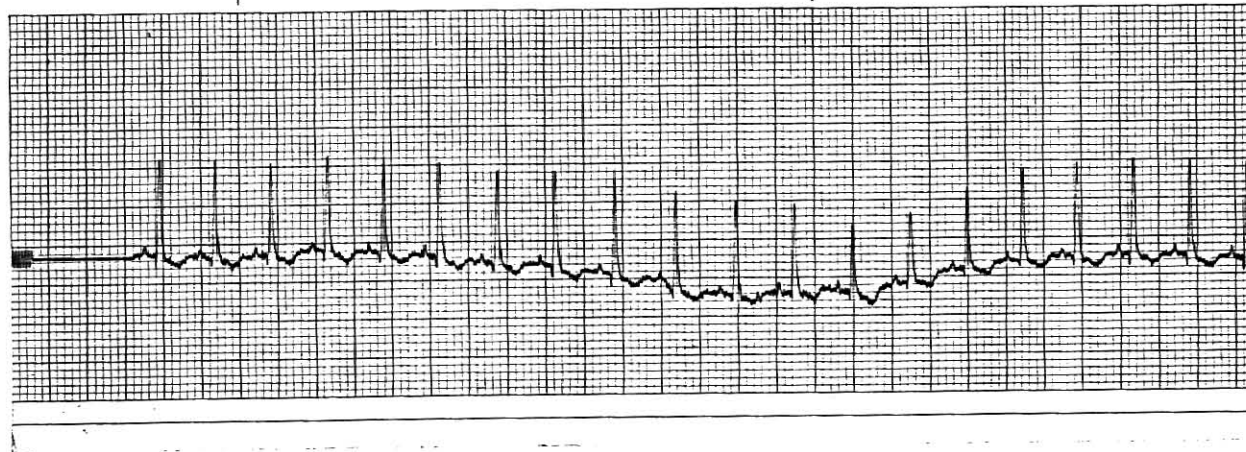
#100 "Patience" 6/24/76 24hour post-digoxin (0.005 mg/lb.), Day 3

Interpretation WNL

BURDICK® EK-500

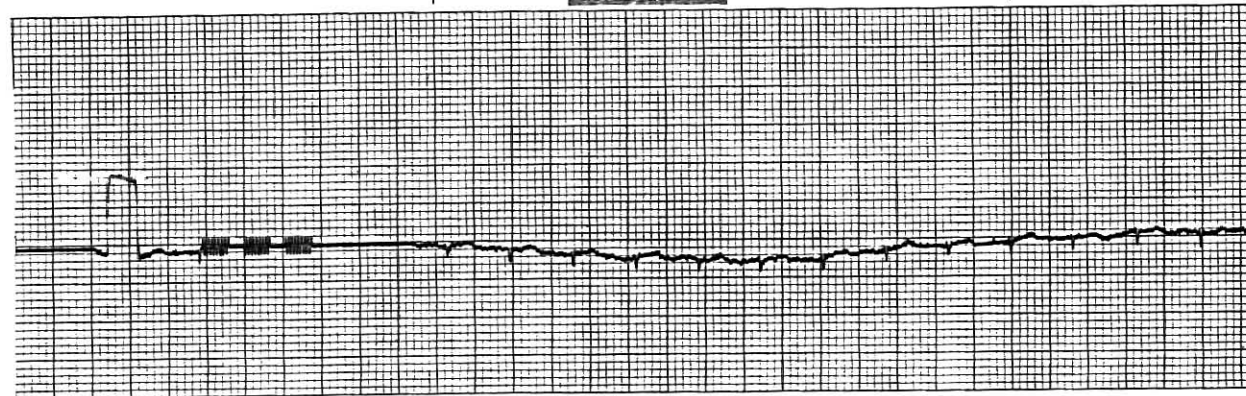


Lead I



Lead II

BURDICK® EK-500



Lead III

Cat #100, "Patience" Date 6-24-76 Trial 0.011 mg/kg; 24 hr PD; Day 3

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .1 mV, Lead II

R wave 1.3 mV, Lead II

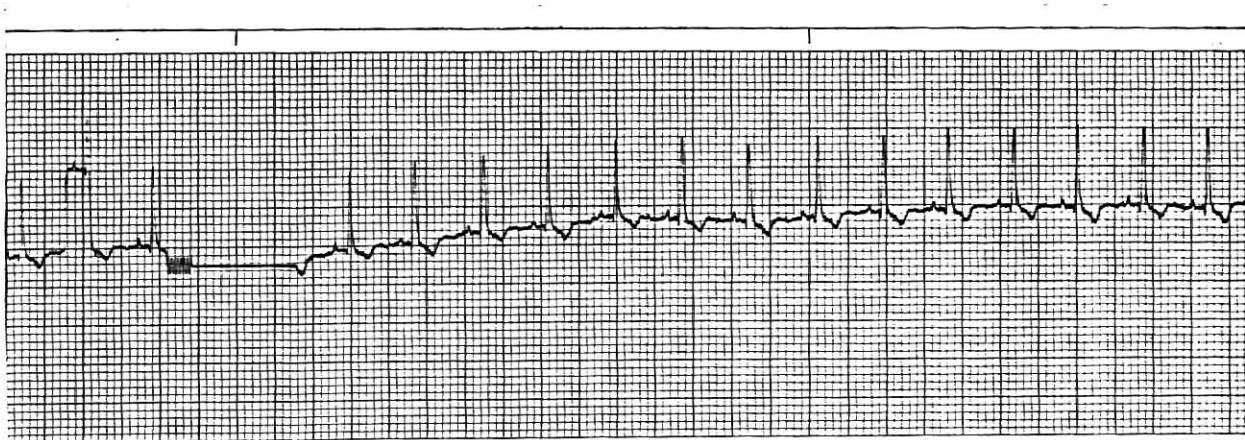
T wave .13 mV, Lead II

REMARKS:

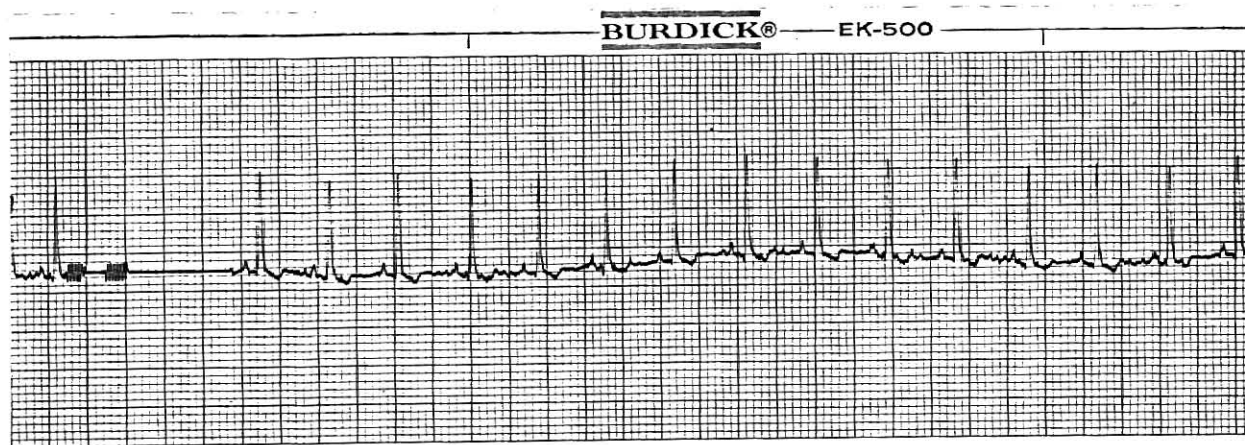
INTERPRETATION: Within normal limits

#100 "Patience" 6/24/76 1 hour post-digoxin (0.005 mg/lb.), Day 4

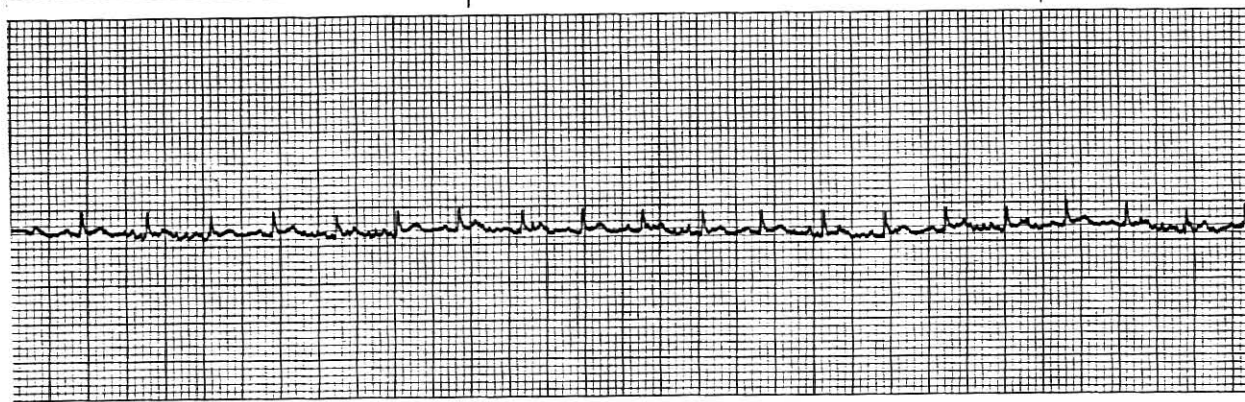
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-24-76 Trial 0.011 mg/kg; 1 hr PD; Day 4

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.12 sec. - Lead II

Maximum Voltage

P wave .15 mV, Lead II

R wave 1.25 mV, Lead II

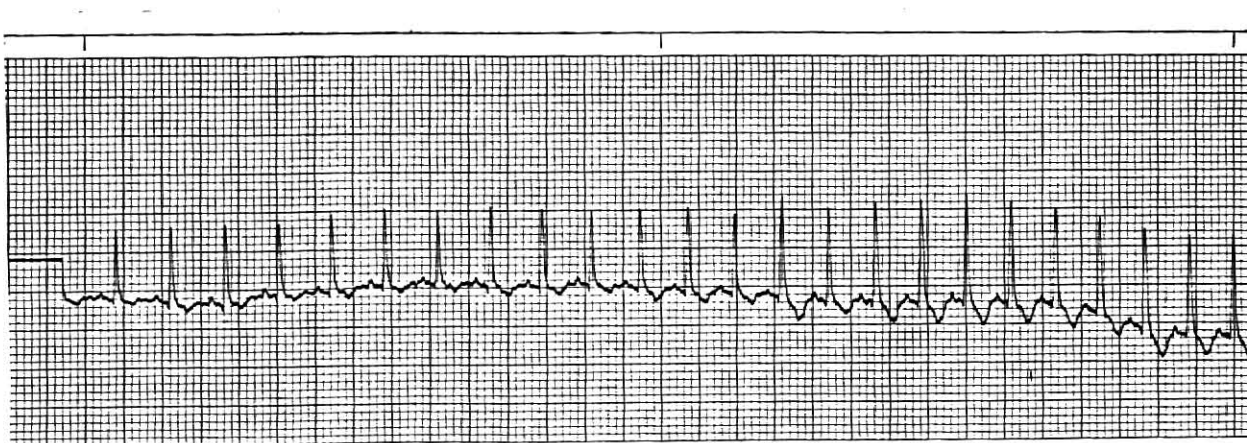
T wave .1 mV, Lead II

REMARKS:

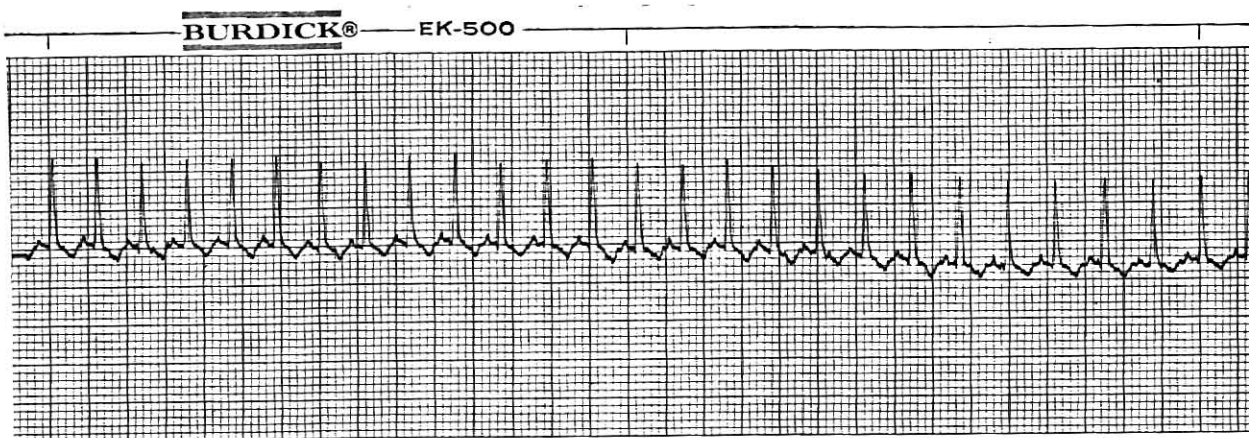
INTERPRETATION: Within normal limits

#100 "Patience" 6/24/76 2 hour post-digoxin (0.005 mg/lb.), Day 4

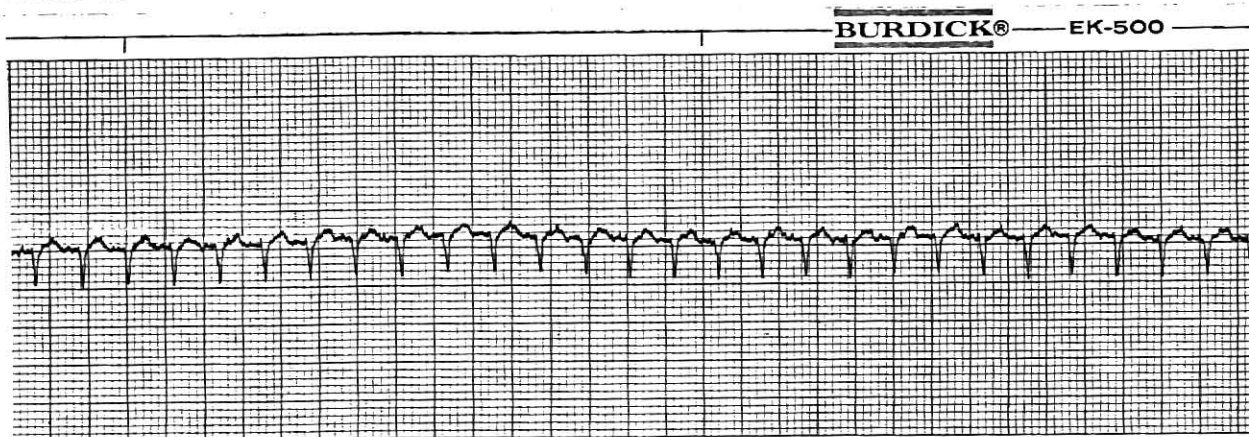
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-24-76 Trial 0.011 mg/kg; 2 hr PD; Day 4

RHYTHM Normal Sinus Rhythm

RATE 260

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .12 mV, Lead II

R wave 1.1 mV, Lead II

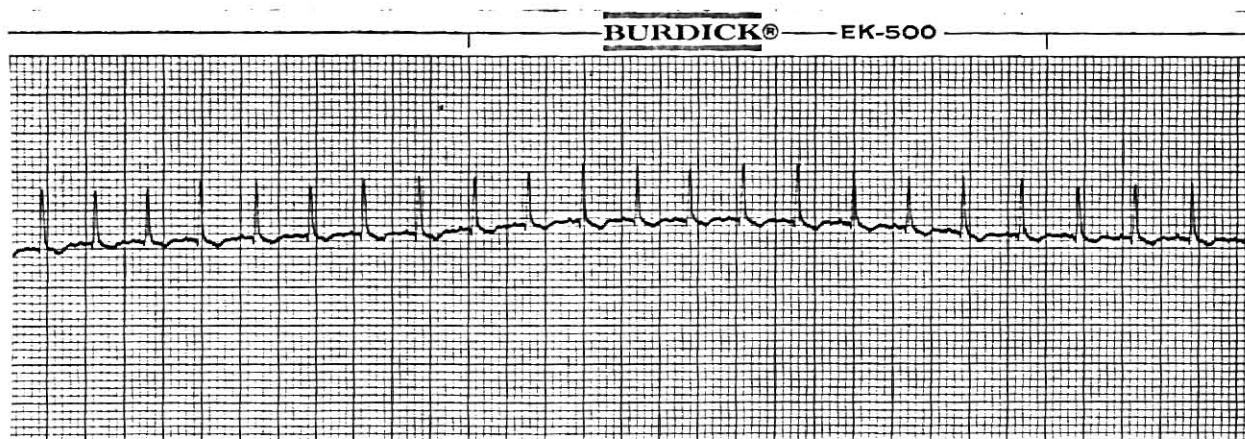
T wave .13 mV, Lead II

REMARKS:

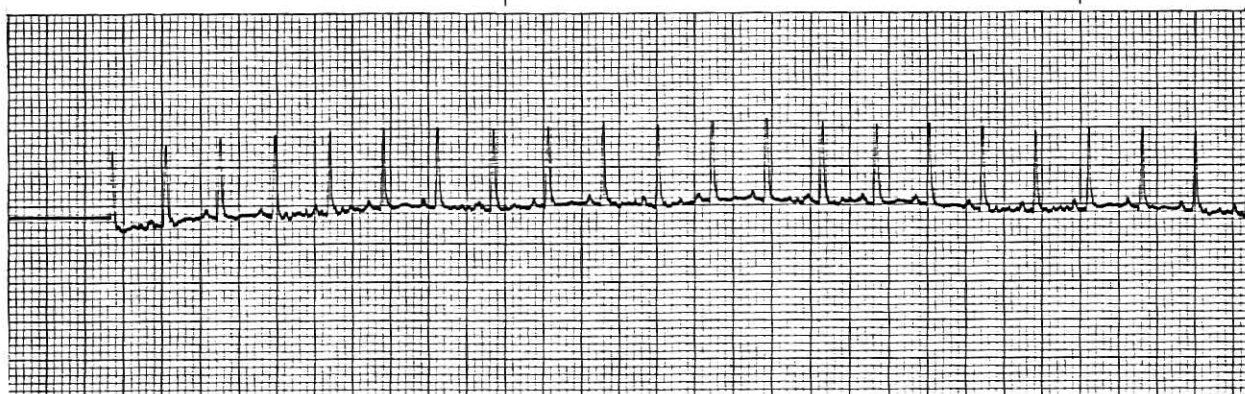
INTERPRETATION: Within normal limits

#100 "Patience" 6/24/76 4 hour post-digoxin (0.005 mg/lb.), Day 4

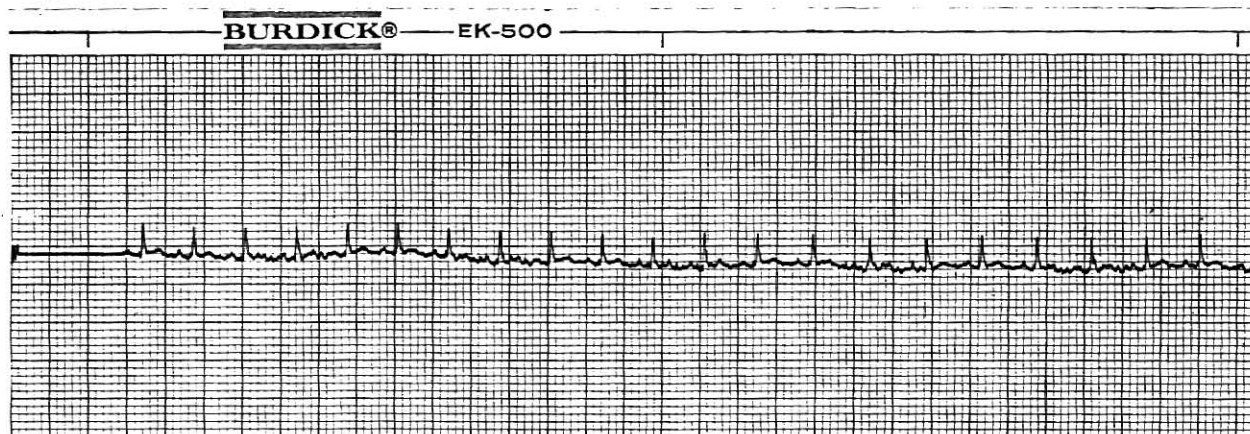
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-24-76 Trial 0.011 mg/kg; 4 hr PD; Day 4

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .1 mV, Lead II

R wave 1.05 mV, Lead II

T wave .07 mV, Lead II

REMARKS: _____

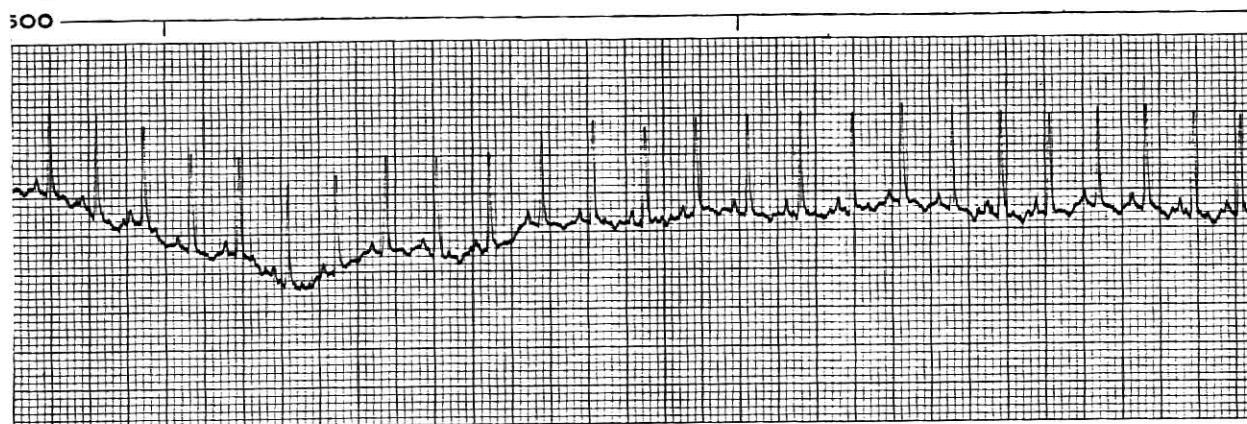
INTERPRETATION: Within normal limits

#100 "Patience" 6/24/76 6 hour post-digoxin (0.005 mg/lb.), Day 4

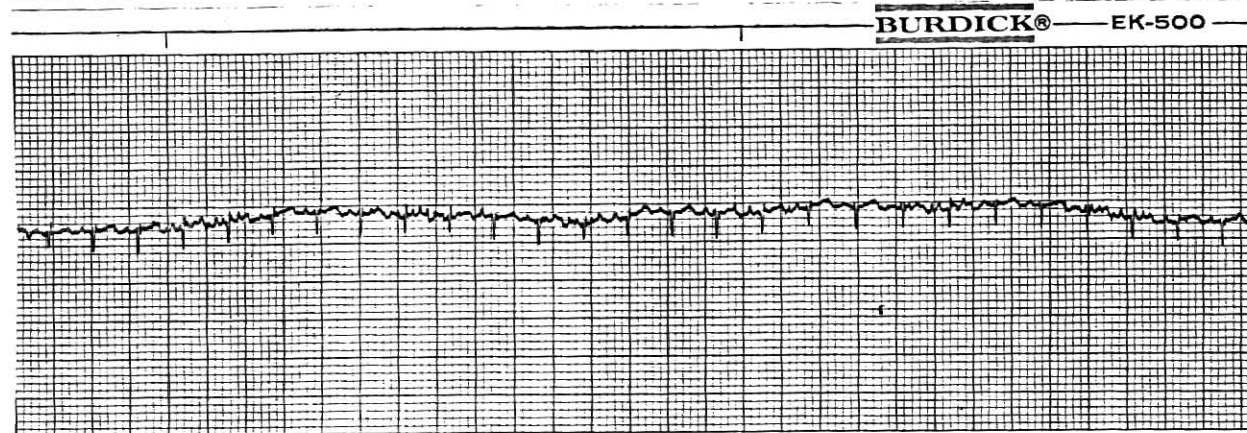
Interpretation WNL



Lead I



Lead II



Lead III

Cat #100, "Patience" Date 6-24-76 Trial 0.011 mg/kg; 6 hr PD; Day 4

RHYTHM Normal Sinus Rhythm

RATE 230

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.05 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .15 mV, Lead II

R wave 1.35 mV, Lead II

T wave .15 mV, Lead II

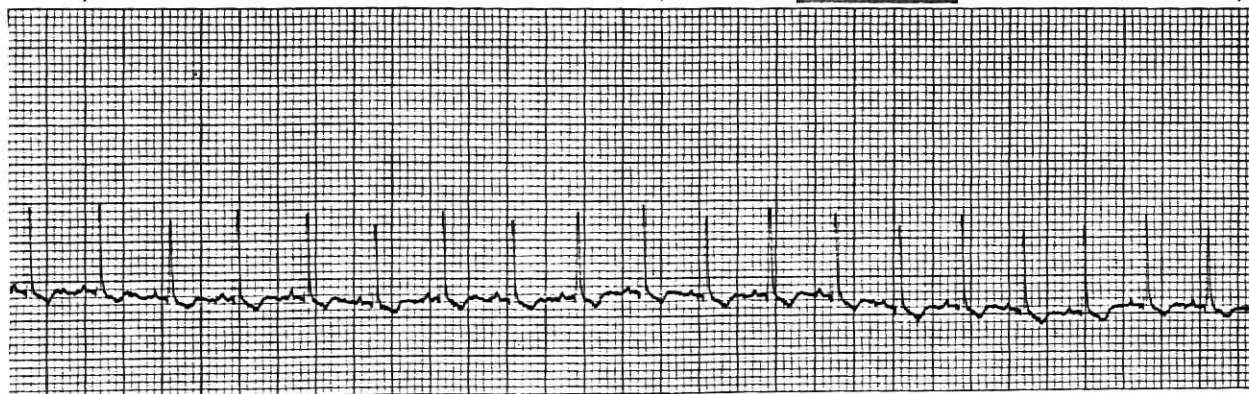
REMARKS:

INTERPRETATION: Within normal limits

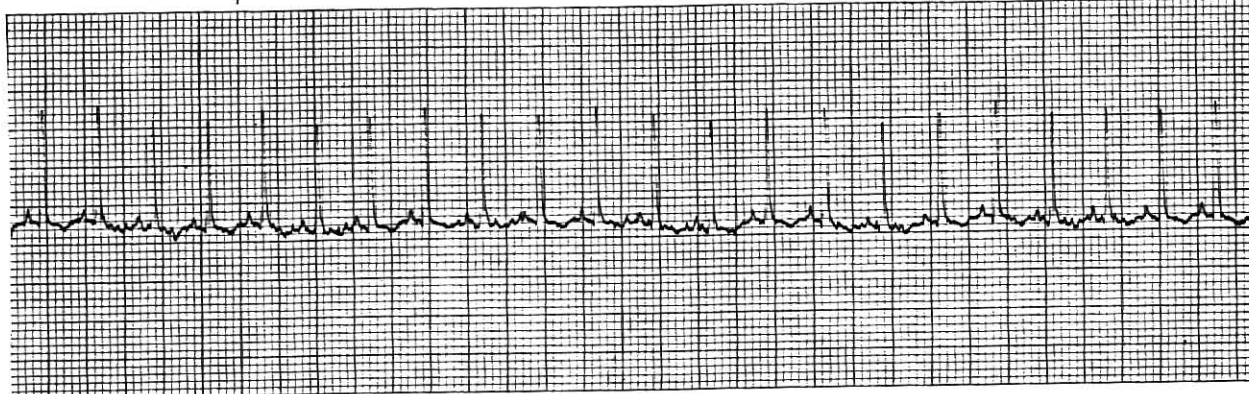
#100 "Patience" 6/25/76 24 hour post-digoxin (0.005 mg/lb.), Day 4

Interpretation WNL

BURDICK® EK-500

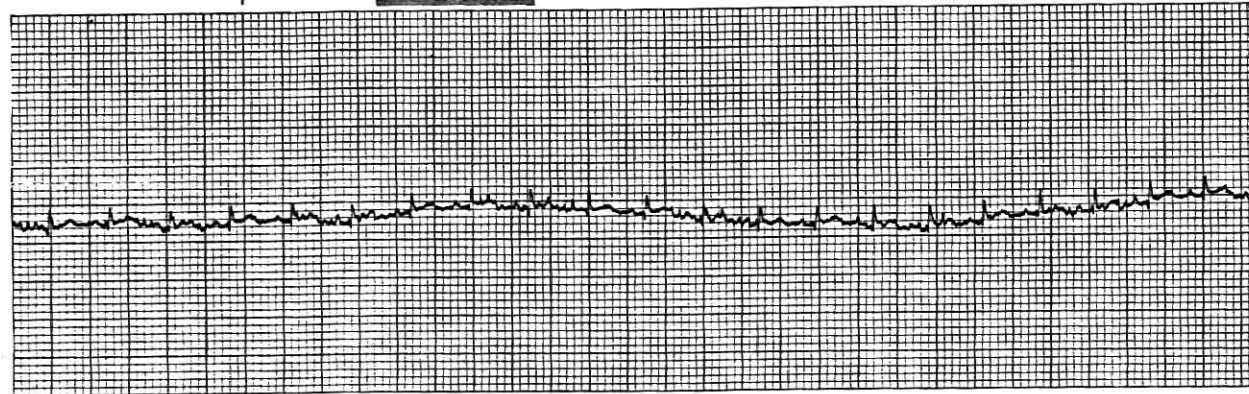


Lead I



Lead II

BURDICK® EK-500



Lead III

Cat #100, "Patience" Date 6-25-76 Trial 0.011 mg/kg; 24 hr PD; Day 4

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.20 sec. - Lead II

Maximum Voltage

P wave .13 mV, Lead II

R wave 1.4 mV, Lead II

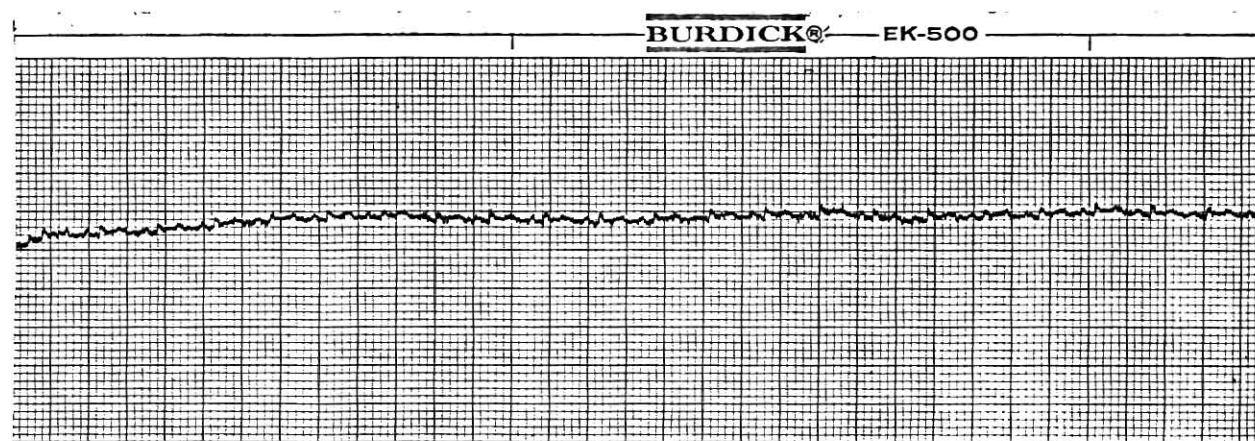
T wave .08 mV, Lead II

REMARKS:

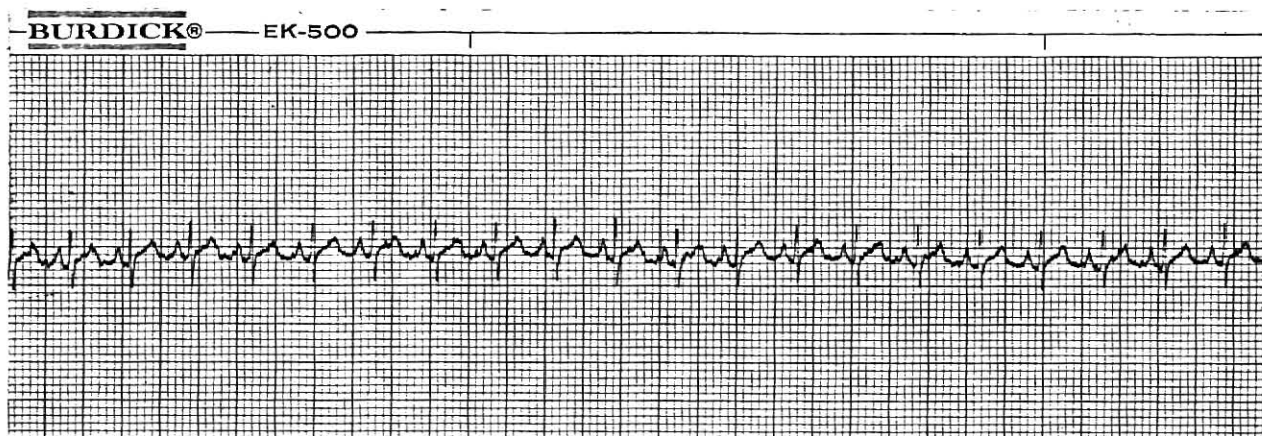
INTERPRETATION: Within normal limits

#14 Petey 7/12/76 Pre-digoxin (0.05 mg/lb.)

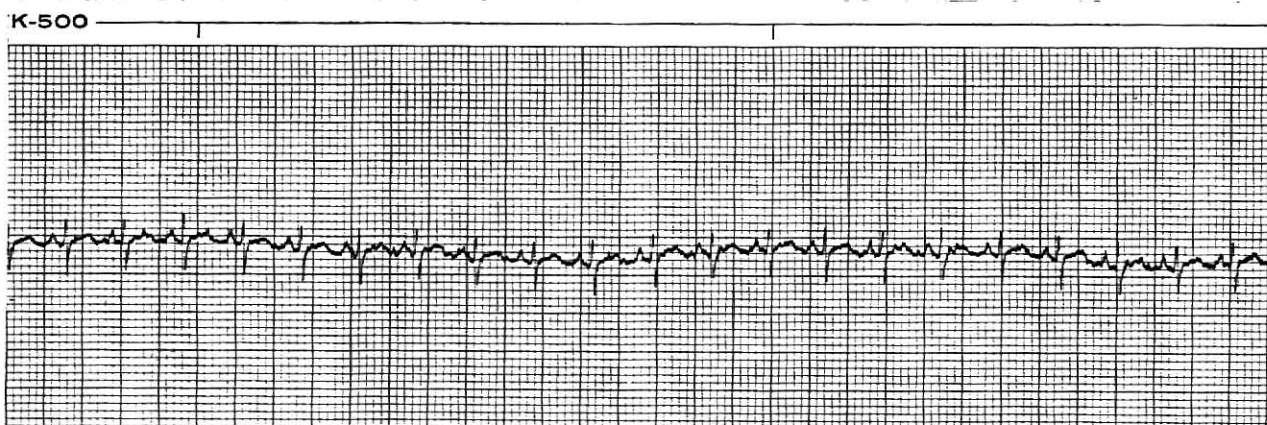
Interpretation Within Normal Limits



Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-12-76 Trial 0.11 mg/kg; Pre D

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.06 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.17 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .5 mV, Lead II

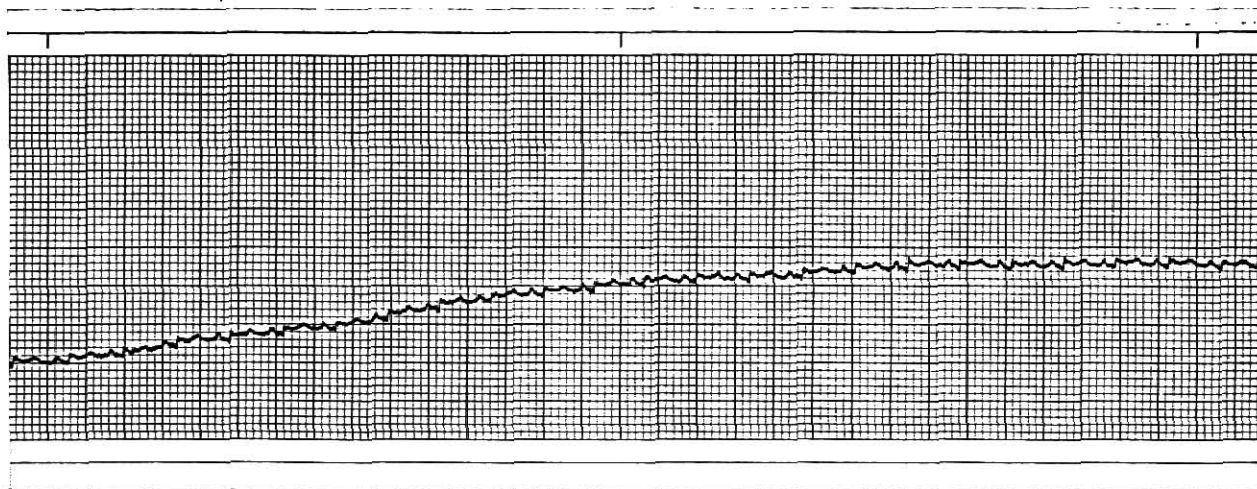
T wave .2 mV, Lead II

REMARKS:

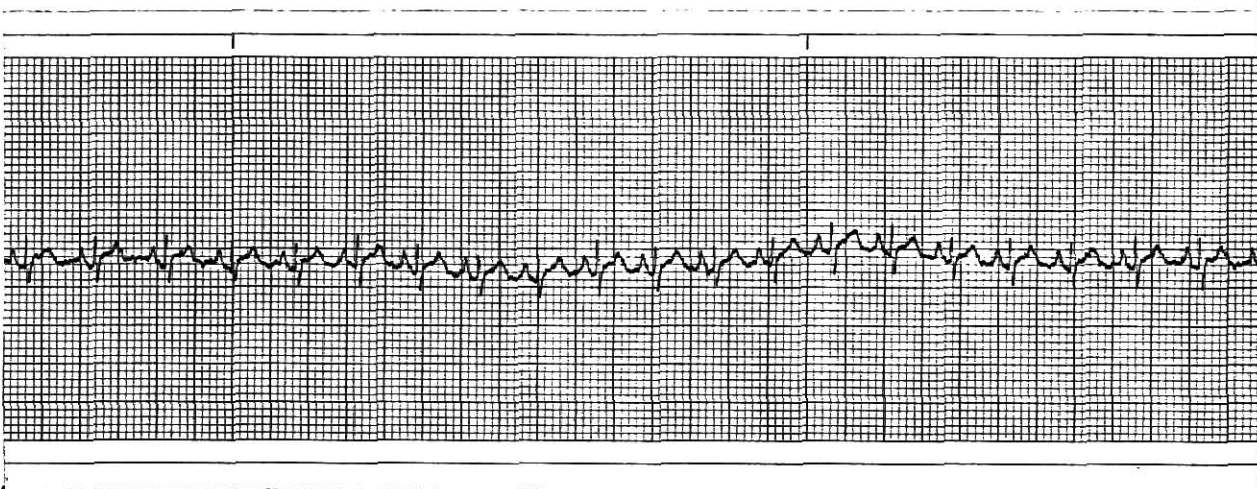
INTERPRETATION: Within Normal Limits

#144 Petey 7/16/76 Pre-digoxin (0.05 mg/lb.)

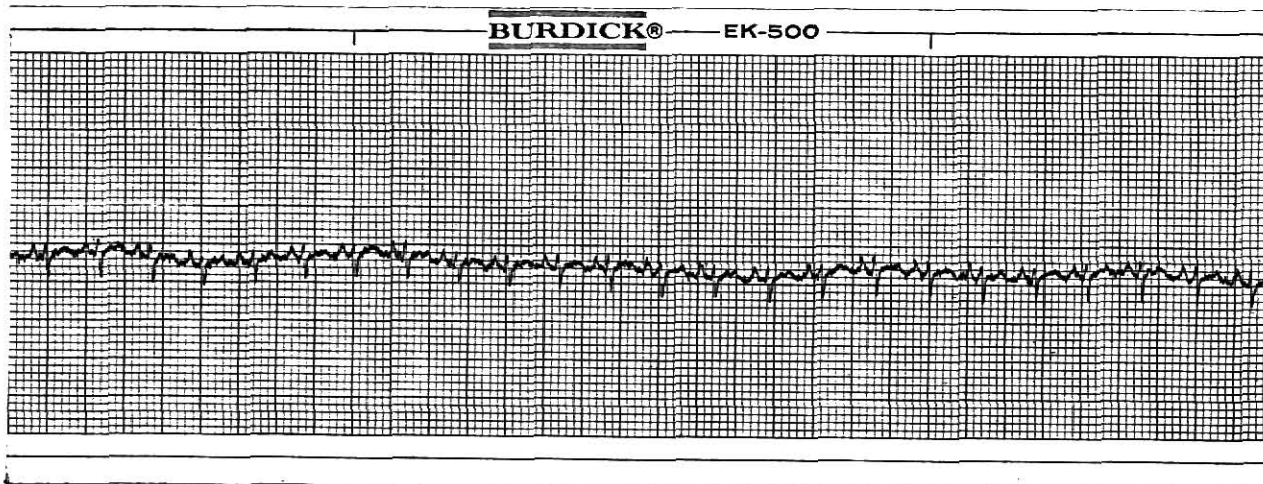
Interpretation WNL



Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-16-76 Trial 0.11 mg/kg; Pre D

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.05 sec. - Lead II

P-Q interval: 0.09 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.18 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .4 mV, Lead II

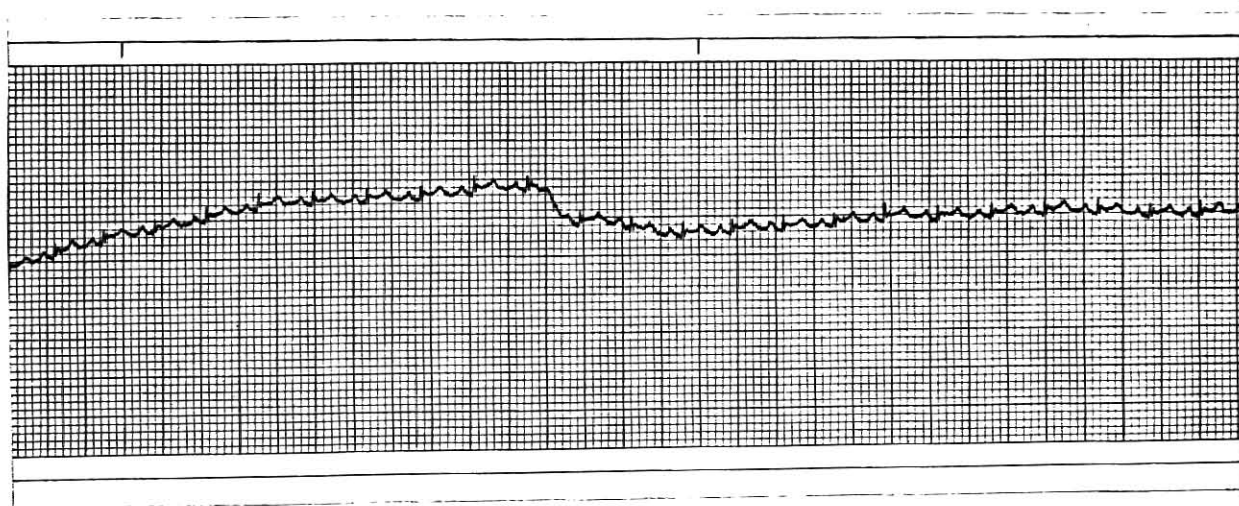
T wave .2 mV, Lead II

REMARKS:

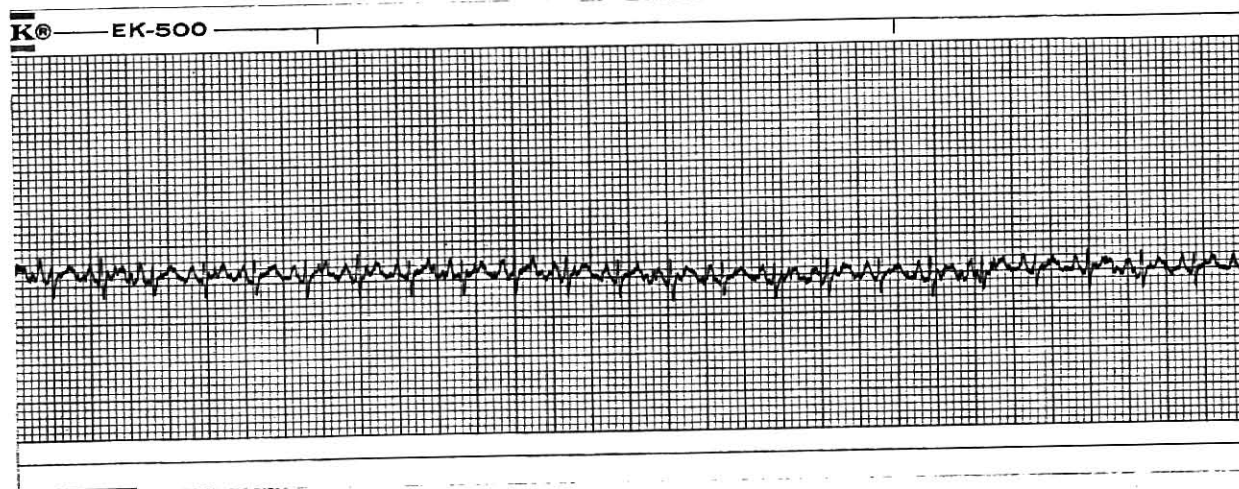
INTERPRETATION: Within Normal Limits

#44 "Petey" 7/20/76 1 hour post-digoxin (0.05 mg/lb.)

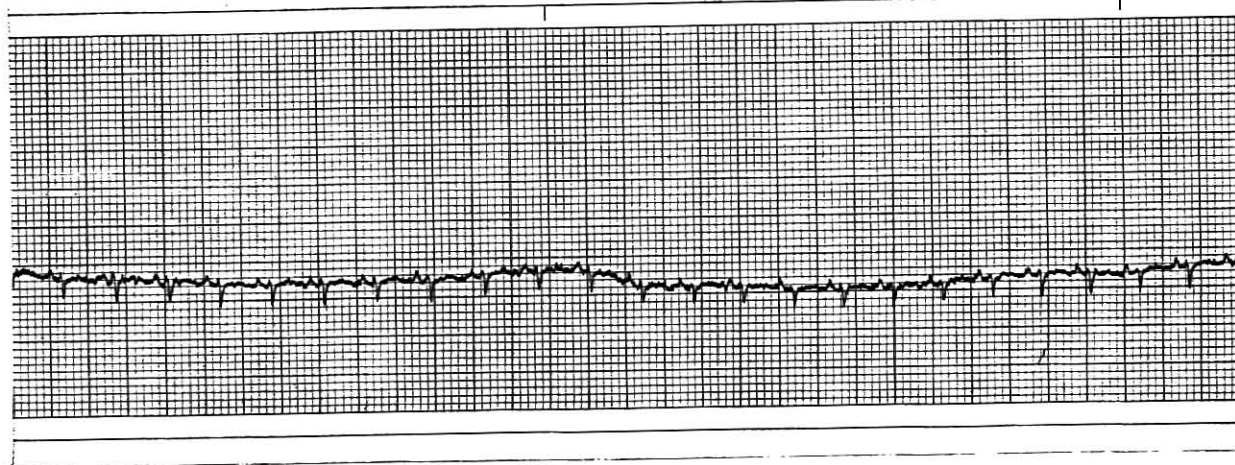
Interpretation Within Normal Limits



Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-20-76 Trial 0.11 mg/kg; 1 hr PD

RHYTHM Normal Sinus Rhythm

RATE 220

P wave duration: 0.05 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .3 mV, Lead II

T wave .2 mV, Lead II

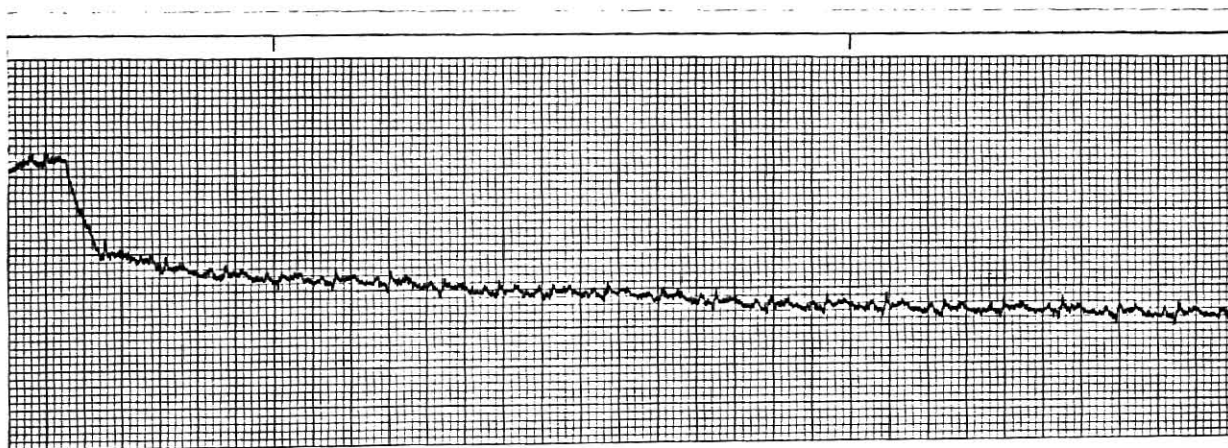
REMARKS:

INTERPRETATION: Within Normal Limits

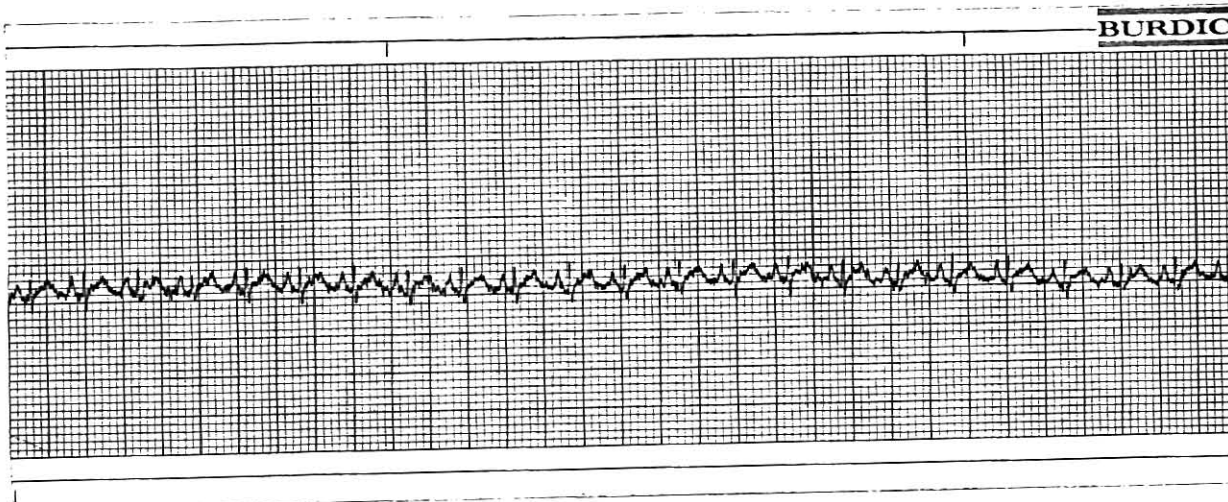
#44 "Petey" 7/20/76

2 hour post-digoxin (0.05 mg/lb.)

Interpretation WNL

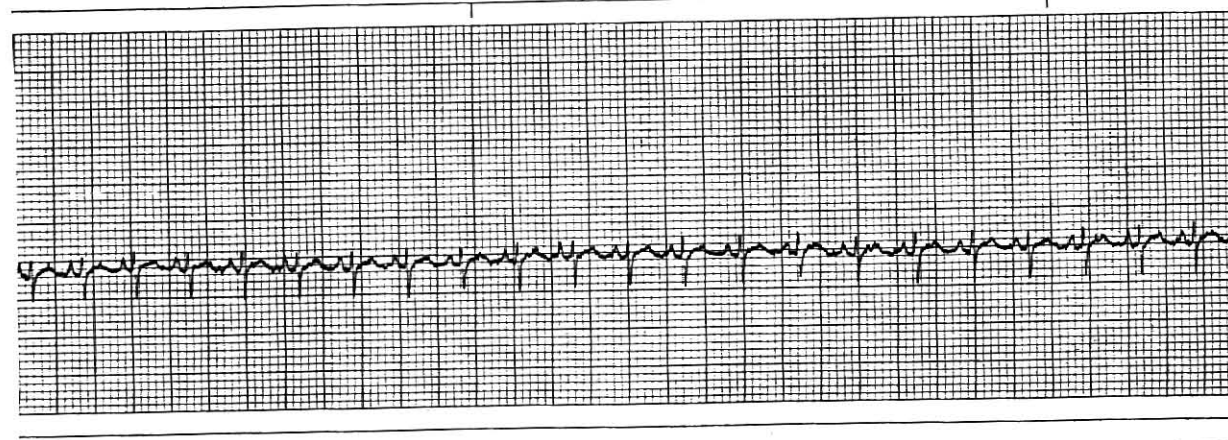


Lead I



BURDIC

Lead II



Lead III

Cat #44, "Petey" Date 7-20-76 Trial 0.11 mg/kg; 2 hr PD

RHYTHM Normal Sinus Rhythm

RATE 210

P wave duration: 0.05 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.17 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .35 mV, Lead II

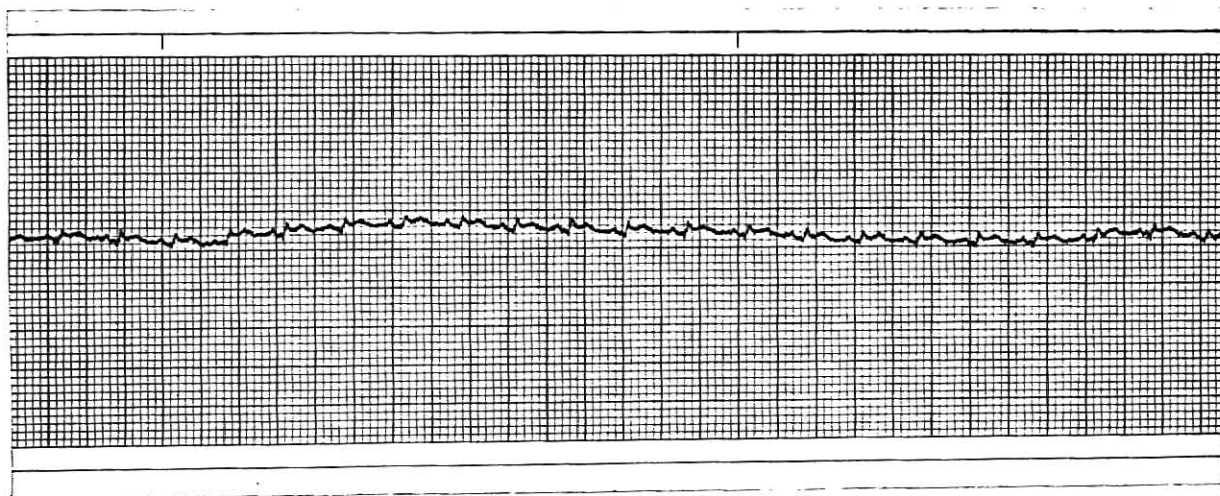
T wave .2 mV, Lead II

REMARKS:

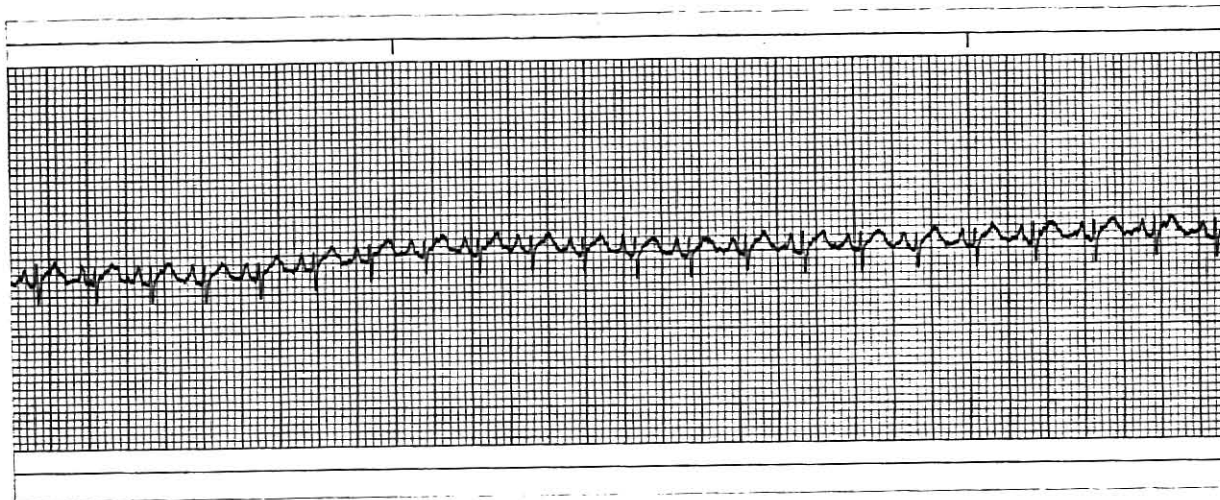
INTERPRETATION: Within Normal Limits

#44 "Petey" 7/20/76

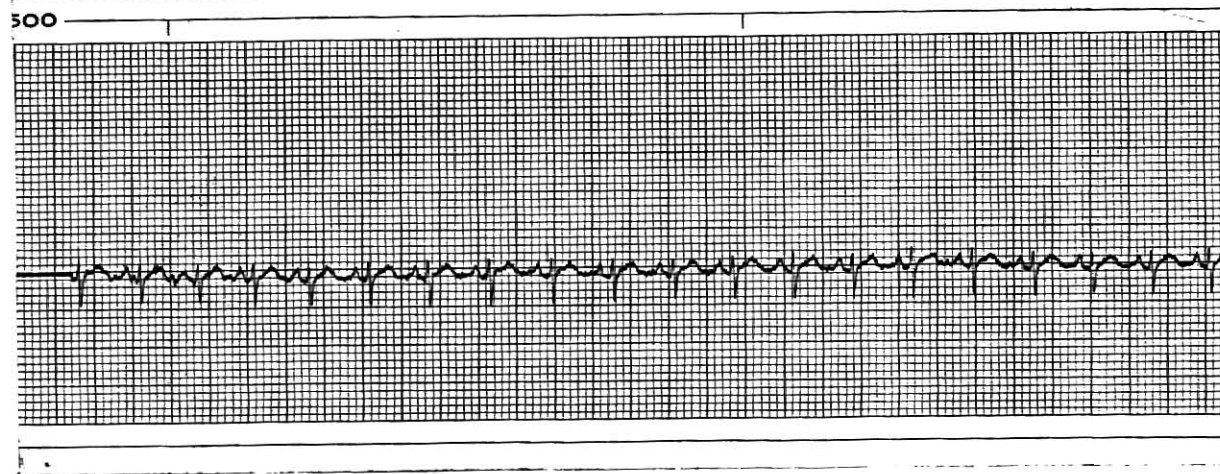
4 hour post-digoxin (0.05 mg/lb.)

Interpretation WNL

Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-20-76 Trial 0.11 mg/kg; 4 hr PDRHYTHM Normal Sinus RhythmRATE 200P wave duration: 0.05 sec. - Lead IIP-Q interval: 0.08 sec. - Lead IIQRS duration: 0.04 sec. - Lead IIQ-T interval: 0.17 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead IIR wave .25 mV, Lead IIT wave .2 mV, Lead IIREMARKS: _____

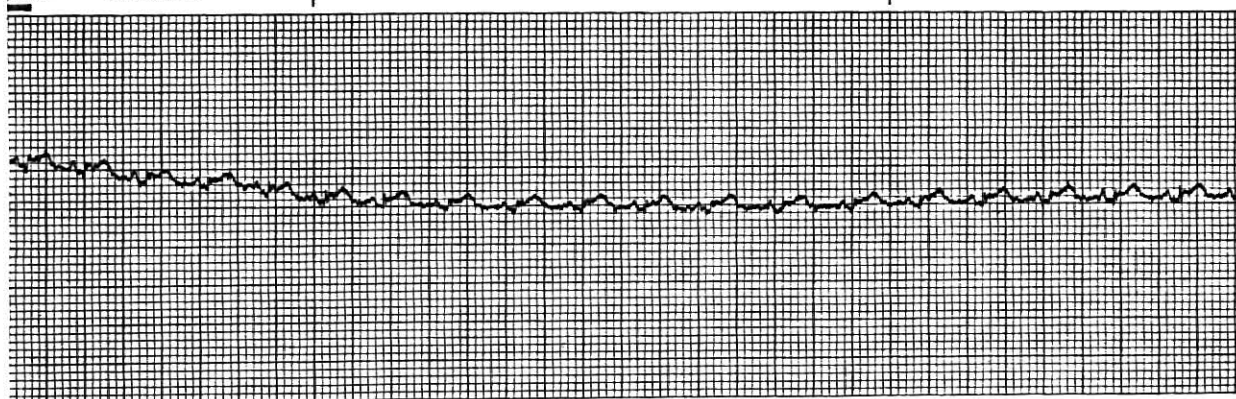
_____INTERPRETATION: Within Normal Limits

#44 "Petey" 7/29/76

6hour post-digoxin (0.05 mg/lb.)

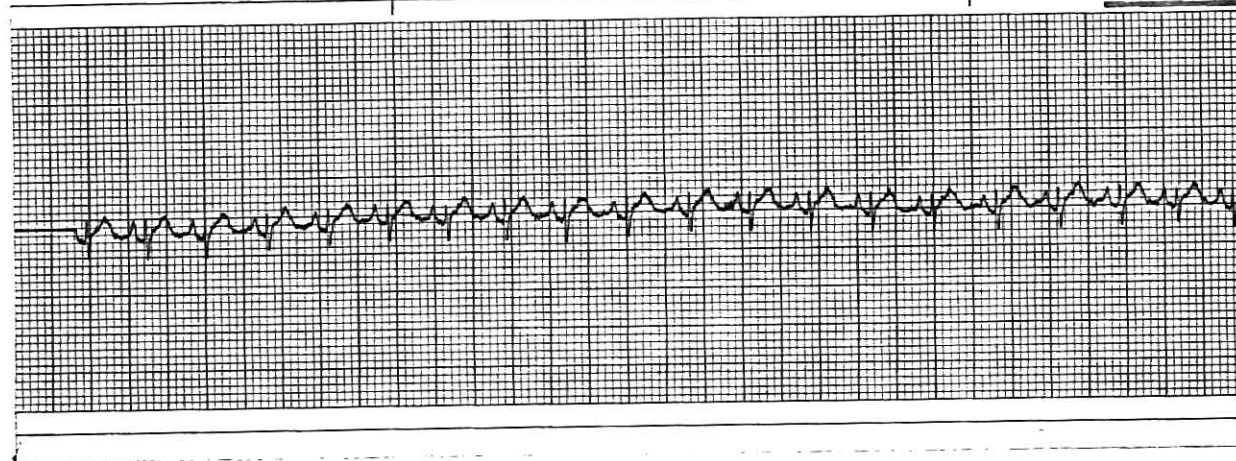
Interpretation WNL

K® — EK-500



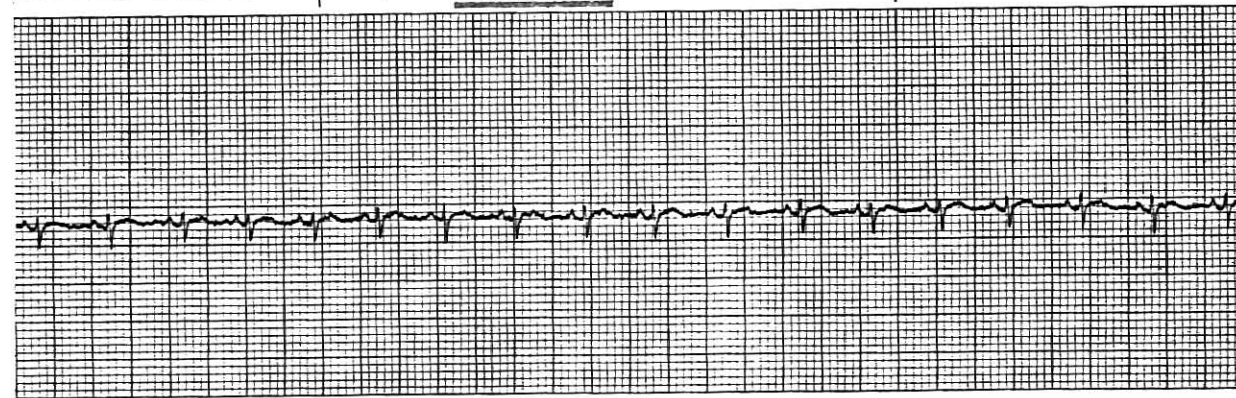
Lead I

BURDICK



Lead II

BURDICK® — EK-500



Lead III

Cat #44, "Petey" Date 7-20-76 Trial 0.11 mg/kg; 6 hr PD

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.05 sec. - Lead II

P-Q interval: 0.10 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .25 mV, Lead II

T wave .25 mV, Lead II

REMARKS:

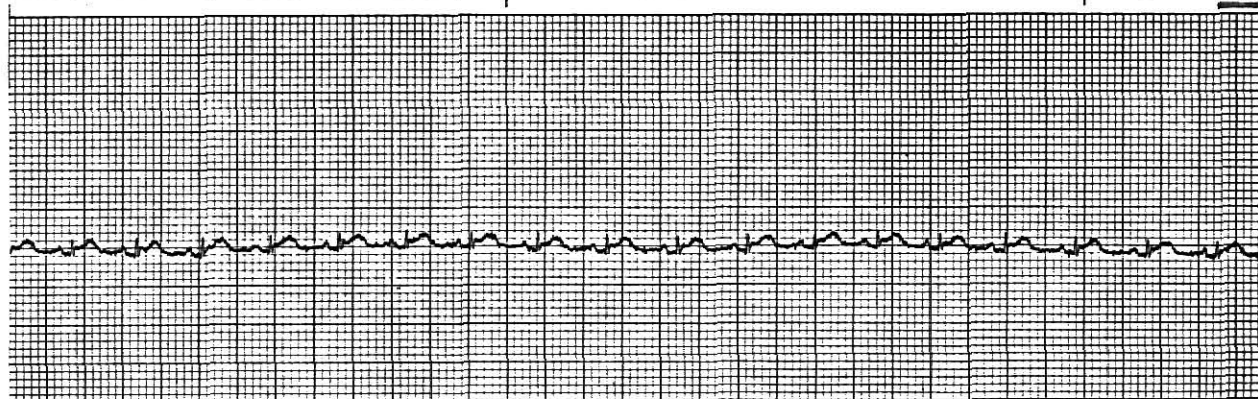
INTERPRETATION: Within Normal Limits

#44 "Petey" 7/20/76

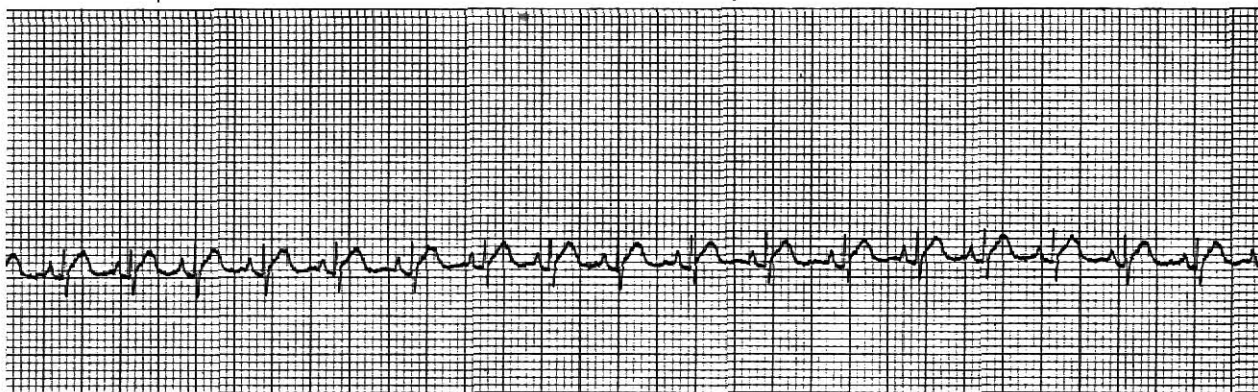
12 hour post-digoxin (0.05 mg/lb.) (Vomition)

Interpretation WNL

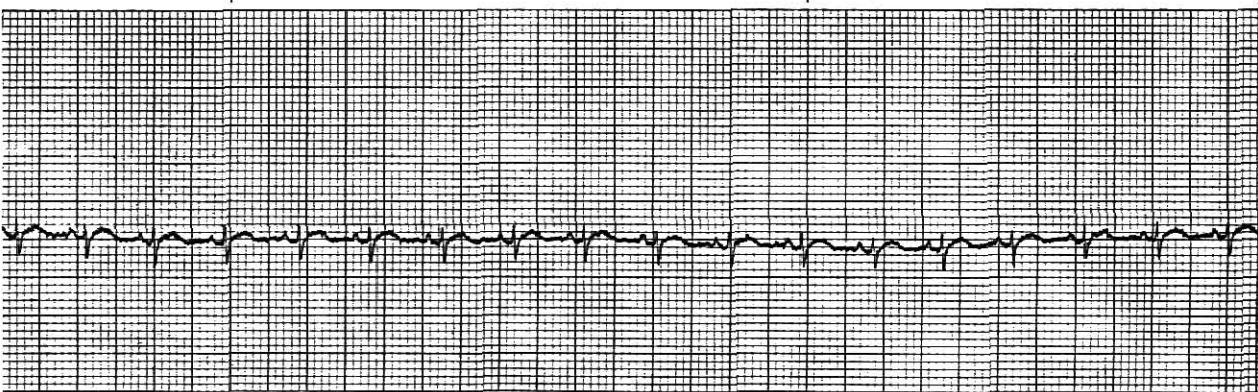
BU



Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-20-76 Trial 0.11 mg/kg; 12 hr PD (vomition)RHYTHM Normal Sinus RhythmRATE 160P wave duration: 0.04 sec. - Lead IIP-Q interval: 0.09 sec. - Lead IIQRS duration: 0.04 sec. - Lead IIQ-T interval: 0.17 sec. - Lead II

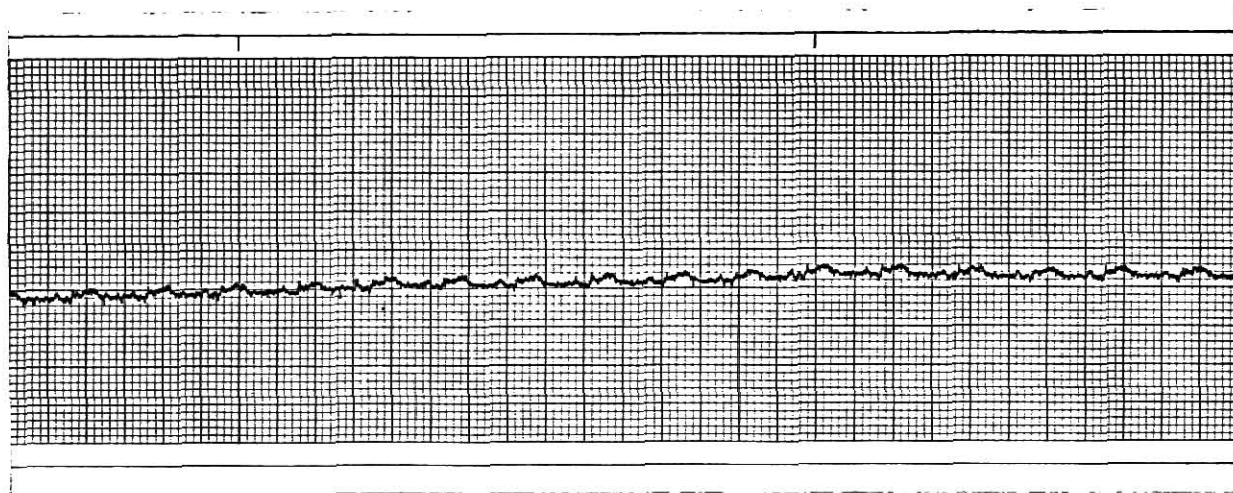
Maximum Voltage

P wave .15 mV, Lead IIR wave .4 mV, Lead IIT wave .35 mV, Lead IIREMARKS: _____

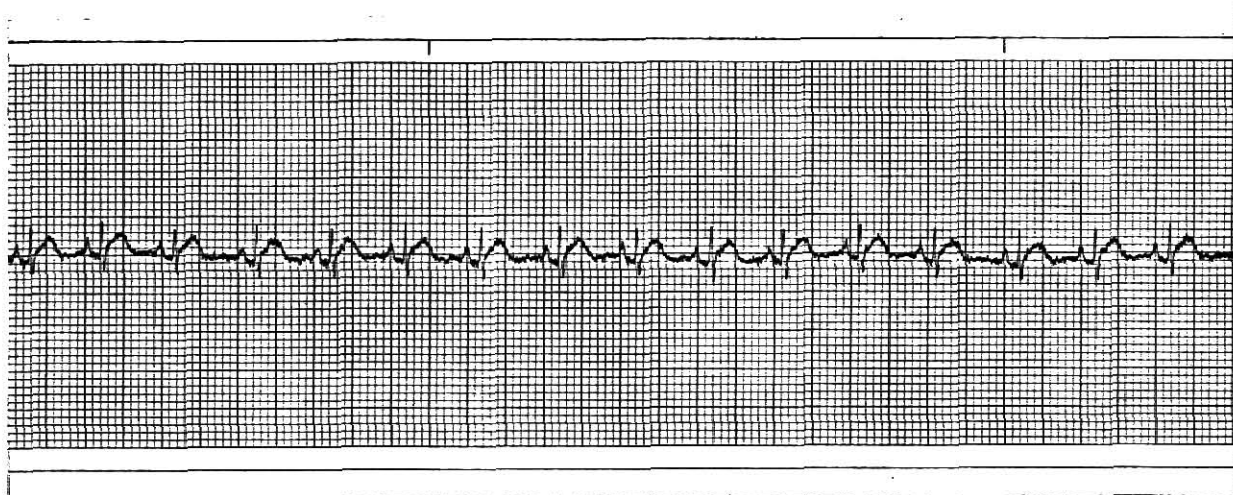
_____INTERPRETATION: Within Normal Limits

#44 "Petey" 7/21/76

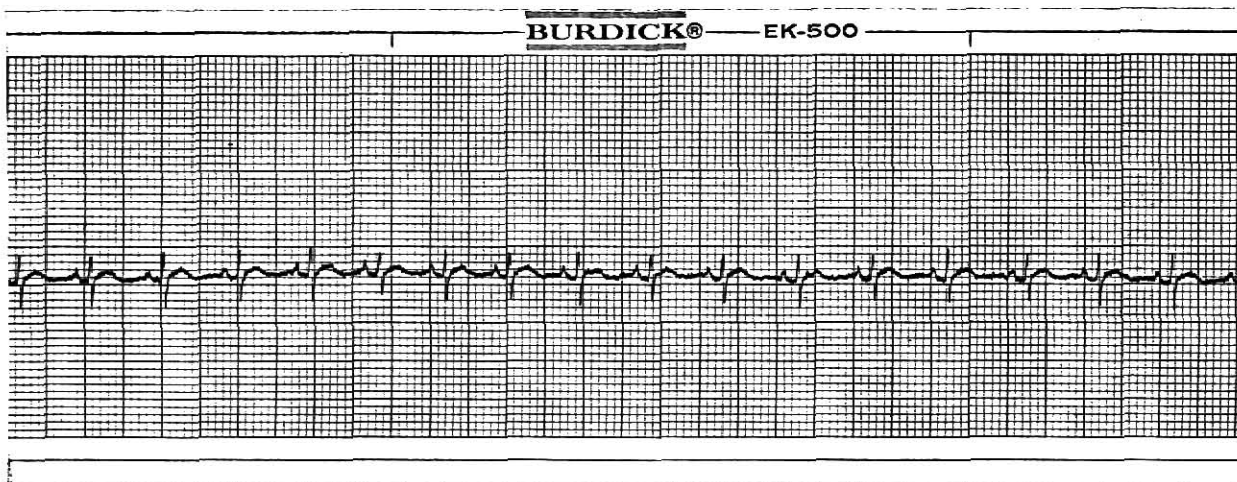
24 hour post-digoxin (0.05 mg/lb.)

Interpretation Decreased heart rate; WNL

Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-21-76 Trial 0.11 mg/kg; 24 hr PD

RHYTHM Normal Sinus Rhythm

RATE 140

P wave duration: 0.04 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .15 mV, Lead II

R wave .4 mV, Lead II

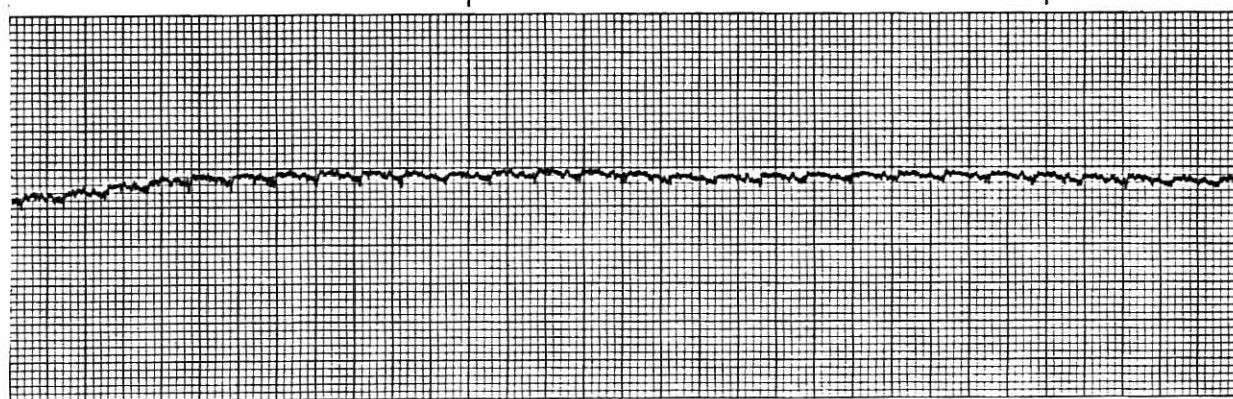
T wave .25 mV, Lead II

REMARKS: Decreased Heart Rate

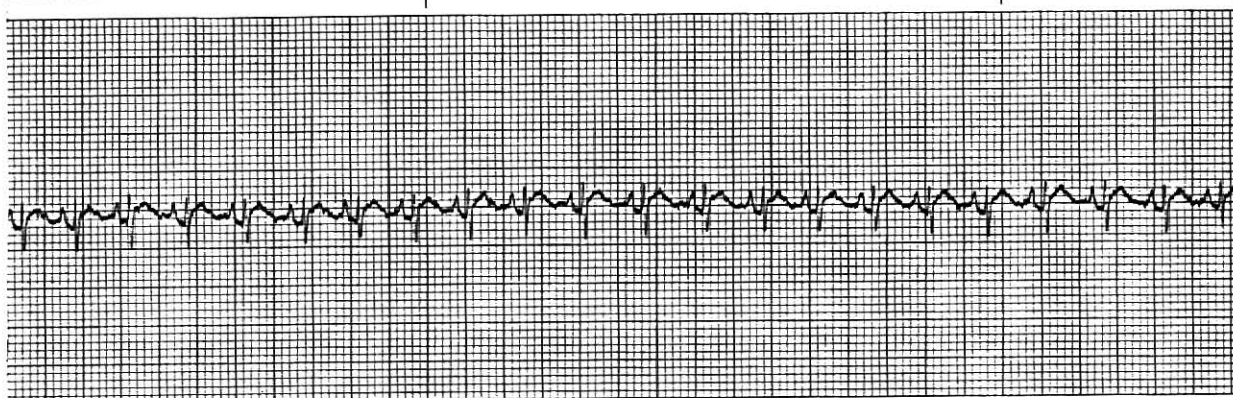
INTERPRETATION: Within Normal Limits

#44 "Petey" 7/22/76

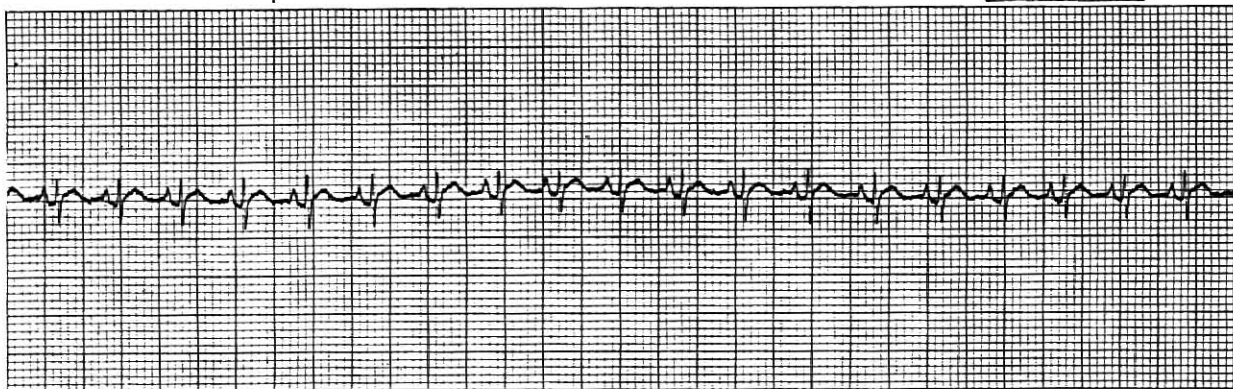
48 hour post-digoxin (0.05 mg/lb.)

Interpretation WNL

Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-22-76 Trial 0.11 mg/kg; 48 hr PD

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.05 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .3 mV, Lead II

T wave .2 mV, Lead II

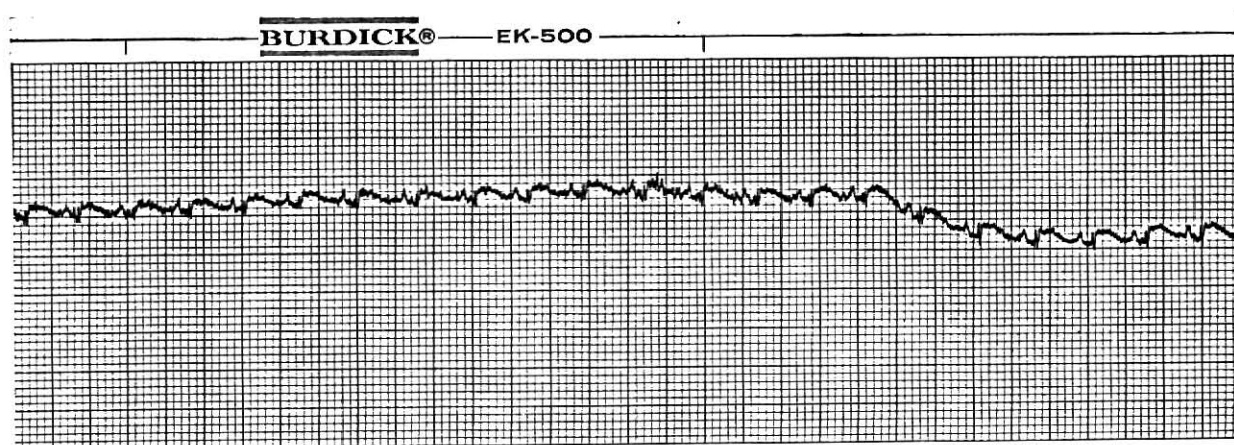
REMARKS: Back to Normal

INTERPRETATION: Within Normal Limits

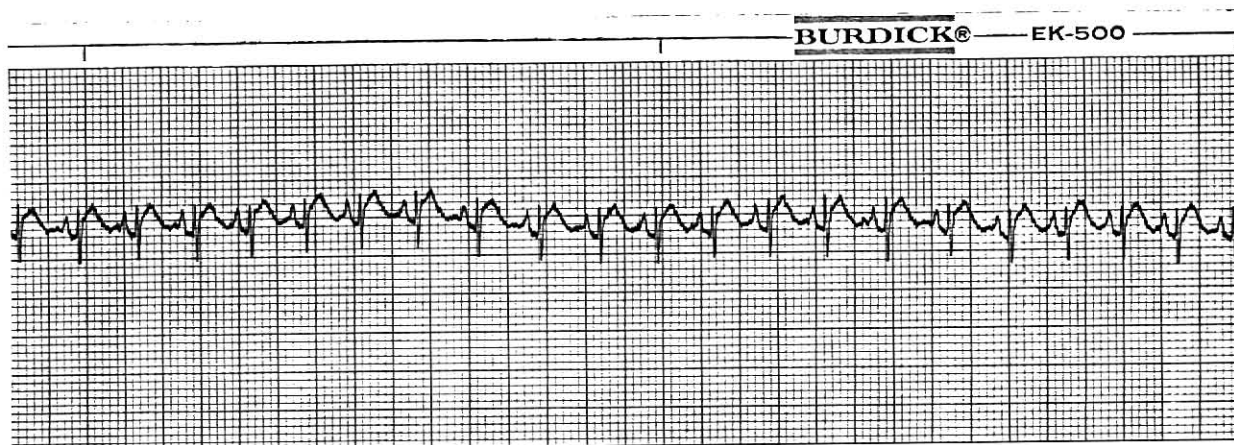
#44, "Petey" 7/23/76

72 hour post-digoxin (0.05 mg/lb.)

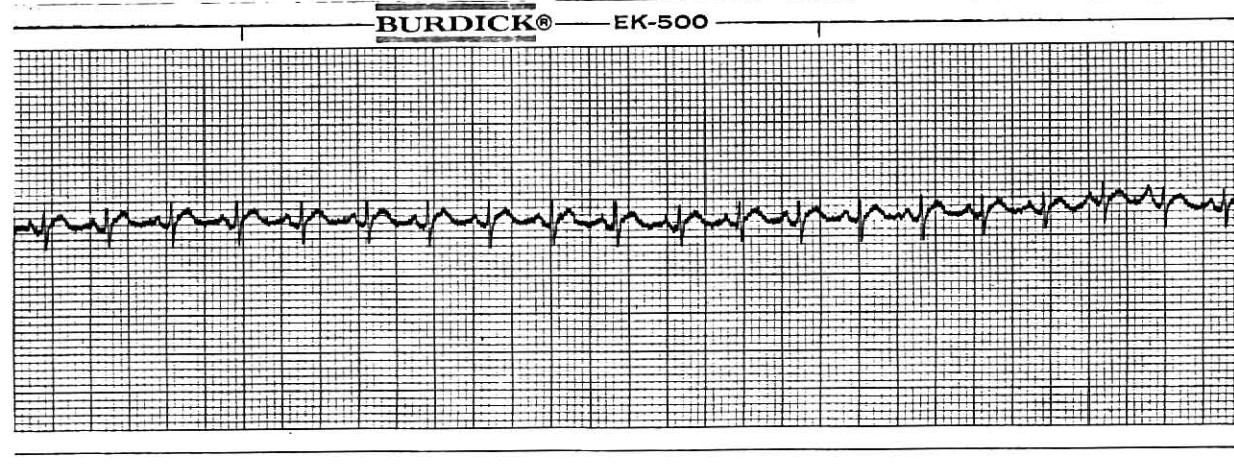
Interpretation Elevated S-T segment; digoxin effect



Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-23-76 Trial 0.11 mg/kg; 72 hr PD

RHYTHM Normal Sinus Rhythm

RATE 200

P wave duration: 0.05 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.18 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .4 mV, Lead II

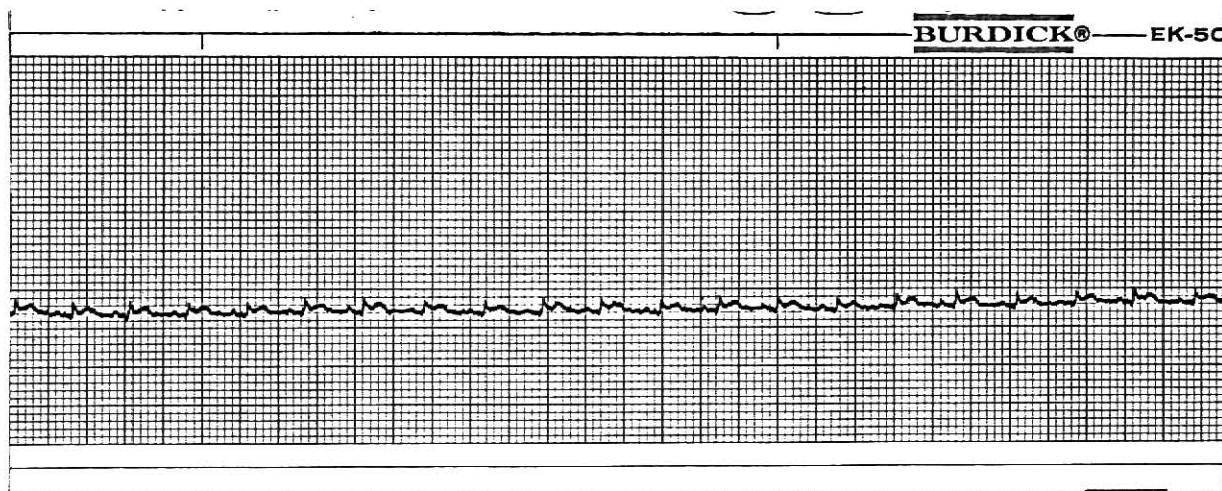
T wave .2 mV, Lead II

REMARKS: Elevated S-T Segment, Lead II

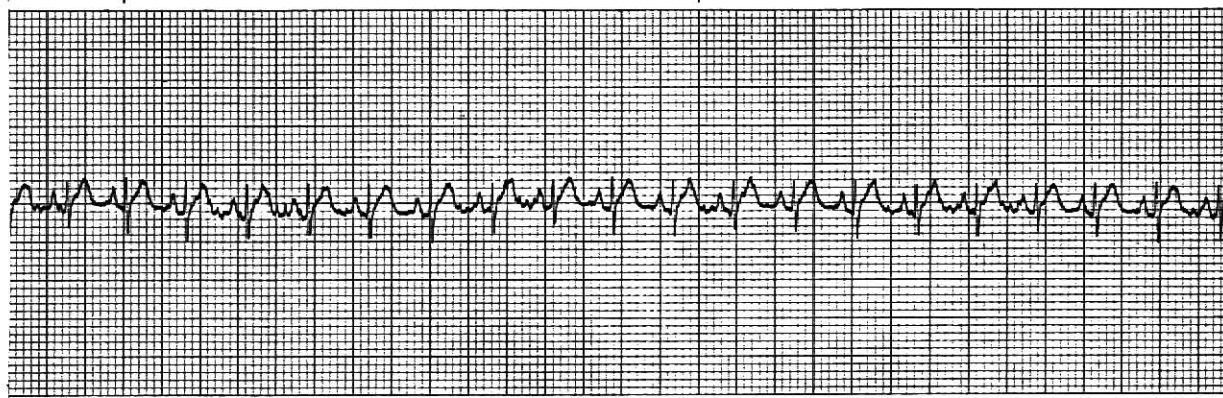
INTERPRETATION: Digoxin Effect

#44 "Petey" 7/26/76

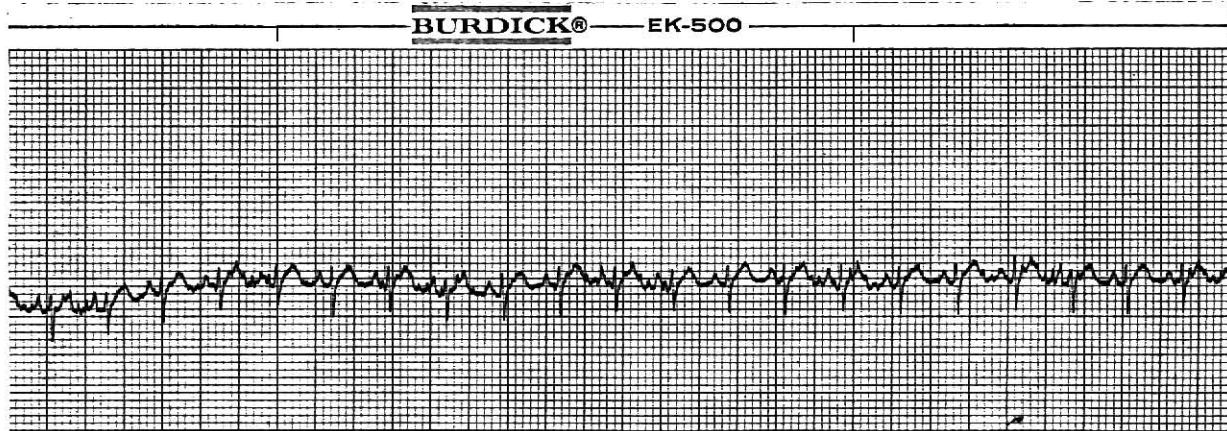
144 hour post-digoxin (0.05 mg/lb.)

Interpretation slightly elevated S-T segment, digoxin effect

Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-26-76 Trial 0.11 mg/kg; 144 hr PD

RHYTHM Normal Sinus Rhythm

RATE 180

P wave duration: 0.05 sec. - Lead II

P-Q interval: 0.08 sec. - Lead II

QRS duration: 0.04 sec. - Lead II

Q-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead II

R wave .4 mV, Lead II

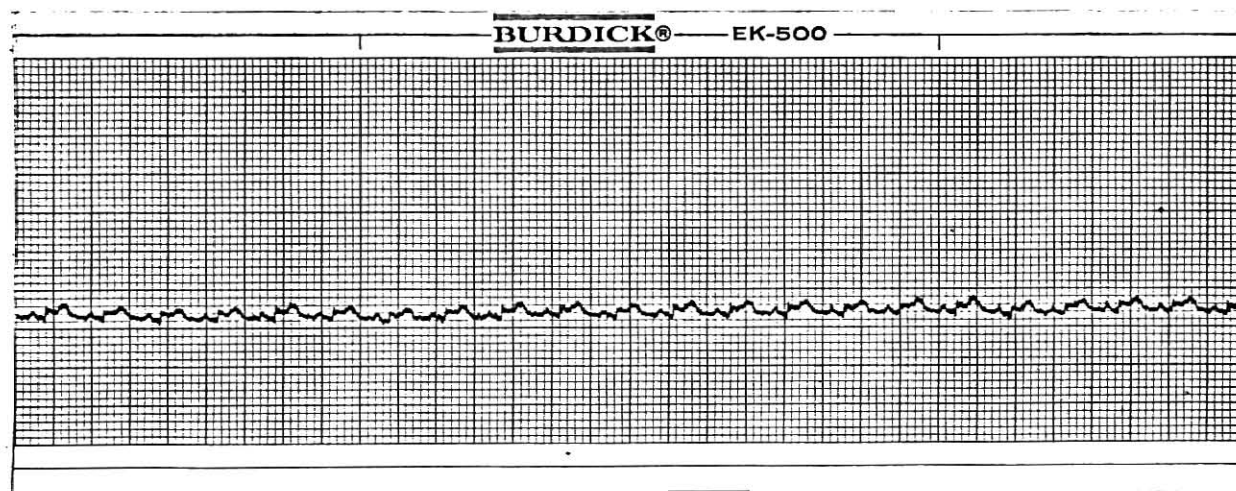
T wave .2 mV, Lead II

REMARKS: Slightly elevated S-T Segment, Lead II

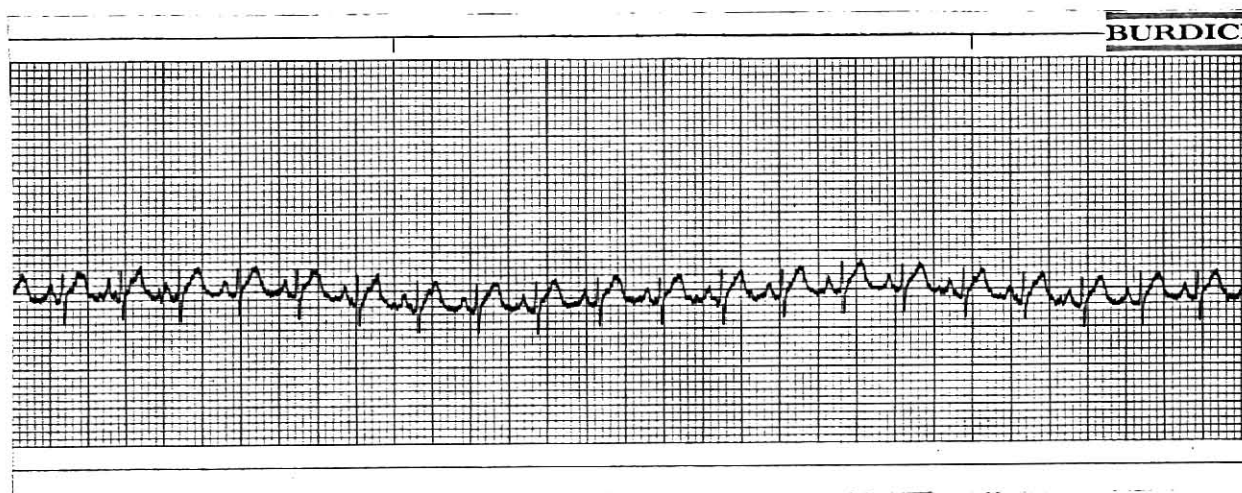
INTERPRETATION: Digoxin Effect

#44 "Petey" 7/27/76

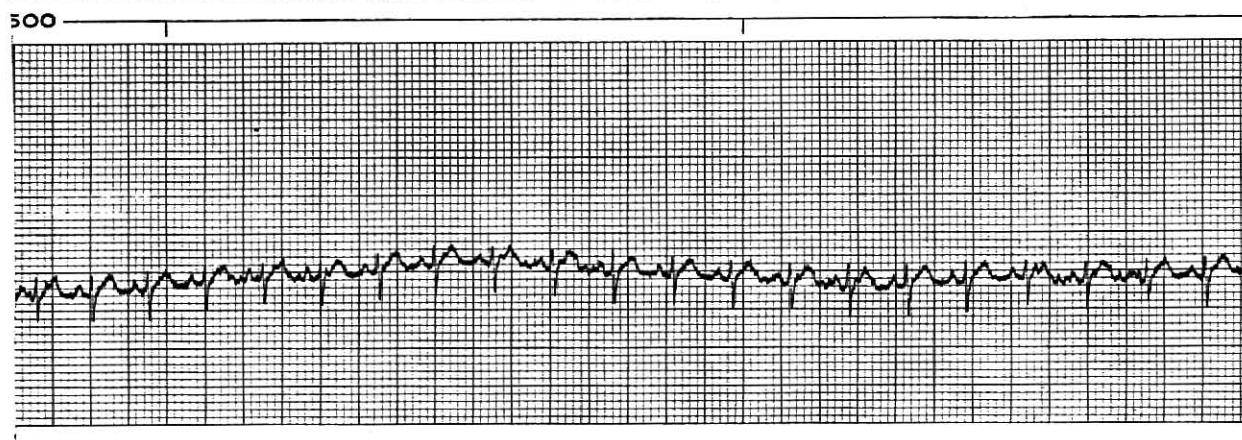
168 hour post-digoxin (0.05 mg/lb.)

Interpretation WNL

Lead I



Lead II



Lead III

Cat #44, "Petey" Date 7-27-76 Trial 0.11 mg/kg; 168 hr PDRHYTHM Normal Sinus RhythmRATE 200P wave duration: 0.05 sec. - Lead IIP-Q interval: 0.08 sec. - Lead IIQRS duration: 0.04 sec. - Lead IIQ-T interval: 0.16 sec. - Lead II

Maximum Voltage

P wave .2 mV, Lead IIR wave .4 mV, Lead IIT wave .3 mV, Lead IIREMARKS: Back to NormalINTERPRETATION: Within Normal Limits

Mean Plasma Digoxin Levels (ng/ml) of Six Cats
After Administration of Digoxin in Elixir,
Tablet, and Crushed Tablet Form

Time (hrs)		Elixir			Tablets			Crushed Tablets		
		6 cats	4 ♀	2 ♂	6 cats	4 ♀	2 ♂	6 cats	4 ♀	2 ♂
.5	$\bar{x}$	1.29	1.18	1.50	.65	.71	.52	.44	.35	.61
	σ	1.25	1.02	2.12	.47	.46	.64	.32	.36	.15
1	$\bar{x}$	1.89	1.62	2.42	1.22	.93	1.81	.66	.51	.96
	σ	1.02	1.20	.14	.74	.51	.97	.35	.34	.08
1.5	$\bar{x}$	1.62	1.19	2.48	.99	.72	1.55	.56	.44	.81
	σ	.99	.87	.59	.53	.25	.53	.22	.11	.14
2	$\bar{x}$	1.50	1.04	2.42	.63	.67	.55	.41	.42	.41
	σ	1.11	.79	1.34	.23	.20	.35	.09	.10	.11
4	$\bar{x}$	.88	.34	1.95	.36	.35	.37	.45	.48	.37
	σ	.92	.28	.72	.28	.23	.49	.23	.28	.01
6	$\bar{x}$	.67	.25	1.50	.57	.43	.87	.33	.35	.30
	σ	.69	.24	.39	.38	.25	.52	.19	.24	.13
8	$\bar{x}$	.47	.19	1.04	.45	.32	.70	.30	.33	.26
	σ	.47	.15	.23	.29	.23	.29	.15	.18	.08
12	$\bar{x}$	.88	.79	1.07	.39	.30	.59	.34	.34	.34
	σ	.60	.75	.11	.26	.28	.08	.16	.20	.13
24	$\bar{x}$	.67	.36	1.29	.29	.19	.49	.15	.17	.10
	σ	.63	.27	.79	.19	.11	.17	.10	.11	.05

Plasma Digoxin Levels for Four-Day
Therapeutic (0.011 mg/kg) Trial

Time (hrs)	#100 ♀	#53 ♀	#68 ♀	$\bar{x}$ ♀	σ ♀ (ng/ml)	#28 ♂	#112 ♂	$\bar{x}$ ♂	σ ♂	$\bar{x}$ ♀&♂	σ ♀&♂
.5 ¹	.62	.33	1.37	.77	.54	1.83	1.00	1.42	.59	1.03	.59
1 ¹	1.19	.53	1.33	1.02	.43	1.80	1.22	1.51	.41	1.21	.45
1.5 ¹	1.60	.20	.76	.85	.70	.80	1.20	1.00	.28	.91	.52
2 ¹	1.17	.14	.45	.59	.53	.73	1.27	1.00	.38	.75	.48
4 ¹	1.07	.10	.50	.56	.49	.27	1.20	.74	.66	.63	.49
6 ¹	.87	.01	.13	.34	.47	.27	1.14	.71	.62	.48	.49
8 ¹	.71	.01	.21	.31	.36	.31	.86	.59	.39	.42	.35
12 ¹	.81	.01	.14	.32	.43	.09	.72	.41	.45	.35	.38
24 ¹	.64	0	.13	.26	.34	.11	.73	.42	.44	.32	.34
1 ²	1.57	1.11	1.45	1.38	.24	2.05	1.56	1.81	.35	1.55	.34
2 ²	.91	.40	1.27	.86	.44	1.78	1.64	1.71	.10	1.20	.56
4 ²	.76	.17	.61	.51	.31	.84	1.38	1.11	.38	.75	.44
6 ²	.85	.15	.54	.51	.35	.78	1.20	.99	.30	.70	.39
24 ²	.87	.07	.19	.38	.43	.60	1.01	.81	.29	.55	.41
1 ³	1.91	1.06	1.49	1.49	.43	2.36	1.93	2.15	.30	1.75	.49
2 ³	1.23	.44	1.02	.90	.41	1.86	1.81	1.84	.04	1.27	.59
4 ³	1.00	.24	.93	.72	.42	1.29	1.62	1.46	.23	1.02	.51
6 ³	.86	.16	.64	.55	.36	1.59	1.58	1.59	.01	.97	.62
24 ³	.94	.30	.55	.60	.32	.83	1.14	.99	.22	.75	.33
1 ⁴	1.76	1.78	2.06	1.87	.17	2.59	1.59	2.09	.71	1.96	.39
2 ⁴	1.27	.57	2.05	1.30	.74	2.39	1.48	1.94	.64	1.55	.71
4 ⁴	1.20	.43	1.10	.91	.42	2.07	1.67	1.87	.28	1.29	.62
6 ⁴	1.06	.35	1.18	.85	.45	2.00	1.38	1.69	.44	1.19	.59
24 ⁴	1.07	.24	1.26	.86	.54	1.53	1.18	1.36	.25	1.06	.49

Plasma Digoxin Levels After Toxic Dose (0.11 mg/kg) of Oral Digoxin

Time (hrs)	#100 ♀	#24 ♀	#68 ♀	$\bar{x}$ 3 ♀	σ 3 ♀	#28 (ng/ml)	#44 ♂	#51 ♂	$\bar{x}$ 3 ♂	σ 3 ♂	$\bar{x}$ ♀ & ♂	σ ♀ & ♂
1	2.0	5.67	9.86	5.84	3.93	4.89	5.26	10.82	6.99	3.32	6.42	3.32
2	5.7	6.95	7.90	6.85	1.10	3.04	6.73	13.92	7.90	5.53	7.37	3.61
4	6.8	5.78	5.63	6.07	.64	3.58	5.52	11.72	6.94	4.25	6.51	2.76
6	7.1	6.15	5.24	6.16	.93	2.32	4.93	13.62	6.96	5.92	6.56	3.81
12	4.7	3.98	3.96	4.21	.42	1.02	4.75	11.12	5.63	5.11	4.92	3.33
24	2.9	2.48	4.14	3.17	.86	1.70	4.87	9.62	5.40	3.99	4.29	2.85
48	2.2	2.87	3.03	2.70	.44	2.51	4.38	7.82	4.90	2.69	3.80	2.11
72	2.9	1.28	2.84	2.34	.92	1.26	3.81	6.42	3.83	2.58	3.09	1.91
96	3.0	1.22	1.85	2.02	.90	.19	1.92	5.62	2.58	2.77	2.30	1.87
120	2.0	.63	1.01	1.21	.71	.40	1.07	5.92	2.46	3.01	1.84	2.07
144	1.4	.50	.67	.86	.48	.11	.68	4.92	1.90	2.63	1.38	1.78
168	.9	.44	1.60	.98	.58	.01	.60	4.72	1.78	2.57	1.38	1.72
Time of vomition (hrs)	5	3.5	3.5	4.00	.87	.50	12	5	5.83	5.80	4.92	3.84
Ng/ml at time of vomition	7.1	4.92	4.45	5.49	1.41	6.77	4.75	12.12	7.88	3.81	6.69	2.88

A STUDY OF PLASMA LEVELS OF DIGOXIN IN THE CAT AFTER ORAL
ADMINISTRATION OF NORMAL AND TOXIC DOSES CORRELATED
WITH CLINICAL AND ELECTROCARDIOGRAPHIC SIGNS

by

DEBORAH FINETTE ERICHSEN

B.S., Kansas State University, 1966
D.V.M., Kansas State University, 1968

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Manhattan, Kansas

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ABSTRACT:

Unanesthetized cats of both sexes were given oral digoxin in three different dosage forms (elixir, tablet, and crushed tablet mixed with food). Peak plasma levels of digoxin were highest with the elixir (1.89 ng/ml mean) and lowest with the crushed tablet mixed with food (0.66 ng/ml mean). Males had a significantly higher mean plasma digoxin level than females.

A second group of unanesthetized cats of both sexes were given digoxin elixir orally at therapeutic levels (0.011 mg/kg) once a day for four consecutive days. The cumulative effect of digoxin resulted in 62% increase in the mean peak plasma level and 231% increase in the 24-hour plasma level of digoxin over the four-day period. Males had a significantly higher mean plasma digoxin level than females. No significant changes in the electrocardiograms were recorded.

A third group of unanesthetized cats of both sexes were given a single toxic (0.11 mg/kg) dose of digoxin elixir orally. All cats showed clinical signs of digitalis toxicity (depression, vomiting, salivation, anorexia, etc.) before electrocardiographic changes appeared. Alterations in the electrocardiograms were minimal; the most significant changes were a slight increase in the P-Q interval, an elevated S-T segment, and decreased heart rate. The cats were clinically ill for 48-96 hours. Results indicate a plasma digoxin level of 2.3 ng/ml is not toxic. Males had higher plasma digoxin levels than females.