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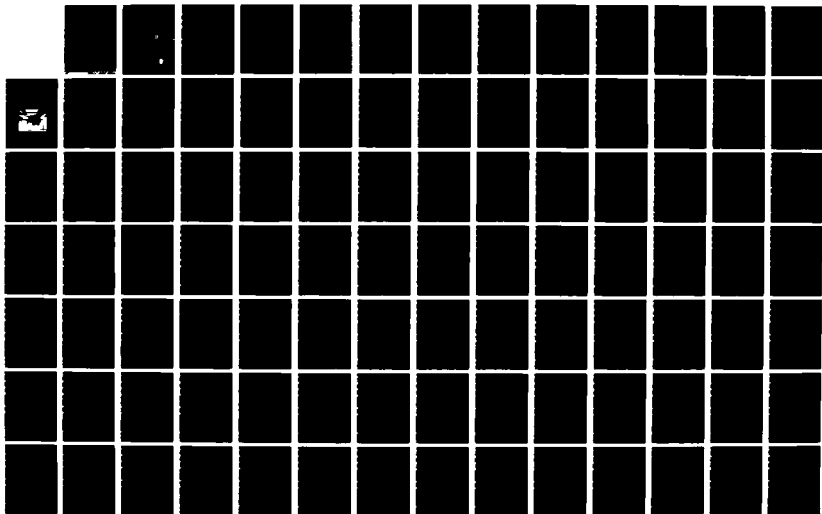
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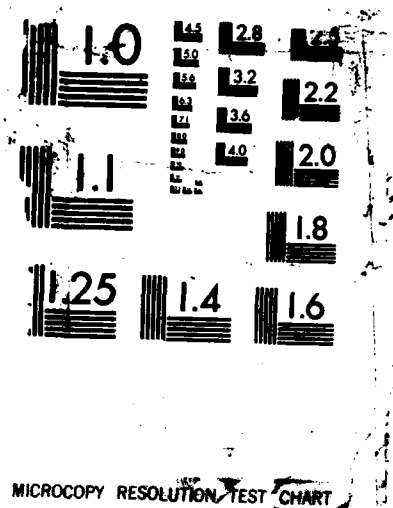
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**LONG-TERM BIOEFFECTS OF 435-MHz
RADIOFREQUENCY RADIATION ON
SELECTED BLOOD-BORNE ENDPOINTS
IN CANNULATED RATS**

Volume 4. Plasma Catecholamines

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Prepared for
USAF SCHOOL OF AEROSPACE MEDICINE
Human Systems Division (AFSC)
Brooks Air Force Base, TX 78235-5301



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NOTICES

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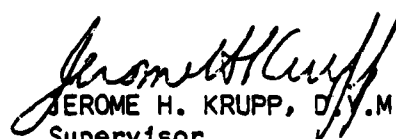
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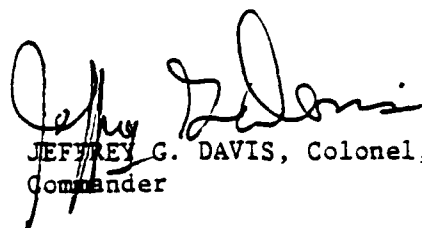
The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources-National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.


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**LONG-TERM BIOEFFECTS OF 435-MHz RADIOFREQUENCY RADIATION
ON SELECTED BLOOD-BORNE ENDPOINTS IN CANNULATED RATS
Volume 4. Plasma Catecholamines**

I. INTRODUCTION

During the past 50 years, the United States has witnessed a period of explosive growth in the radar and communications fields. This growth has increased the demand for available bandwidth and thus has pushed radar and communications frequencies into higher and higher ranges. Higher frequency ranges have permitted faster data transmission rates and reduced intersystem electromagnetic interference. However, these advances have come at the expense of altering the planet's radiofrequency radiation (RFR) environment. Until the advent of advanced radar and communications, cosmic rays and background radiation were the primary sources of the Earth's electromagnetic environment. Radar and communications transmissions have since increased the electromagnetic background or ambient radiation at the planet's surface by several orders of magnitude. At this time, the biological effects of exposure to this omnipresent electromagnetic environment are not well understood, despite studies conducted over the past several decades.

This report presents the results of plasma catecholamine (norepinephrine, epinephrine, and dopamine) assays of blood samples drawn from a large population of male Sprague-Dawley rats exposed to a 1.0 mW/cm^2 , 435-MHz pulsed-wave (1.0 μs pulse width, 1-kHz pulse rate) RFR environment for a 6-month duration. The exposure group consisted of 100 cannulated rats housed in Plexiglas cages arrayed on the tiers of a stacked, parallel-plate circular waveguide. Engineering aspects of this waveguide and the exposure environment it generated have been previously reported [1]. The sham-exposure group consisted of 100 cannulated rats housed in an identical, but unenergized, collocated facility. Results reporting blood chemistry and hematology in these same animals will be published in the next volume of this series. Other volumes have already published results on adrenocorticotrophic hormone (ACTH) and corticosterone [2] and prolactin [3].

The sympathetic-adrenal medullary system plays a critical role in the maintenance of cardiovascular and metabolic homeostasis. Plasma catecholamines have been measured to assess the functional activity of the sympathetic-adrenal medullary system under resting conditions or during stressful stimulation.

Norepinephrine, the neurotransmitter of the sympathetic nervous system, occurs in tissues of neural crest origin, sympathetic nerve endings, the adrenal medulla, and other chromaffin tissues as well as in the brain. Norepinephrine is synthesized from dopamine by the enzyme dopamine- β -hydroxylase [4]. The predominant sources of circulating norepinephrine are sympathetic nerve endings and the adrenal medulla. Both norepinephrine and dopamine- β -hydroxylase are secreted from sympathetic nerve terminals in proportional amounts during nerve stimulation [5,6] and can be accurately measured in the blood. This circulating norepinephrine derives largely from the sympathetic innervation to vascular walls--especially to small arteries and arterioles which provide the main source for peripheral resistance and therefore crucially influence blood pressure. The extent of norepinephrine "spillover" from the synaptic cleft to the general circulation depends on the cleft width: perisynaptic norepinephrine concentrations are relatively low for narrow gaps but high for wide gaps where the concentrations approach those estimated to be attained in the synapse. Since vascular intramural synapses have wide gaps, it seems likely that their proportional contribution to circulating norepinephrine is large when compared to nonvascular noradrenergic synapses such as in the vas deferens, which typically have narrow gaps. Thus the level of plasma norepinephrine reflects both adrenomedullary and sympathetic nerve activity.

The adrenal medullary responses were described first as endosecretory responses to stress. The release of epinephrine is part of this response and was first demonstrated in 1914 [7] in cats exposed to barking dogs. Similar responses occur after many psychological or physical stimuli. The release of epinephrine correlates with the degree of stress.

The physiologic functions of the dopamine receptors include vasodilation, increased sodium excretion, and increased myocardial contractility. Even change in the position (from standing on four legs to exploring the cage while standing on hind legs) is associated with enhanced sympathetic activity. Similar changes have been found in man by Sundin [8].

Exercise increases plasma catecholamines. High workloads or prolonged work stimulates several-fold increases in both norepinephrine and epinephrine concentrations. Many other stresses increase the release of catecholamines (particularly epinephrine and norepinephrine). Thus the plasma level of norepinephrine, epinephrine, and (to a lesser degree) dopamine fluctuates widely in a mammal reflecting increasing or decreasing physical activity or exposure to

various stressful environments [9]. The determination of catecholamine levels is used to quantitatively measure the level of stress induced on the autonomic nervous system. Sympathetic neuronal discharge, with adrenomedullary release of catecholamines into the blood, is a recognized component of the immediate physiological response to stress [7,10]. Even gentle handling produces an increase in epinephrine, whereas immobilization produces massive elevations of circulating levels of both epinephrine and norepinephrine. Decapitation or restraint lead to a 10-fold increase in circulating norepinephrine and an 80-fold increase in circulating levels of epinephrine, whereas dopamine increases to a lesser degree (Table 1). The high levels of plasma catecholamines in rats when compared with other animals and humans, and changes produced in pharmacological and physiological experiments, probably reflect environmentally induced changes in sympathoadrenomedullary activity rather than differences in basal sympathetic neuronal activity.

TABLE 1. CHANGES IN HORMONE LEVELS IN CANNULATED AND DECAPITATED RATS

Rat #	Cannulated			After decapitation		
	NOR	EPI	DA	NOR	EPI	DA
1	-	-	-	825	960	185
2	104	126	30	1275	2795	235
3	123	144	39	1740	1570	210
4	144	126	25	1870	3565	235
5	185	113	58	1435	2875	170
6	174	104	76	2660	5430	465
7	144	159	74	1170	1830	365
8	153	193	28	-	-	-
9	137	154	61	1425	2235	205
10	162	148	74	940	1345	260
11	144	177	43	1520	2975	255
12	-	-	-	1930	5295	440
$\bar{X}$	147	144	51	1526	2807	275
S.D.	24	28	20	515	1485	102

All hormone concentrations are in pg/mL.

II. MATERIALS AND METHODS

For this study, the concentrations of the plasma catecholamines norepinephrine, epinephrine, and dopamine were chosen as sensitive indicators of possible environmental stresses induced by RFR. To detect and quantitatively evaluate possible increases in plasma catecholamine levels induced by RFR, blood was sampled and assayed from 65 exposed and 64 sham-exposed animals (in the case of epinephrine); 63 exposed and 63 sham-exposed animals (in the case of norepinephrine); 64 exposed and 64 sham-exposed animals (in the case of dopamine). Analysis of the data obtained from the blood sample assays determined whether there were any RFR-induced changes in plasma catecholamine concentrations.

Animals. The rat represents a comparatively inexpensive and homogeneous population. For this reason, it is often desirable to use this species as the animal model in physiologic studies.

In this study, male Sprague-Dawley rats were used. All experimental animals were obtained from the same building and room at CAMM Research Labs, Wayne, New Jersey. The animals, weighing approximately 60 g, were delivered to Emory University where they were caged singly and given water and food (Purina Rat Chow) ad libitum. Temperature in the animal rooms was maintained at 24 ± 1 °C and the photoperiod was 12 hours/12 hours, with the lighted phase occurring between 8 AM and 8 PM.

Experimental Facility. The Georgia Tech Research Institute's Radiofrequency Radiation Facility [1] consisted of 8 collocated rooms on the basement floor of the Baker Building on the main campus. These 8 rooms provided a closed, complete facility for long-term bioeffects studies involving rodents.

The 100 exposure and 100 sham-exposure animals were housed in 2 identical, collocated rooms in the RFR Facility. Each room contained a stack of circular, parallel-plate waveguides fed by a slotted-cylinder antenna system for radiating the animals. The stacks of parallel waveguides consisted of five, 3.6-m (12 ft.) diameter plates that made up 4 sets of circular waveguides. Twenty-five individually housed rats were positioned around the circumference of each waveguide set. The walls of both rooms were lined with anechoic absorbing material and shielded with aluminum foil to prevent excessive microwave leakage radiation.

The circular, parallel-plate waveguide assembly provided a 1.0 mW/cm^2 exposure field around the circumference of the plates. The 45.7-cm (18 in.) plate separation distance permitted propagation of a TE_{10} mode wave with horizontal polarization. The power density displayed a cosine-squared dependency between the plates, with the maximum power density occurring midway between each set of plates. This arrangement positioned the electric field vector parallel to the rat's longitudinal axis, thereby maximizing the coupling between the electric field and the rat.

A slotted-cylinder antenna with the proper diameter, thickness, slot length, and slot width dimensions fed the stack of circular waveguides in a manner that provided an essentially constant electric field intensity in the azimuth plane.

Cages. The cages were constructed of clear Plexiglas, which was essentially RFR-transparent at 435 MHz. Clear (rather than colored) Plexiglas was chosen to permit visual observation of the rats. Each cage was 22.9-cm (9 in.) long by 12.7-cm (5 in.) wide by 17.8-cm (7 in.) tall. These dimensions complied with dimensions recommended by the National Institutes of Health for long-term housing of rats [11]. The food hopper and water bottle were placed on the distal side of the cage to minimize their interaction with the exposure field. The glass floor rods in the cage were oriented perpendicular to the cage's long axis to induce the rats to preferentially align themselves parallel to the electric field vector. The sipper tubes of the water bottles were made of glass to be nonperturbing in the field. Evaluations of the cages conducted in the circular, parallel-plate waveguide assembly showed field scattering from the Plexiglas to be below the range of detection.

The RFR Facility contained a data acquisition system for storing and processing experimental data, an electronic balance for weighing the rats during the study, and rooms for transmitter operation, blood sampling, cage washing, and materials storage.

To avoid the possible effects of noise during this study, the entire Radiation Facility was kept locked to avoid unauthorized entry. Only the animal caretaker and the technician who sampled blood from the animals were permitted uncontrolled entry to the Facility.

Cannulation. To detect and quantitatively evaluate changes in plasma catecholamines, the resting levels of these hormones first had to be determined. To obtain the real resting values of the three hormones in undisturbed animals,

many routine techniques for handling the animals and for sampling the blood were unsuitable for this study. For example, guillotine blood sampling techniques commonly employed in many endocrinological studies were immediately ruled out. To use each animal as its own control, arterial blood was sampled by means of chronically implanted aortic cannulas [12,13,14]. This simple, inexpensive technique permitted remote, stress-free blood sampling in conscious, unrestrained and resting rats. Arterial blood drawn through the resting rat's chronically implanted cannula was assayed for plasma norepinephrine, plasma epinephrine, and plasma dopamine.

The idea of sampling venous blood from the animals was abandoned. In venous blood vessels, the flow regime is laminar with blood flowing in discrete layers. The layers of blood in the middle of the vessels travel much faster than those close to the vessel walls. The most important consideration, however, was that blood layers do not mix in venous blood vessels. Thus, a sample of venous blood, withdrawn with a needle or a cannula, might represent the blood returning from one part of the body or the other, from a single organ or muscle, or from any one of the endocrine glands. For this reason, we decided to sample arterial blood, which is always fully mixed. The mixing occurs in the left ventricle of the heart and in early parts of the aorta. Only small amounts of arterial blood (up to 0.6 mL) were withdrawn from resting rats about once every 3 to 5 weeks. Removing greater volumes of blood has been shown to elevate plasma norepinephrine concentrations in the rats (Fig. 1).

We used PE-10 arterial cannulas in this study. Larger PE-50 cannulas were unsuitable because they could develop large blood clots if not drained frequently. Large cannulas require multiple flushing to remain patent, but flushing might induce multiple strokes in the animals. Chronic cannulation of the aorta with a PE-10 cannula was preferable to cannulation of other arterial blood vessels. Cannulation of the abdominal aorta provided long-term functional cannulas, but the cannulation procedure was lengthy (20-30 min) and required opening the abdominal cavity and temporary dislocation of the gastro-intestinal system. The abdominal aortic cannula had a much larger dead space than the aortic cannula. Cannulation of the aorta through the left carotid artery, on the other hand, required an incision of 1-1.5 cm that neither penetrated body walls nor entered the abdominal cavity. Further, this cannulation could be completed in about 8 min.

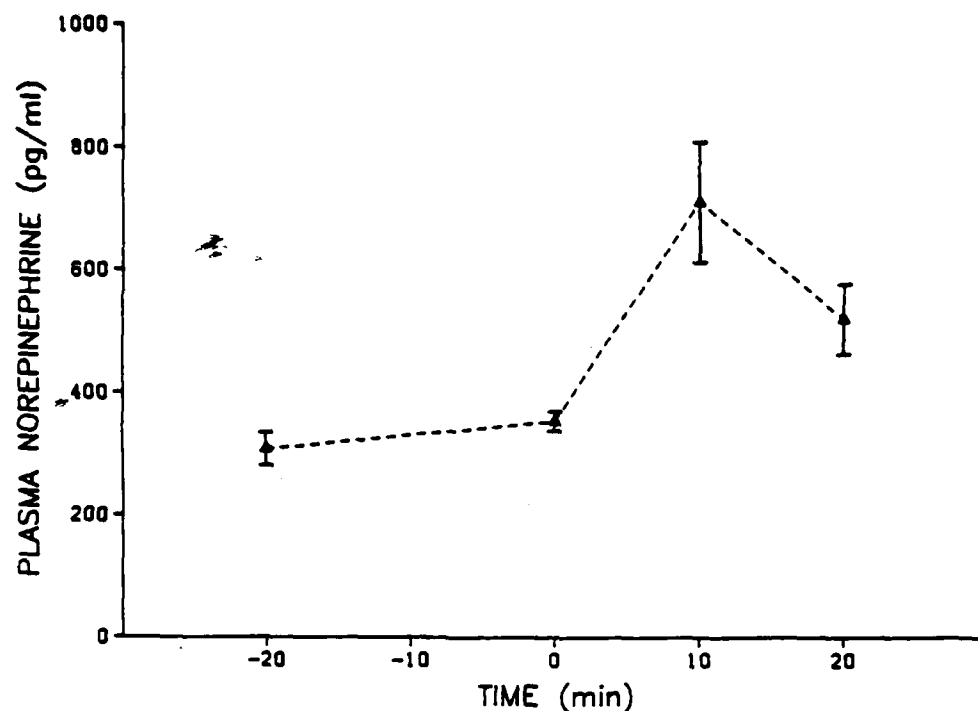


Figure 1. Effect of 1.0 mL bleeding on resting plasma norepinephrine concentration.

The carotid artery of the animal was cannulated 8 to 10 days before the animals entered the study. The surgery was done using ketamine-xylazine anesthesia (1:1 mixture; ketamine 100 mg/mL, xylazine 20 mg/mL, i.m. 0.1 mL / 100 g of body weight). The catheter was filled with slightly heparinized saline*, and the distal end was sealed with a nylon plug. Stress hormone levels returned to the basal values about 3 days after implantation of the chronic arterial cannulas. The first blood sampling occurred 10 days after aortic cannulation.

Blood Sampling. Although the half-life of plasma catecholamines is only 1 to 3 min [15], a strong stimulus leaves plasma catecholamine levels relatively high for a period of up to 15-20 min. Normal handling (lifting the rat) evoked a 75% increase in epinephrine concentration accompanied by a small increase in norepinephrine concentration. However, the animals had to be handled when they were removed from their exposure cage and placed in the "sampling box" in preparation for blood withdrawal. To avoid the undesired effects of handling on catecholamine levels, blood from the aortic cannula was sampled 30 min after the animal was placed in the sampling box. This procedure permitted the altered plasma catecholamine levels sufficient time to return to their basal (resting)

*0.5-cm³ heparin sodium (from beef lung), 1000 units/mL per 30 cm³ saline.

values. Each animal was preconditioned for the sampling box through a regime of several 30-min-long experiments conducted during a 1-week period before entering the study.

After acclimating for 30 min in the sampling box, the rat's cannula was positioned through the slot in the top of the box (Fig. 2). The heparinized saline was then removed from the cannula, and a 0.6 mL blood sample was taken from the resting rat using a sterile 1-cm³ tuberculin syringe fitted with a 30-ga needle. The syringe and needle were rinsed with ethylene glycol-bis tetraacetic acid (EGTA)/glutathione before sampling. The blood sample was placed in an EGTA/glutathione-treated 1.0 mL capillary blood collection container (prepared in-house and stored under refrigeration to prevent chemical breakdown), shaken, and then placed on ice. The blood sampling procedure required about 2 min for each rat.



Figure 2. Sampling blood from the chronic aortic cannula of a resting, unrestrained, and unanesthetized rat.

Plasma catecholamine levels in conscious unrestrained rats with chronic indwelling catheters were considerably lower than previously reported for the rat [16].

Blood Sampling Schedule. Figure 3 shows the sampling schedule designed for the experiment. The 200 rats were introduced into the study in 4 groups of 50 animals each. The groups entered in a staggered manner to facilitate the process of logging-in and establishing the new animals. Each group contained 25 exposure and 25 sham-exposure animals. Of the 25 exposure (or sham-exposure) animals, 20 were sampled for plasma stress hormones, while the remaining 5 were used for hematology studies.

The sampling duration was 36 weeks long, including a 6-week preexposure adaptation period, a 24-week exposure period, and a 6-week postexposure period. With group staggering taken into account, the experiment duration was 42 weeks long (since introduction of the 4 groups was staggered in 2-week intervals). Plasma catecholamines were to be sampled for all periods marked (B) in Figure 3. Therefore, each animal should have been sampled for plasma norepinephrine, epinephrine, and dopamine at weeks -5, -2, 1, 4, 7, ..., 28. This schedule was rather rigorous and therefore could tolerate slight fluctuations in protocol without ill effects.

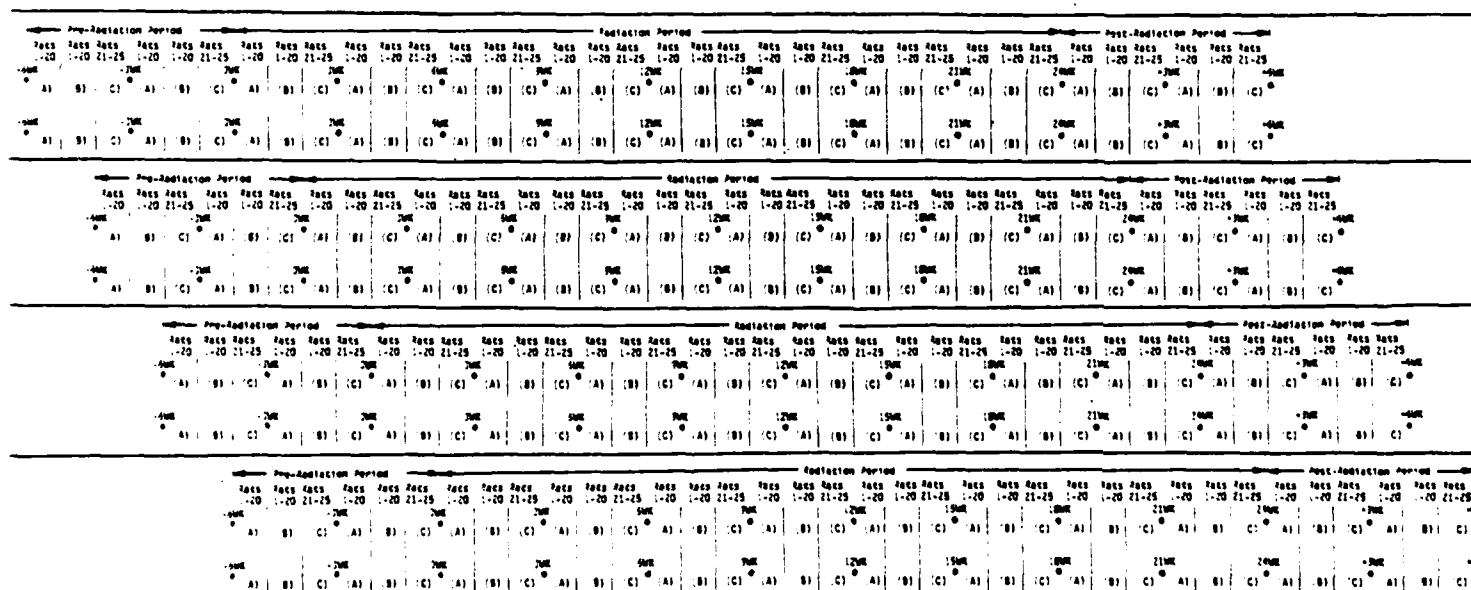


Figure 3. Sampling and exposure timetable.

Plasma Catecholamine Determinations. Plasma catecholamines were measured with a radioenzymatic method according to Penler and Johnson [17]. Briefly, the three catecholamines were first converted to their o-methylated analogues by catechol-o-methyl-transferase in the presence of S-adenosyl-methomine-³H and thereafter extracted following addition of sodium tetraphenylbyrate. This extraction, together with an improved quick chromatographic separation and the oxidation of the epinephrine and norepinephrine derivatives to vanillin, yielded an extremely high sensitivity and specificity of the method. The assay allowed the determination of norepinephrine, epinephrine, and dopamine in plasma volumes of 20-100 μ L.

III. RESULTS AND ANALYSIS

Plasma Norepinephrine. Appendix A contains the data collected during the preradiation and radiation periods for both the exposure and sham-exposure groups. The high variance displayed by the data for the entire sampling period indicated various degrees of animal activity at the time of blood sampling. Since the boxes had opaque walls, the activity of each animal before sampling was not recorded. However, as previously mentioned, it was unlikely that the stimulation of placing the rats in the sampling boxes had a major effect on resting norepinephrine concentration, since the increase in norepinephrine secretion induced by animal handling would disappear 20 to 30 min following the stress.

Figures 4 and 5 present the raw norepinephrine concentration in scatter diagram form (the dotted lines pass through the mean response at each week data were collected). Despite a 3-week effort to precondition the animals to the sampling box environment before drawing blood samples, the basal resting value of plasma norepinephrine decreased during weeks -3, -2, and 0. This same behavior was also observed in plasma ACTH, plasma corticosterone, and plasma prolactin [2,3]. After the first week, the data displayed a nearly linear response. The "spikes" occurring at weeks 10 and 17 (sham-exposure group) are the mean values resulting from 7 and 3 observations, respectively; the spike at week 11 (exposure group) is the mean value resulting from 5 observations. The wide range spanned by the 2-sided 95% confidence interval at each value indicated that these "spikes" may not represent drastic deviations from the established norepinephrine resting concentration. Noise and unfamiliar persons visiting the Radiation Facility may have also contributed to the sham-exposure group spike at week 10.

Mean plasma norepinephrine concentrations in the exposure and sham-exposure groups did not appear significantly different when plotted on the same axis (Fig. 6). This was preliminary evidence indicating that chronic exposure to 435-MHz RFR did not affect the resting level of plasma norepinephrine. A statistical analysis was subsequently performed on the data to test this hypothesis.

The analysis involved using multiple linear regression techniques to build a model describing plasma norepinephrine levels as a function of time and incident RFR. Terms of the polynomial model thus obtained were tested for their

Plasma norepinephrine
concentration (in pg/mL)

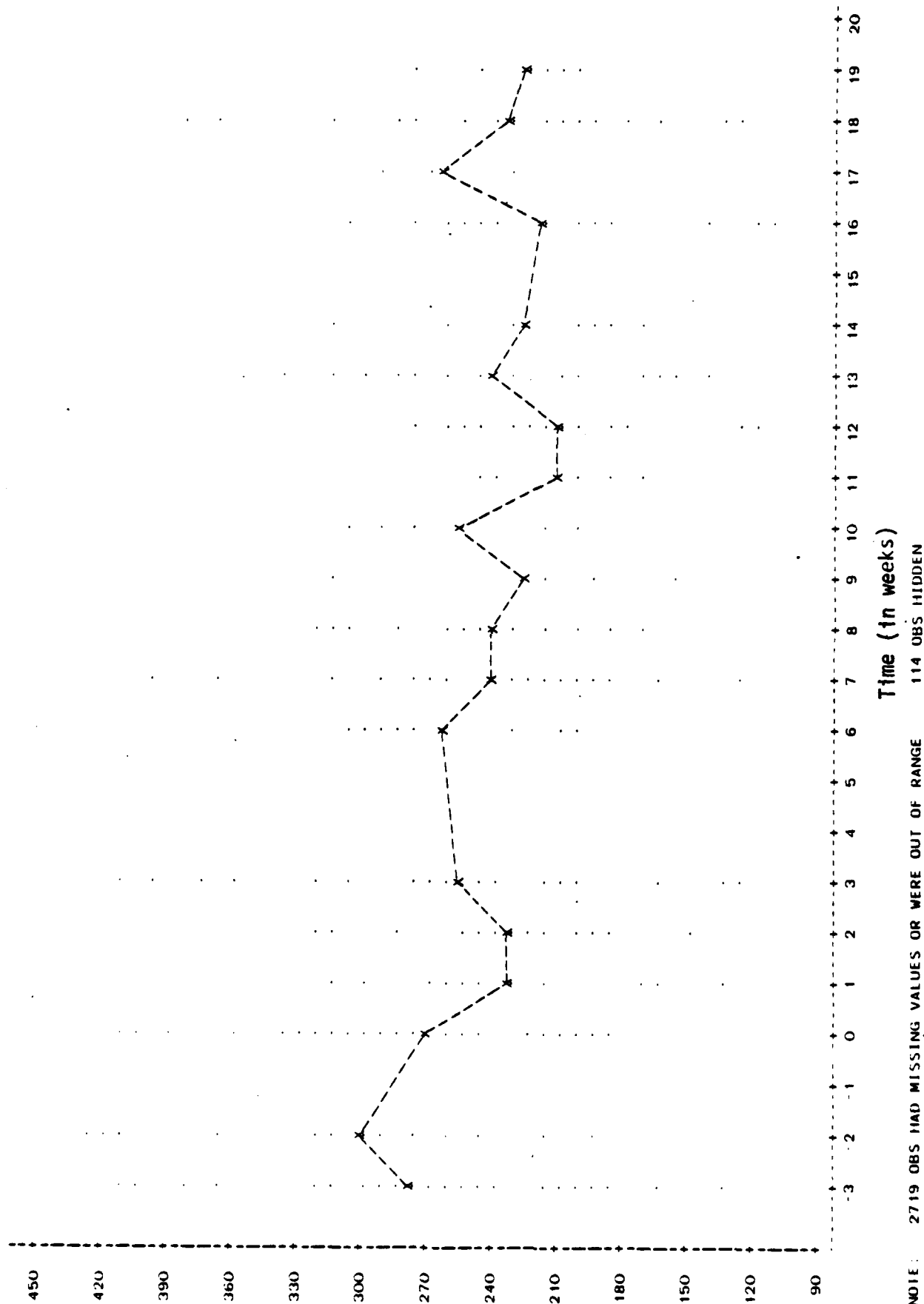
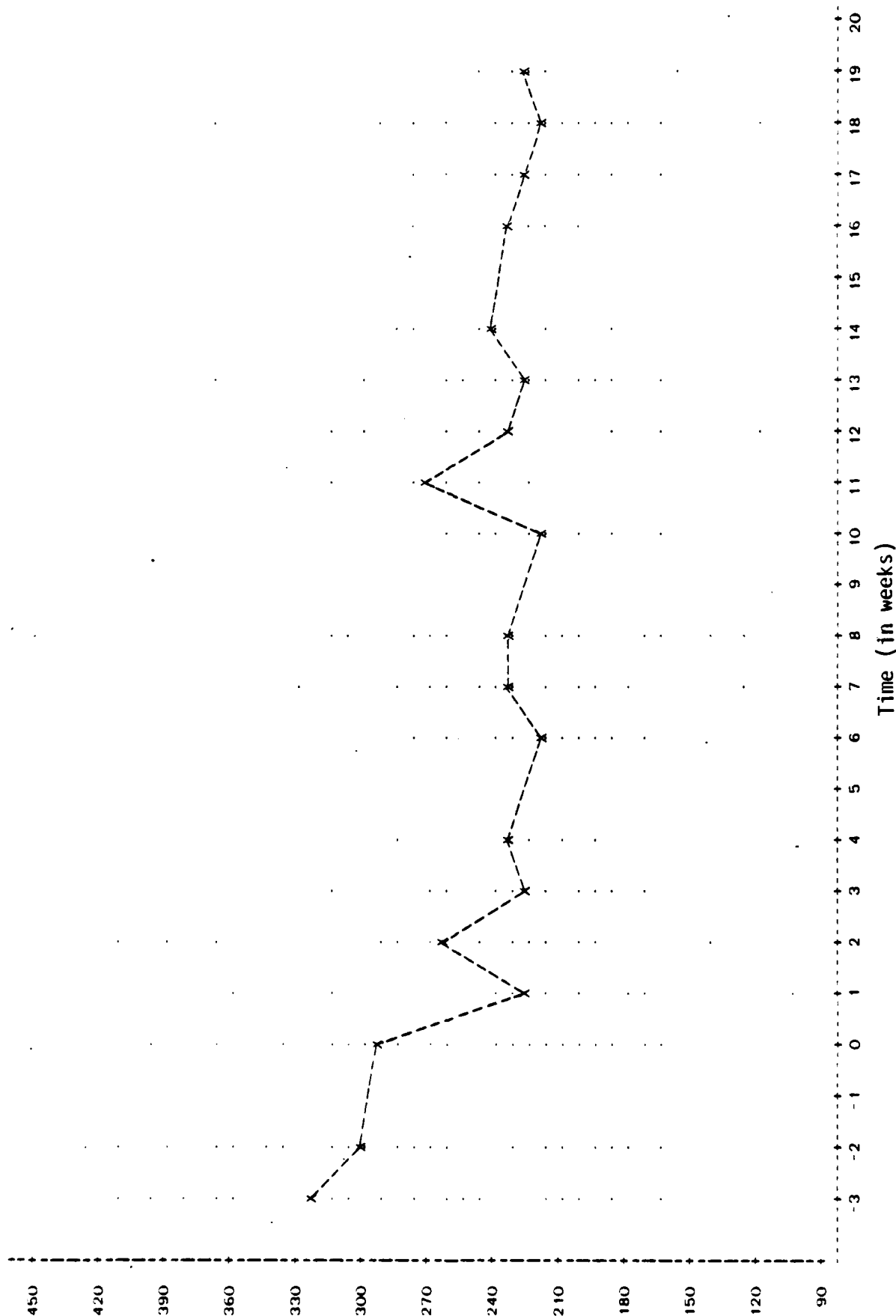


Figure 4. Norepinephrine concentration data scatter diagram (sham-exposure group).

Plasma norepinephrine
concentration (in pg/mL)

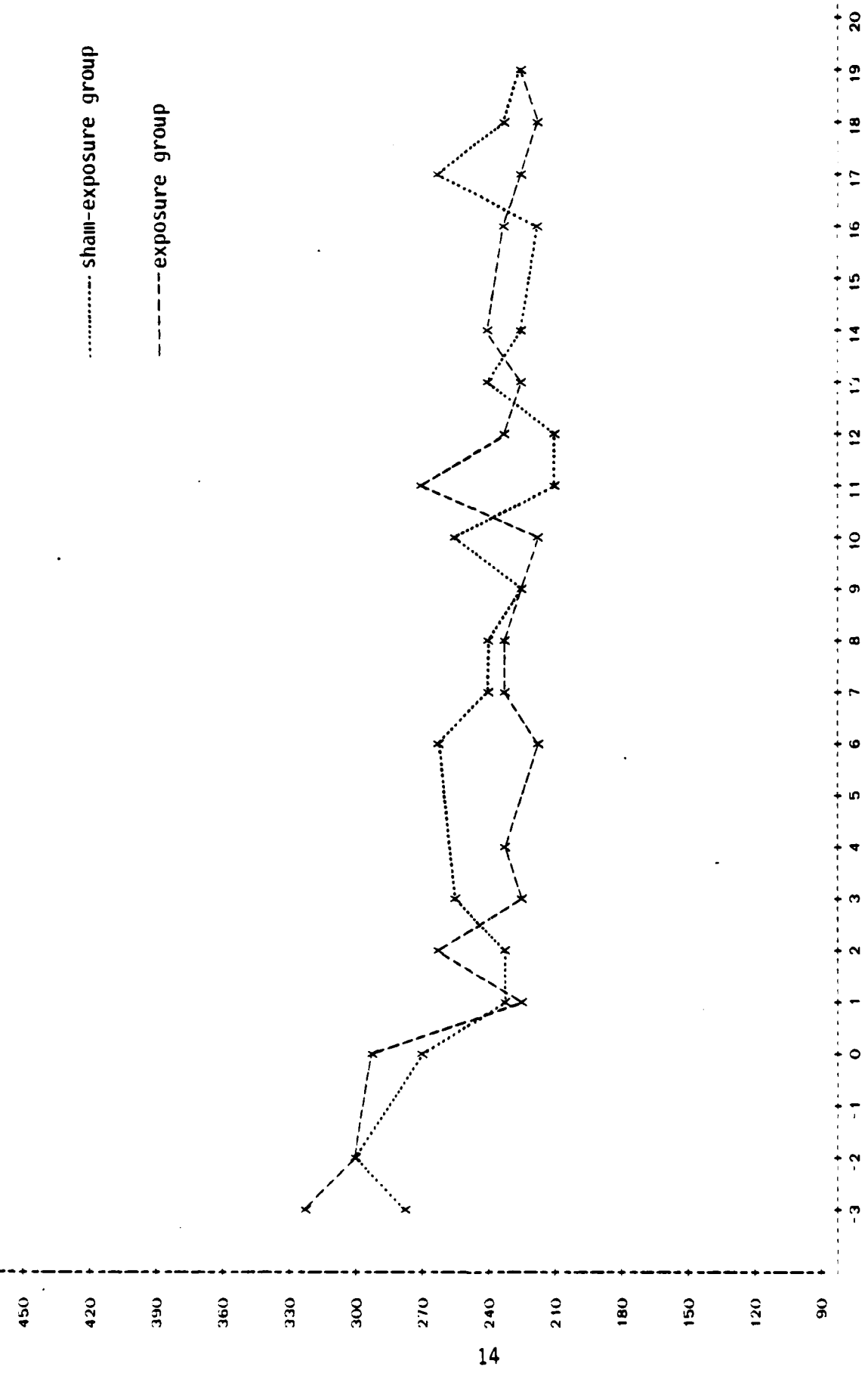


NOTE: 2735 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 118 OBS HIDDEN

Figure 5. Norepinephrine concentration data scatter diagram (exposure group).

Plasma norepinephrine
concentration (in pg/ml)

..... sham-exposure group
----- exposure group



Time (in weeks)

NOTE: 3034 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 2 OBS HIDDEN

Figure 6. Mean plasma norepinephrine concentrations versus time.

significance in describing the collected data. Various diagnostic procedures, including model lack-of-fit tests, residual analysis, and autoregressive analysis, were then applied to the model to check its validity. Appendix B contains a detailed description of this statistical methodology, as well as the individual analyses for each of the three catecholamines.

The statistical analysis indicated that there was no significant difference between the sham-exposure and exposure groups. The final polynomial model was solely a function of time. Resting norepinephrine levels were at their highest value (approximately 299 pg/mL, as calculated from the model derived in the norepinephrine statistical analysis of Appendix B) at the study onset (week -3). The resting level then gradually declined, reaching its lowest point of an estimated 222 pg/mL at week 13 of the study. Norepinephrine concentration then appeared to rise, reaching a value of about 232 pg/mL at week 19 of the study, which was the last week for which data was available. Since no data were taken beyond week 19, there was no effort to extrapolate a value for week 29 of the study.

Further analysis determined the smallest change in resting norepinephrine concentration (between exposure and sham-exposure groups) that the protocol was capable of detecting. If there were any RFR-induced effects on the resting concentration of norepinephrine, they would have to lie within the range of ± 15 pg/mL from the estimated resting concentration of 273 pg/mL. Since values of norepinephrine between 258 pg/mL and 288 pg/mL are considered normal in unstressed rats, there was no indication that chronic RFR exposure resulted in any stress to the animals, as measured by plasma norepinephrine.

Plasma epinephrine. Appendix G contains the data collected during the pre-radiation and radiation periods for both exposure and sham-exposure groups. Like norepinephrine, this hormone also displayed a variance about the established resting level due to varying amounts of animal activity. Since plasma epinephrine concentrations were sensitive to handling and related stresses, each animal was given 30 min to allow the epinephrine concentration to return to the basal value.

Figures 7 and 8 present the raw epinephrine concentration data in scatter diagram form (the dotted lines pass through the mean epinephrine response at each week data were collected). Once again, the mean epinephrine values in both exposure and sham-exposure groups declined in the initial 3 weeks of the study. This decline was attributed to the animals being inadequately preconditioned to

Plasma epinephrine
concentration (in pg/ml.)

16:13 TUESDAY, JULY 7, 1987

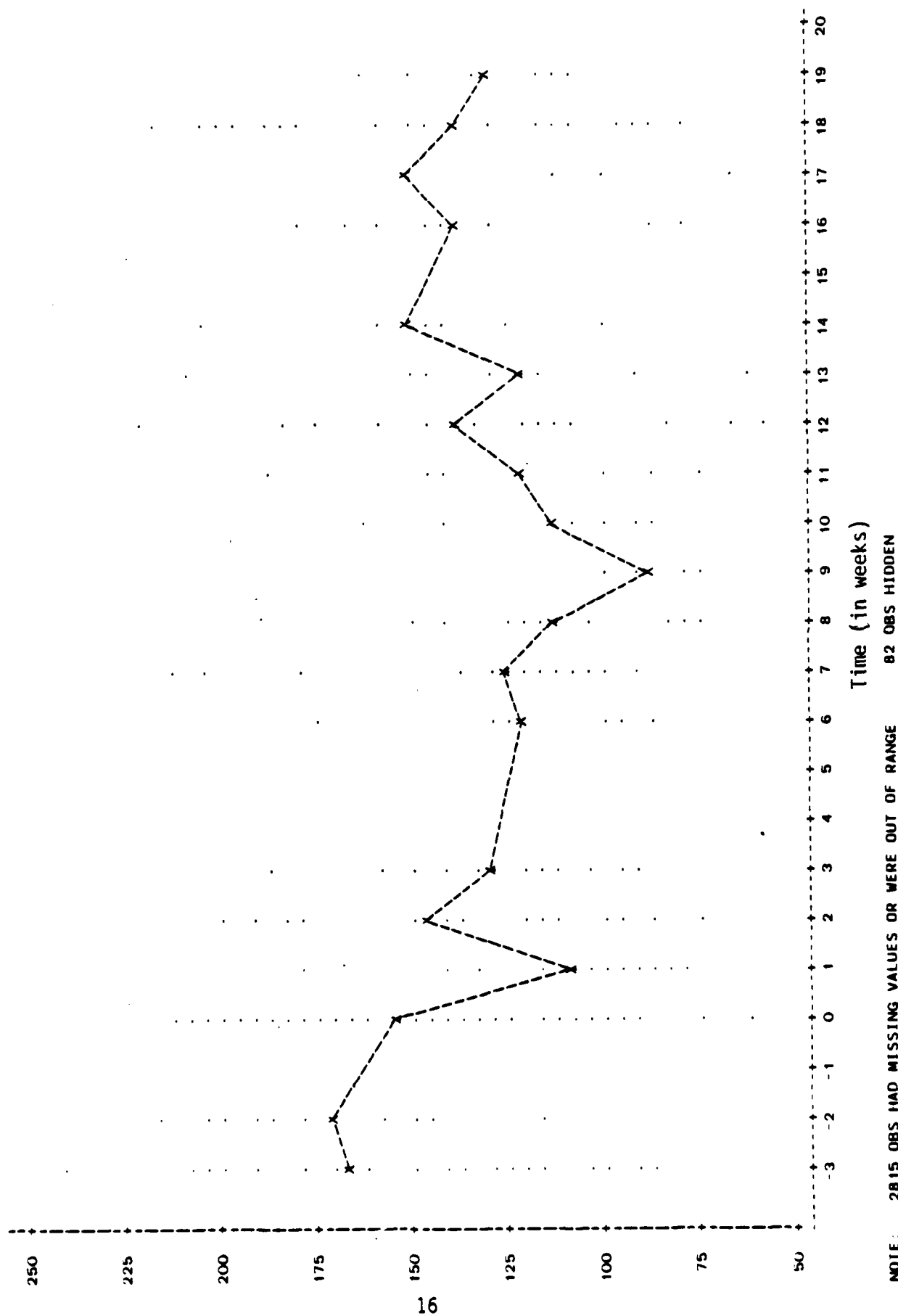
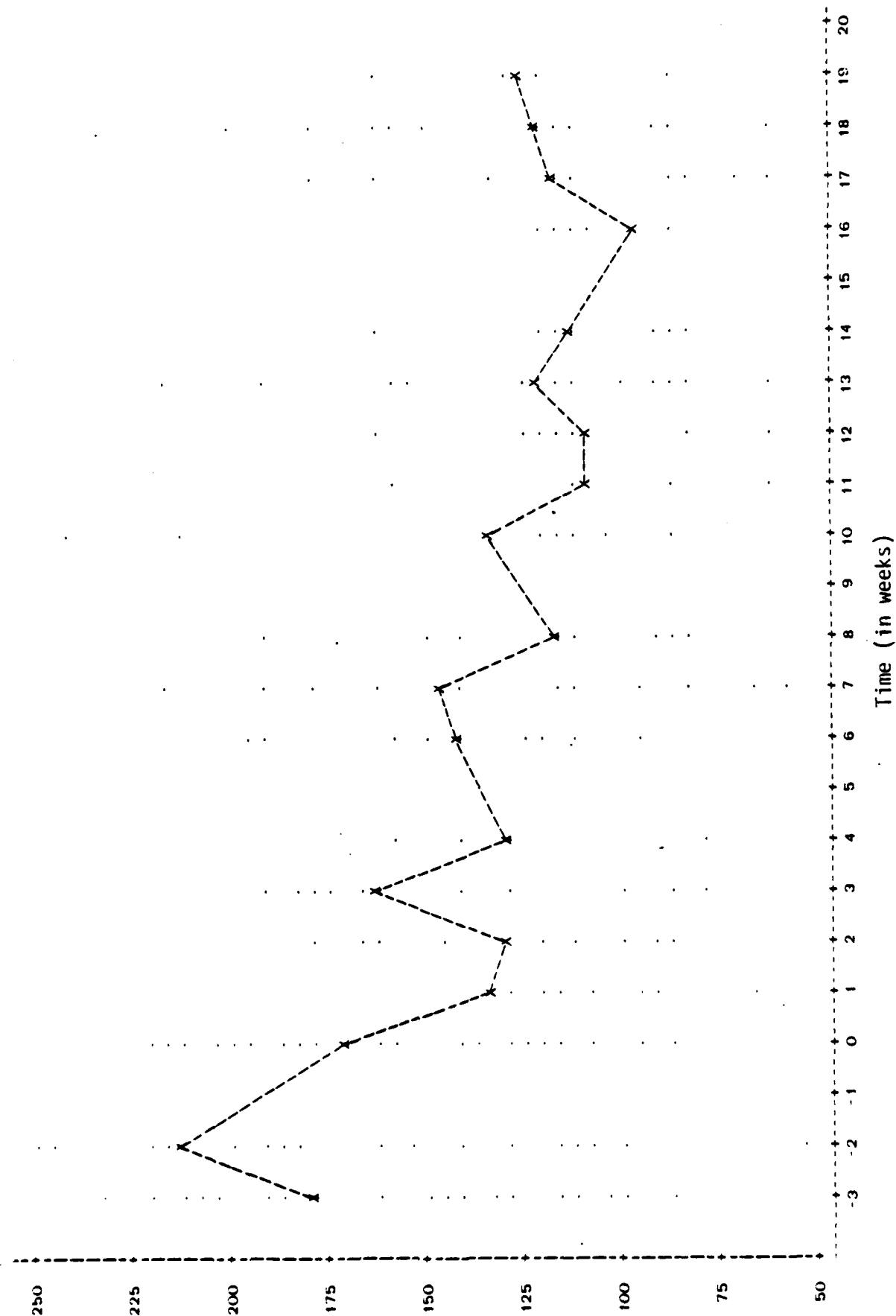


Figure 7. Epinephrine concentration data scatter diagram (sham-exposure group).

Plasma epinephrine
concentration (in pg/ml)

16:13 TUESDAY, JULY 7, 1987



NOTE: 2889 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 78 OBS HIDDEN

Figure 8. Epinephrine concentration data scatter diagram (exposure group).

the sampling boxes. Once the animals adapted to the sampling box environment, the epinephrine concentrations in both RFR-exposed and sham-exposed animals remained about the same. The small amount of "spikiness" in the plots was the random effect of sampling within a population.

The mean epinephrine concentrations in the exposure and sham-exposure groups did not seem to be significantly different when the two plots were compared to one another (Fig. 9). This evidence suggested that chronic exposure to 435-MHz RFR did not affect the resting concentrations of plasma epinephrine. A statistical analysis was then performed on the epinephrine data to test this hypothesis.

The statistical analysis involved building a polynomial function relating epinephrine concentration, time, and RFR radiation in the same manner as the previous hormones (ACTH, corticosterone, prolactin, and norepinephrine). The terms of the polynomial model were then tested to determine their significance in describing the epinephrine data set. The final model, which was independent of RFR, was then verified using lack-of-fit, residual analysis, and autoregression techniques. The complete statistical analysis is included in Appendix B.

The analysis concluded that RFR had no effect on the exposure group when compared to the sham-exposure group. Epinephrine concentration during the study did display a time dependence, however, decreasing from an estimated initial concentration of 181 pg/mL at the study onset (week -3) to a low of 119 pg/mL during the exposures (week 12), and then increasing to about 134 pg/mL at week 19, the last week for which data were available. Once again, no effort was made to use the epinephrine model as a forecasting tool for week 29. Further analysis indicated that, if there were any RFR-induced effects, they had to lie within a range of ± 13 pg/mL from the resting value of 159 pg/mL. Since resting epinephrine concentrations between 146 pg/mL and 172 pg/mL are considered normal in unstressed rats, there was no indication that long-term RFR exposure produced any stress as measured by plasma epinephrine concentrations.

Plasma dopamine. Appendix L contains the data collected during the pre-radiation and radiation periods for both exposure and sham-exposure animals. The variance in the data, as mentioned before, derived principally from various levels of animal activity immediately before sampling. The 30-min acclimation time allowed dopamine concentrations to return to the resting, basal level.

Plasma epinephrine
concentration (in pg/mL)

16:13 TUESDAY, JULY 7, 1987

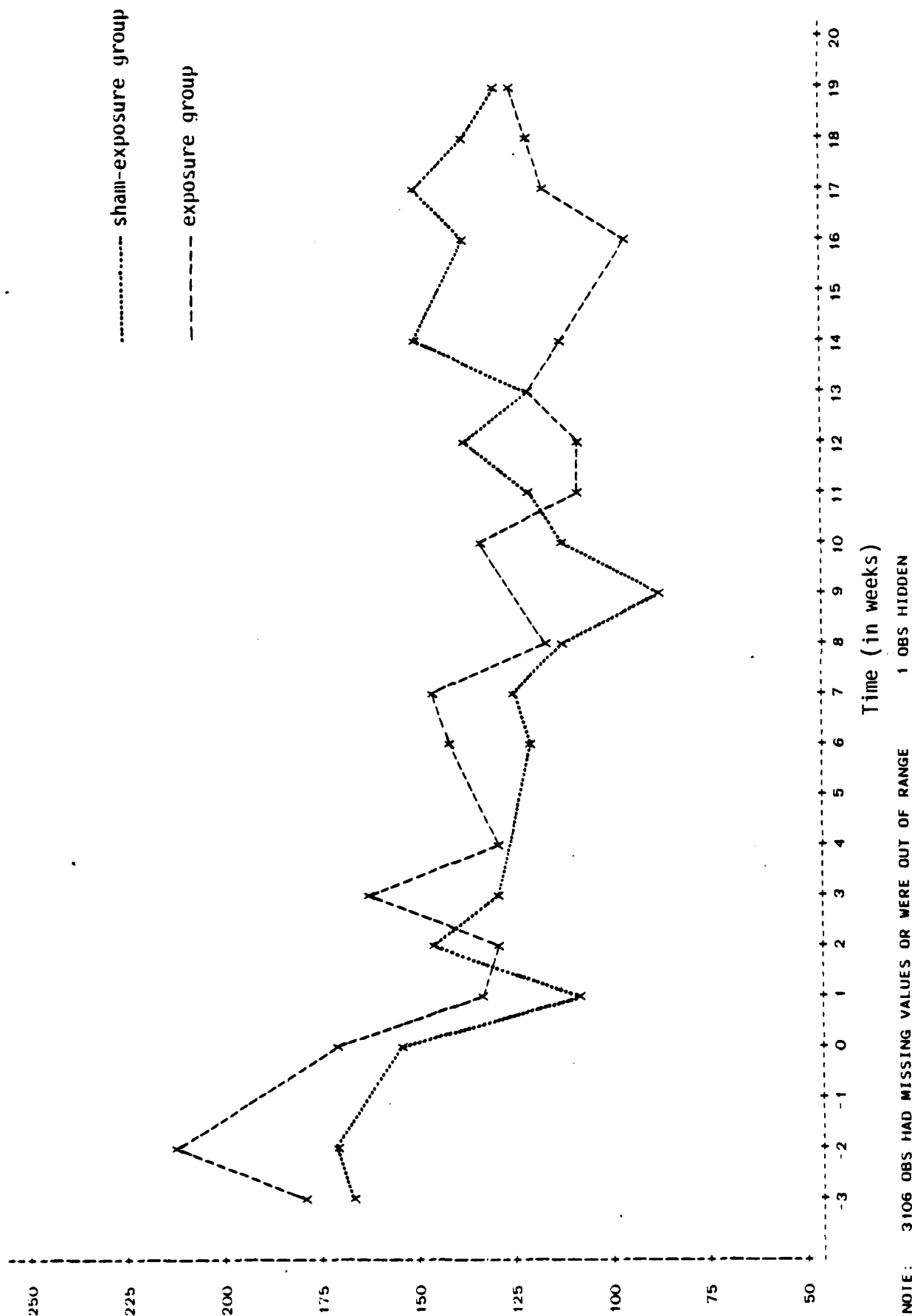


Figure 9. Mean plasma epinephrine concentrations versus time.

Figures 10 and 11 present the raw dopamine concentration data in scatter diagram form (the dotted lines pass through the mean dopamine response at each week data were collected). Again, the mean dopamine response in both exposure and sham-exposure groups declined in the initial 3 weeks of the study. This decline was similar to the observations noted in the other hormones assayed (ACTH, corticosterone, prolactin, norepinephrine, and epinephrine) and was attributed to the same source (animals inadequately preconditioned to sampling box). After the animals adapted to the sampling box environment, the dopamine values in both exposure and sham-exposure groups tended to stabilize (weeks 1 through 19). The spikiness in the plots was a result of random sampling within both populations.

Mean plasma dopamine concentrations did not appear to be larger in the exposure group when compared to the sham-exposure group (Fig. 12). If anything, the opposite seemed to be the case for the length of the experiment. This result indicated that chronic exposure to 435-MHz RFR did not induce physiological changes in the rat population that were manifested as increased resting dopamine concentrations. A statistical analysis was therefore performed on the data set to test this hypothesis.

The statistical analysis performed was identical in procedure to that used in the analysis of the other study hormones. A detailed description of the general methodology, and the specific dopamine analysis, is given in Appendix B. The analysis for all hormones used the SAS Statistical Software resident on the Georgia Tech IBM 4381 mainframe to run tests and produce the analysis hardcopy.

The analysis gave no indication of increased plasma dopamine in the exposure group when compared to the sham-exposure group. In fact, the estimated dopamine concentration in the exposure group remained significantly smaller than that of the sham-exposure group from the initiation of exposures to the termination of the experiment. Resting dopamine values were at their highest for week -3 of the study (about 62 pg/mL sham-exposed, 65 pg/mL exposed). The resting levels of both groups then declined, reaching the lowest value of 32 pg/mL at week 12 (sham-exposed); 20 pg/mL at week 16 (exposed). Beyond these points, dopamine concentration gradually increased, with estimated concentrations of 39 pg/mL (sham-exposed) and 21 pg/mL (exposed) at week 19, the last week for which data were collected.

Further analysis showed that the smallest change in resting dopamine concentration that the protocol could reliably detect was about 6 pg/mL above or

Plasma dopamine
concentration (in pg/mL)

16:46 TUESDAY, JULY 7, 1987

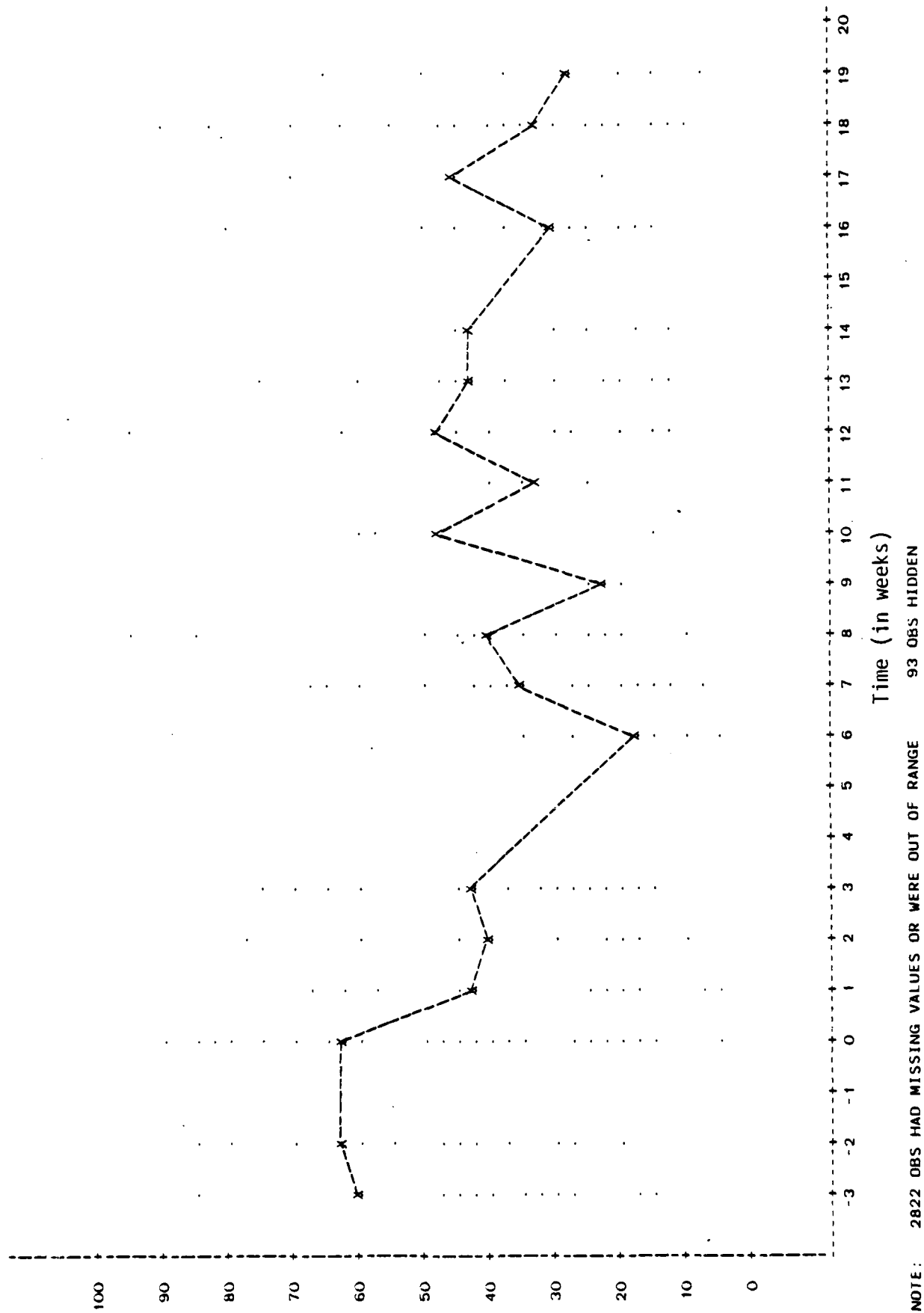
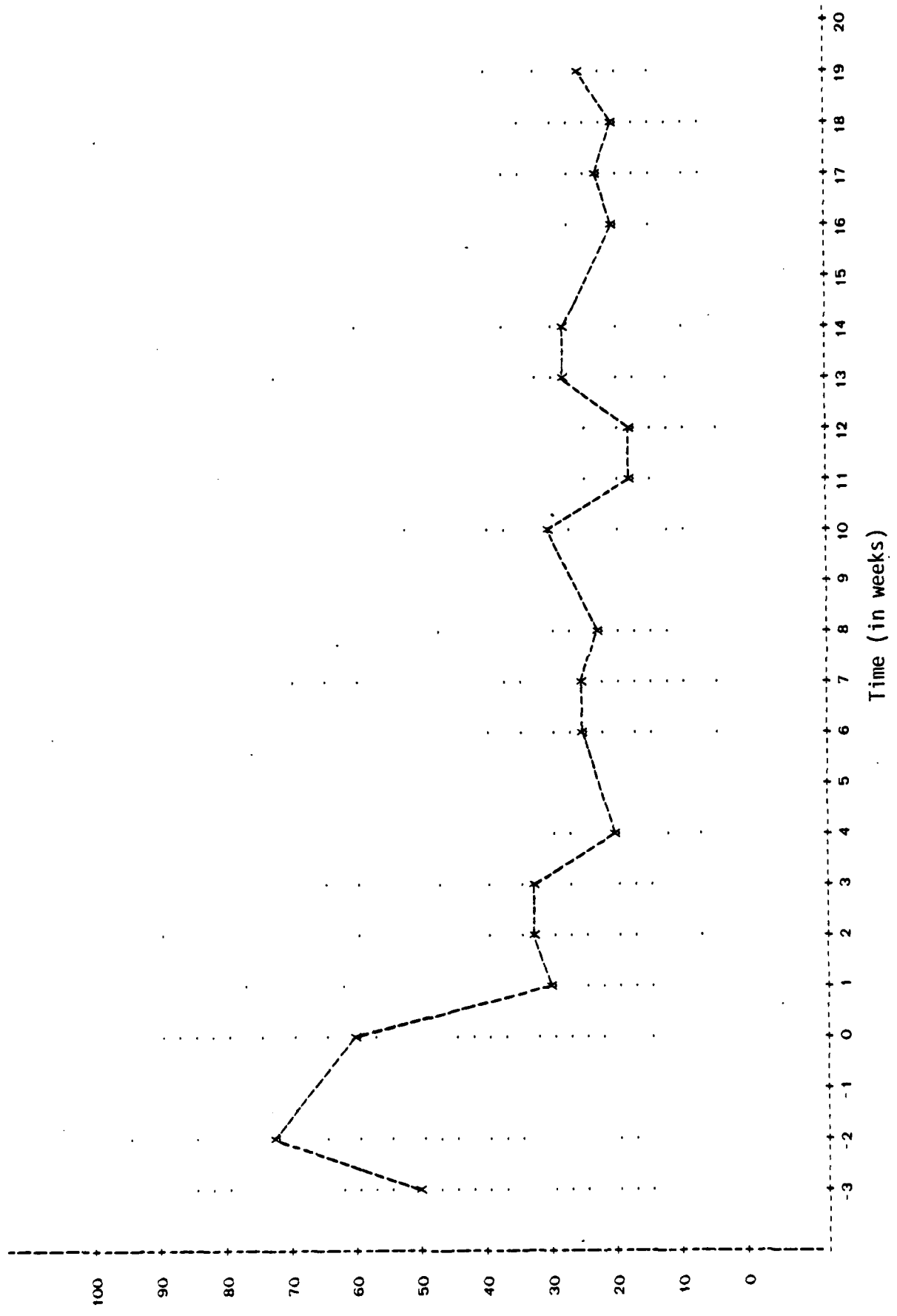


Figure 10. Dopamine concentration data scatter diagram (sham-exposure group).

Plasma dopamine
concentration (in pg/mL)



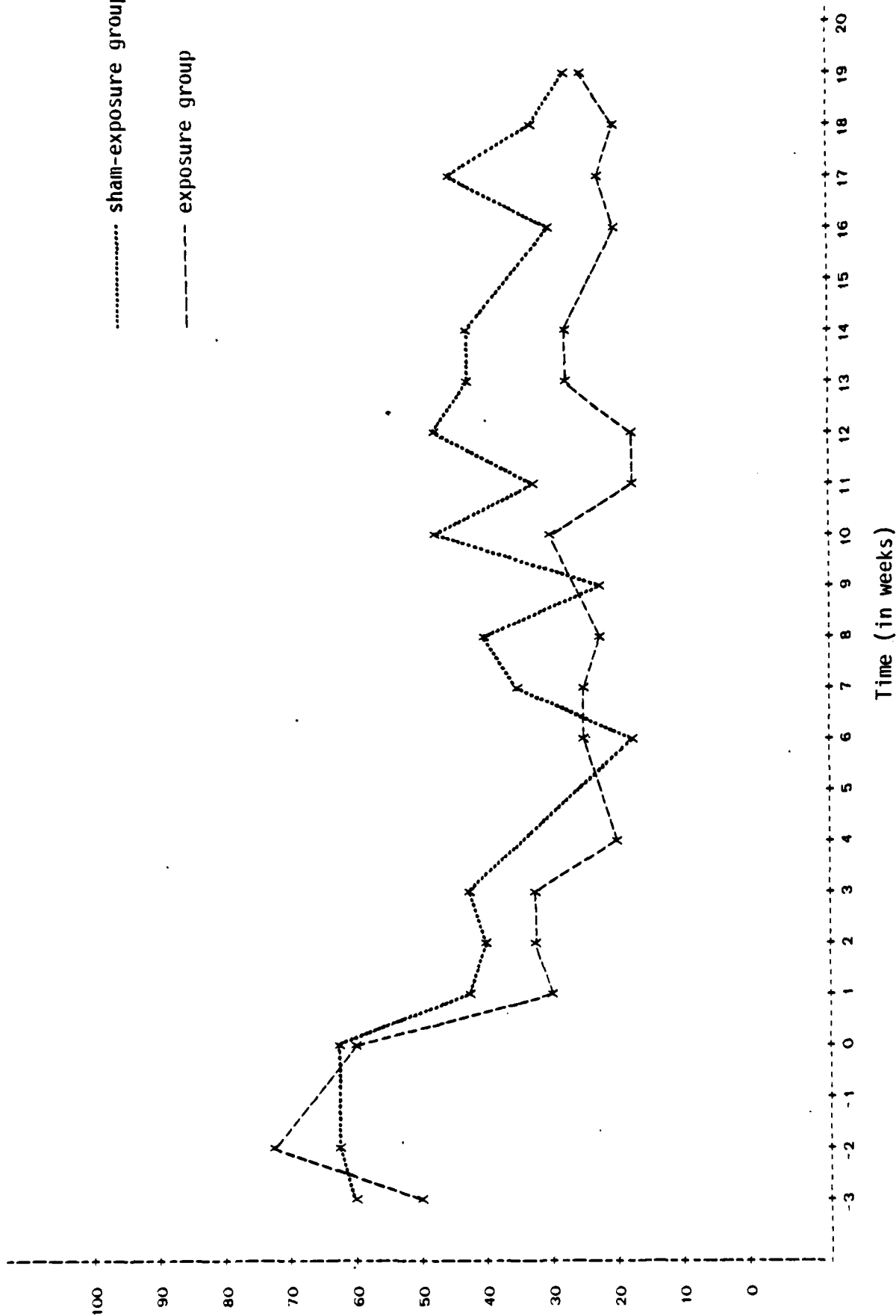
NOTE: 2836 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 94 OBS HIDDEN

Figure 11. Dopamine concentration data scatter diagram (exposure group).

16:46 TUESDAY, JULY 7, 1987

Plasma dopamine
concentration (in pg/mL)

..... sham-exposure group
----- exposure group



NOTE: 3082 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

Figure 12. Mean plasma dopamine concentrations versus time.

below an estimated resting concentration of 51 pg/mL. This analysis indicated that, if RFR increased resting dopamine levels above 57 pg/mL, the protocol would have found a significant positive RFR effect. In fact, dopamine concentrations of up to 120 pg/mL were considered normal for a population of healthy, unstressed Sprague-Dawley rats. Therefore, there was no indication that chronic exposure to low-level 435-MHz RFR produced any stress in the exposure group (when compared to the sham-exposure group) as measured by the concentration of blood-borne dopamine.

IV. DISCUSSION

Minute amounts of free (unconjugated) catecholamines are normally found in both human and animal blood plasma. These hormones undergo rapid changes which reflect sympathetic nerve activity [18,19]. The radioenzymatic techniques available for quantitative determinations of norepinephrine, epinephrine, and dopamine in a few microliters of plasma permit monitoring of the sympathoadrenal activity in small laboratory animals such as the rat.

Arterial blood pressure, ambient temperature, body temperature, physiological activity, and certain biological characteristics (e.g., animal strain) have an effect on the level of circulating plasma catecholamine concentrations [20]. Different strains of rats have dissimilar levels of resting catecholamines [21,22]. Both normotensive and hypertensive rats show the same catecholamine response at rest, but hypertensive rats show a greater catecholamine response during stress [21,23].

For a particular strain of animal, the resting level of plasma catecholamines is always the same [24], permitting measurement of increases in plasma catecholamine concentration and (from these increases) evaluation of the level of stress an animal underwent [25,26]. The stronger a stress and the longer its duration, the higher the concentration of plasma epinephrine, norepinephrine, and in some cases dopamine [27]. Even a small reduction of blood volume increases plasma catecholamine levels [28,29].

To obtain reliable measurements of circulating catecholamines in rats required appropriate methods for blood collection to avoid catecholamine increase due to physical stress [16]. In this study, resting levels of catecholamines were considerably lower in rats whose blood samples were collected from indwelling cannulas than values where blood was obtained by decapitation or other stressful methods.

The results of our experiment indicate that exposure to chronic low-level RFR did not represent a stress measurable as an increase in norepinephrine and epinephrine concentration of irradiated rats. Similar results were obtained when plasma ACTH, plasma corticosterone, and plasma prolactin were determined in identical situations [2,3].

In this study, plasma dopamine decreased in RFR-exposed animals. Though significant, the small plasma dopamine decrease might not be physiologically important. It would be of interest to ascertain whether this lowered dopamine

concentration persists after RFR exposure is interrupted for several days or weeks (the rats were removed from the RFR field for 30 min to obtain the blood samples). The large individual variation observed in the plasma catecholamine levels of both RFR-exposed and sham-exposed animals was probably the consequence of various levels of animal physiological activity during or just before blood sampling. It is known, for instance, that during sleep plasma levels of norepinephrine and epinephrine are below those of the resting state [30].

Although plasma catecholamine half-life is only 1 to 3 min [15], a strong stimulus leaves plasma catecholamine levels relatively high for 10 to 15 min. For this reason, blood was sampled from the resting animals 30 min after gentle placement in the sampling boxes, permitting plasma catecholamine levels to return to the resting level.

During the 6-month study duration, the rats aged somewhat. Some investigators have reported changes in catecholamine secretion induced by aging [31,32,33]. However, new studies demonstrate that aging does not change the rat's responsiveness to either internal or external stimuli that evoke catecholamine secretion [34]. The same study failed to find changes over a several month period in resting plasma catecholamine concentration of rats.

In conclusion, our results indicated that a 435-MHz pulsed-wave environment did not increase resting plasma catecholamine concentrations in rats. The statistical analysis of the data indicated that if there were any RFR-induced effects on resting plasma catecholamine concentrations, they would lay within a range of ± 15 pg/mL from an estimated resting concentration of 273 pg/mL in norepinephrine; ± 13 pg/mL from an estimated resting concentration of 159 pg/mL in epinephrine; and ± 6 pg/mL from an estimated resting concentration of 51 pg/mL in dopamine. These values are not typical of rats exposed to stress. Therefore, this study concludes that a 1.0 mW/cm^2 435-MHz pulsed-wave (1.0 μs pulse width, 1 kHz pulse rate) RFR environment did not induce any detectable increase in stress, as measured by resting catecholamine concentrations in the exposure group of cannulated male Sprague-Dawley rats when compared to the sham-exposure group.

V. REFERENCES

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APPENDIX A
RAW NOREPINEPHRINE DATA SPREADSHEETS

TCRE (pg/ml) Control I

Bat #	Group	TIME																				-2	-5
		1:00	1:05	1:10	1:15	1:20	1:25	1:30	1:35	1:40	1:45	1:50	1:55	2:00	2:05	2:10	2:15	2:20	2:25	2:30	2:35		
1		245	220	220				207			219			200									
2		274	247	255				206			201			186									
3		210	190	220				233			199			194									
4		300	290	317				290			280			217									
5		285	320	260				281			310			310									
6		280	317	235				303			305			280									
7		460	405	270				282			-			120									
8		320	327	301				307			290			146									
9		318	310	-	2			290					261			180							
10		266	222	190	2			198					-			-							
11		240	203	255				204					245			-							
12		200	-	225				219					230			209							
13		190	196	218				216					202			213							

NCRE (pg/ml) controls II

		TIME																			
Bat #	Group	-TIME	-TIME	TIME	TIME	TIME	-TIME	TIME	TIME	TIME	TIME	TIME	TIME	TIME	TIME	TIME	TIME	TIME	TIME	+2	+5
14		264	315	224		211				247							217				
15		280	261	241		210				189							231				
16		293	317	255		266				131							207				
17		221	210	231		218				208							232				
18		293	308	237		225				217							241				
19		212	189	235		218				215							180				
20		256	227	218		228				260							197				
21		-	191	240		232				230							240				
22		164	-	217					221				261				235				
23		132	190	240					317				205				205				
24		264	252	212					161				-				-				
25		260	261	264					218				264				219				
26		271	220	218					198				231				207				

NORE (pg/ml) Control III

Box #	Group	TIME																								+2	+3	
		1TIME	2TIME	3TIME	4TIME	5TIME	6TIME	7TIME	8TIME	9TIME	10TIME	11TIME	12TIME	13TIME	14TIME	15TIME	16TIME	17TIME	18TIME	19TIME	20TIME	21TIME	22TIME	23TIME	24TIME			
27		880	299		207			202						170							272							
28		245	207		-			312						314							-							
29		263	260		311			371						186							250							
30		267	218		307			268						174							-							
31		318	294		373			186						193							205							
32		325	360		-			126						265							131							
33		190	216		270			185						-							205							
34		280	210	163				257						276							194							
35			430	301	138			260						171							360							
36			410	-	170			-						302							198							
37			370	290	-			205						159							318							
38			320	270	265			256						-							136							
39			195	207	250			283						206							207							

NORE (pg/ml.) Control IV

[illegible]

NORE (pg/ml) Control V

Box #	Group	TIME																								-2	-5			
		-3HR	-2HR	0HR	1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR			22HR	23HR	24HR
53		-	312		202						204					213								278						
54		412	390		325						317					249								229						
55		186	-		361						204					287								207						
56		216	-		164						-					235								317						
57		296	219		125						325					164								381						
58		-	269		250						171					139								254						
59		-	280		138						232					300								-						
60		198	245		168						-					315								168						
61		318	262		249						187					216								268						
62		318	229		241						235					281								231						
63		402	315		202						218					254								290						
64																														

NORE (pg/ml) MWI

Box #	Group	TIME																								-2	-5				
		-3HR	-2HR	0HR	1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR			22HR	23HR	24HR	
1		312		232	220						226				217	212									262						
2		307		270	260						266				205											241					
3		-		202	217						217				202											218					
4		264		242	203						203				197											197					
5		199		196	171						176				185											162					
6		-		138	202						192				220											191					
7		376		235	214						277				245											271					
8		231		190	222						203				261											275					
9				190	195						235					235										245					
10				271	-						235				-		197									-					
11				212	321						-				-			197								251					
12				260	-						-				197											271					
13				37	260						198				197											235					

NORE (pg/ml) MW II

Set #	Group	TIME																								-2	-5				
		-2HR	-2HR	0HR	1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR			22HR	23HR	24HR	
14		386	241	241						-				246																	
15		266	-	219						241				-																	
16		261	263	245						218				237																	
17		-	342	-	-					207				261																	
18		-	300	221						194				217																	
19		164	284	220						180				219																	
20		191	204	271						224				228																	
21		261	220	271						242				164																	
22		281	188							205																					
23		316	217							202																					
24		240	281							240																					
25		263	164							220																					
26		25	180							201																					

NORE (pg/ml) MW III

Set #	Group	TIME																										-2	-5		
		-2HR	-2HR	0HR	1HR	2HR	3HR	4HR	5HR	6HR	7HR	8HR	9HR	10HR	11HR	12HR	13HR	14HR	15HR	16HR	17HR	18HR	19HR	20HR	21HR	22HR	23HR			24HR	
27		325	-				283				260						216							216							
28		316	305				392				-						246							246							
29		416	520				416				271						286							156							
30		564	305				370				235						-							216							
31		264	216				214				215						278							236							
32		255	-				-				215						- F						-								
33		315	305	206							270						185						185								
34		-	69	206							265						275						225								
35		-	460	-							266						-						-								
36		425	-	187							-						370						370								
37		208	180	216							170						168						168								
38		186	207	242							168						227						227								
39		216	-	228							125						165						165								

NORE (pg/ml) MW IV

Lot #	Group	TIME	1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+3
40		219	514	201				181			219			277														
41		218	365	421				272			285			-														
42		210	191	-				126			251			272														
42		-	176	271				272			-			279														
44		412	211	214				277			-			-														
45		252	214	209				-			279			281														
46		-	227	-				282			318			-														
47		315	316		171			276			301																	
48		412	-		276			142			120			201														
49		305	288		239			-			265			188														
50		218	266		-			447			257																	
51		262	167		187			212			-			204														
52		411	202		357			201			-			291														

NORE (pg/ml) MW V

Lot #	Group	TIME	1WK	2WK	3WK	4WK	5WK	6WK	7WK	8WK	9WK	10WK	11WK	12WK	13WK	14WK	15WK	16WK	17WK	18WK	19WK	20WK	21WK	22WK	23WK	24WK	+2	+3
53		213	210		219				212				218															
54		365	282		-				214				265								196							
55		315	215		261				306				241								195							
56		400	277		205				235				190								228							
57		272	400		286				268				237								241							
58		315	420		316				-				301								285							
59		612	640		-				207				68								270							
60		415	474			222			316				312								285							
61		412	290		282			247					264								265							
62		257	412		210			240					195								281							
63		261	301		158			246					250								190							

APPENDIX B
STATISTICAL METHODOLOGY

APPENDIX B

STATISTICAL METHODOLOGY

The balanced design of this experiment (requiring that 25 animals from each 100 animal group be sampled once every 3 weeks for stress hormones) should have produced data easily tested by balanced, 2-way analysis of variance (ANOVA) statistics with 12 levels of factor A (time) and 2 levels of factor B (RF radiation). However, data collection did not proceed according to protocol in that, in numerous cases, samples were collected at odd intervals (invalidating the orthogonality of the design) and the number of samples taken per week varied above and below the 25 animal mark (unbalancing the design). These two factors combined to lower the power of ANOVA statistics (power being defined as the ability to reject the null hypothesis given the null hypothesis should be rejected) trying to test the model

$$y_{ijk} = \mu + \tau_i + \beta_j + \tau\beta_{ij} + \epsilon_{ijk}, \quad (B-1)$$

where y_{ijk} = hormone concentration (response),
 μ = the normal hormone resting concentration,
 τ_i = the change in hormone resting concentration induced by RFR,
 β_j = the change in hormone resting concentration induced by time,
 $\tau\beta_{ij}$ = the change in hormone resting concentration induced by the interaction between RFR and time, and
 ϵ_{ijk} = noise within the system (sampling and assaying errors)

for the following hypotheses:

$$\begin{aligned} H_0: & \tau_0 = \tau_1 = 0, \\ H_1: & \tau_0 \text{ or } \tau_1 \neq 0 \text{ (RFR-induced effects),} \end{aligned} \quad (B-2)$$

$$\begin{aligned} H_0: & \beta_1 = \beta_2 = \dots = \beta_{12} = 0. \\ H_1: & \text{at least one } \beta_j \neq 0 \text{ (time-induced effects),} \end{aligned} \quad (B-3)$$

$$\begin{aligned} H_0: & \tau\beta_{ij} = 0, \text{ and} \\ H_1: & \text{at least one } \tau\beta_{ij} \neq 0 \text{ (interaction between RFR and time).} \end{aligned} \quad (B-4)$$

However, examination of the collected data suggested an alternative approach in that the data resembled what might have been collected in an unplanned experiment monitoring over time the operation (in this case, characterized by resting animal hormone concentrations) of an established RF radiation facility. Data of this type are often successfully treated by employing linear regression techniques to develop, build, and test a linear (or intrinsically linear) model whose parameters can be used to predict the system response at various treatment levels. Therefore, we decided to proceed with a regression approach to data analysis.

Plasma Norepinephrine Statistical Analysis.

Examination of the norepinephrine scatter diagrams of Figures 4 and 5 yield an essentially linear norepinephrine response versus time beyond week 0 of the study. There was, however, a certain amount of positive curvature present at both the study initiation and study conclusion, particularly in the sham-exposure group. Therefore, a quadratic polynomial function was empirically chosen to test for RFR effects within the exposure and sham-exposure groups. Thus, the norepinephrine response was modelled with a nonzero intercept β_0 and an RFR-induced effect on this intercept (α_0z), a nonzero linear slope β_1 and an RFR-induced effect on this slope (α_1z), and a quadratic coefficient β_{11} and RFR-induced effect on this curvature ($\alpha_{11}z$). The statistical significance of these terms determined the importance of their contribution to the final model. The equation describing the initial model was therefore:

$$y = \beta_0 + \beta_1x + \beta_{11}x^2 + \alpha_0z + \alpha_1zx + \alpha_{11}zx^2 \quad (B-5)$$

where y = plasma norepinephrine concentration (in pg/mL),
 x = time (in weeks), and
 z = a categorical variable with value 0 for animals in sham-exposure group and value 1 for animals in exposure group.

Raw data from the norepinephrine spreadsheet (Appendix A) were put on computer file. A Statistical Analysis System (SAS) formatting program (Appendix C) was prepared to read the data and perform the desired statistical tests on the model.

The first test identified terms within the model which contributed the least toward forming a statistically significant regression. These procedures

were used in combination with an initial regression on the general model (not included) to evaluate the statistical significance of terms modelling the norepinephrine concentration time dependency and terms modelling the RFR-induced effects on norepinephrine concentration. Two types of model "building" procedures were used: forward stepwise regression and maximum R^2 regression. Forward stepwise regression produced a model by calculating F statistics for all variables not in the model, and then adding a variable to the model if its F statistic was significant at a given α risk (for this reason, the forward procedure begins with no variables in the model). Once a variable was added to the model, the procedure recalculated F statistics for all the terms in the model, and rejected any terms whose F statistic rose above a given α risk. In this manner, forward stepwise regression eventually settled on a model including all terms whose α risk was low enough to permit initial entry and then not be rejected upon the addition of other terms.

Maximum R^2 regression took this procedure further, producing lists of the best 1-parameter model, best 2-parameter model, best 3-parameter, etc., until all of the parameters were included in the final model. This procedure permitted discrimination of different models using number of parameters as a judgement criterion.

Both forward stepwise and maximum R^2 regressions indicated that the model which best fit the data was:

$$y = \beta_0 + \beta_1 x + \beta_{11} x^2, \quad (B-6)$$

where

$$\begin{aligned} \beta_0 &= 272.8, \\ \beta_1 &= -7.79, \text{ and} \\ \beta_{11} &= 0.30. \end{aligned}$$

The entry and exit α risk was 0.10. The outputs of both regression procedures are included in Appendix D. Note that the absence of α terms indicated that, at a 0.10 risk, there was no statistical difference in plasma norepinephrine concentrations between the exposure and sham-exposure group. The estimated resting concentration of plasma norepinephrine, 272.8 pg/mL (β_0), agreed well with established values cited in the literature (300 ± 40 pg/mL). This agreement was an indication of no systematic error within the sampling/assaying procedure.

Both exposure and sham-exposure groups did display a time dependency in norepinephrine concentration. Resting norepinephrine levels were at their highest value (about 298.9 pg/mL) at the study onset (week -3). The resting level then gradually declined, reaching its lowest point of 221.8 pg/mL at week 13 of the study. Norepinephrine concentration then seemed to rise, reaching a value of 232.0 pg/mL at week 19 of the study, which was the last week data were taken. All of the just mentioned values were well within the normal bounds of plasma norepinephrine concentration in healthy, unstressed rats. Therefore, it seemed that chronic exposure to 435-MHz RFR did not result in an increase in stress (as measured by the concentration of plasma norepinephrine) in the exposure group when compared to the sham-exposure group.

The just mentioned conclusions could only be accepted once the assumptions used to build the final model were verified. These assumptions included no model lack-of-fit, $NID(0, \sigma^2)$ residual distribution (meaning residuals were normal and independently distributed with mean zero and variance σ^2), and no model multicollinearity.

Since multiple observations of norepinephrine concentration were taken for the weeks containing data, it was possible to perform a model lack-of-fit test on the regression. The lack-of-fit involved breaking the sum-of-squares error from the regression into two components: sum-of-squares pure error, representing the actual variation due to the sampling and assaying process and sum-of-squares lack-of-fit, representing the variation due to the difference between the mean value at one week when compared to the fitted value at the same week. A test statistic was then computed comparing the sum-of-squares lack-of-fit to the sum-of-squares pure error; sufficiently high values of the test statistic indicated model lack-of-fit.

Sum-of-squares error was obtained from the ANOVA table produced in the regression procedure output. Sum-of-squares pure error was obtained by analyzing the experiment from 2-way, fixed effects ANOVA viewpoint. The sum-of-squares lack-of-fit was then computed from the difference of sum-of-squares error minus sum-of-squares pure error. Calculations to compute the critical value F_0 are detailed in Appendix E.

Since the computed test statistic F_0 was smaller than the critical value, there was insignificant model lack-of-fit. This indicated that the quadratic function modelling norepinephrine concentration versus time was a good empirical description of the data set. Under no lack-of-fit conditions, the mean square

error and mean square pure error should both estimate the population variance σ^2 . Indeed, $MS_E = 4462.5$ and $MS_{pe} = 4443.1$, producing estimated sample standard deviations of 66.80 pg/mL and 66.66 pg/mL. These standard deviations were somewhat larger than those listed in the literature (by the criterion that a normal range covers a distance of about 4σ , the standard deviation indicated by the literature is about 20 pg/mL). However, the given estimates of σ were inflated by the presence of potential outliers. Since the value of Cook's D was not considered extreme (all had Cook's Ds of between 0.01 and 0.04), the 4 possible outliers (corresponding to animal 130 (week -3), animal 159 (week -3), animal 159 (week -2), and animal 134 (week 0)) were not rejected from the data set. The high values of these observations (all above 600 pg/mL) did tend to raise the mean values at those weeks, and thus inflated the estimates of the standard deviation.

The next model verification step involved examining the residual and partial residual plots to confirm the least squares regression assumption that the model errors were $NID(0, \sigma^2)$. This step would defend the use of F tests to determine the statistical significance of the parameters. Additionally, this step would validate the statistics which produced tables listing confidence intervals of the norepinephrine concentrations. A number of residual plots suggested themselves immediately: residuals versus time, residuals versus predicted value of norepinephrine concentration, residuals versus animal case number, studentized residuals versus the previous three, and partial residual plots corrected for the model terms β_0 , β_1 , and β_{11} . Examination of the residual plots yielded no discernible patterns in the distribution of the residuals. Thus, the residuals were normally distributed with mean 0 and variance σ^2 . The residual plots are included in Appendix F.

Since the data from this study arose as a time series, there was a possibility that the residuals were in some part autocorrelated to prior observations. To determine the extent of this autocorrelation, an autoregressive model building procedure (PROC AUTOREG from the SAS ETS series) was used with lag times of 0, 1, 2, 3, and 4 weeks.

Results of the autoregression (not included in report) indicated a significant amount of correlation between data at one week to data at the previous week (lag-1 autocorrelation). The autoregression also detected a considerably smaller (although statistically significant) lag-2 autocorrelation. Lag-1 correlation indicated that the best predictor of any single observation

was the previous observation for that particular animal (rather than the value yielded by substituting the parameter estimates and week number into the derived norepinephrine model). If the study purpose were to determine a predictive model of norepinephrine behavior in the rats, then the just mentioned conclusion would have dire consequences with regards to the model obtained in Appendix D. However, the main reason regression was chosen to model this data was not to produce a predictive model of norepinephrine versus time, but rather to determine whether or not two blocked groups (exposure and sham-exposure) displayed any differences in norepinephrine behavior. For this purpose, non-independence in the residuals does not call into question the overall conclusions drawn from the model. To compensate for this deficiency, it would only be necessary to raise the α risk used in determining the norepinephrine model. Since β_0 , β_1 , and β_{11} were found to be significant at probabilities less than 0.0001, this alteration of significance had no practical effect on the final model determined in the analysis. The large number of observations taken essentially made this data set relatively insensitive to potential problems (such as lack-of-fit or nonindependence in the residuals).

To complete the analysis, diagnostics to check for model multicollinearity and correlation between the terms were used. Examination of the listed condition numbers and matrix eigenvalues (being provided under separate cover) detected no troublesome values. This review indicated that the model did not display a significant degree of multicollinearity. Similarly, examination of the correlation matrix showed that correlations between the estimated values of β were all within tolerable limits. The highest degree of correlation was between the x and the x^2 term, which often occurs when using a polynomial model in linear regression.

For future reference, and for the sake of completeness, tables listing animal case number, observations (if taken) at each week, predicted value of norepinephrine concentration, standardized error of prediction, 95% confidence intervals on the mean value of the norepinephrine concentration, and residuals were prepared, as were tables containing animal case number, regular and studentized residual values, a graphical display of student residual values, and influence statistics (such as Cook's D). These tables were used to detect both outliers and influential data points in the norepinephrine data set.

To arrive at a conservative estimate of the minimum change due to RFR in resting norepinephrine concentrations which this protocol was capable of

detecting, the value of the operating curve parameter ϕ_B corresponding to the RFR factor (B) discussed at the beginning of the statistical methodology was calculated. This parameter was given by

$$\phi_B^2 = \frac{naD^2}{2b\sigma^2} \quad (B-7)$$

where n = number of replications per cell = 40,
 a = number of levels of factor A = 12,
 b = number of levels of factor B = 2,
 σ^2 = population variance, and
 D^2 = detection threshold.

Substituting in values for a , b , n , and the MS_{pe} as an estimate of σ^2 provided an operating curve parameter of

$$\phi_B = 0.1643 D. \quad (B-8)$$

To obtain a value of ϕ from the operating curve, the type I risk α and type II risk β were set to 0.05 and 0.10, respectively. Then, the value ϕ was read from the fixed effects ANOVA curve with $\nu_1 = 1$ and $\nu_2 = 936$. This value was

$$\phi_B = 2.4. \quad (B-9)$$

Note that the degrees of freedom for the numerator, ν_1 , and the degrees of freedom for the denominator, ν_2 , were calculated with the equation

$$\nu_1 = b-1, \text{ and} \quad (B-10)$$

$$\nu_2 = ab(n-1). \quad (B-11)$$

The detection level was therefore

$$D_B = 14.60 \text{ pg/mL}. \quad (B-12)$$

Thus, this protocol was able to conservatively detect an increase in resting plasma norepinephrine concentrations of 14.60 pg/mL about 90% of the time.

Plasma Epinephrine Statistical Analysis.

In many ways, the epinephrine scatter diagrams of Figure 7 and 8 closely resembled the norepinephrine scatter diagrams. Therefore, epinephrine concentration was modelled in a similar manner to norepinephrine. The equation

$$y = \beta_0 + \beta_1x + \beta_{11}x^2 + \alpha_0z + \alpha_1zx + \alpha_{11}zx^2 \quad (B-13)$$

where y = plasma epinephrine concentration (in pg/mL)
 x = time (in weeks), and
 z = a categorical variable with value 0 for animals in the sham-exposure group and value 1 for animals in the exposure group,

was tested for the significance of the coefficients α_0 , α_1 , and α_{11} . These terms described the RFR-interaction with the resting epinephrine concentration.

Data from the epinephrine spreadsheets (Appendix G) were subsequently put into a new file and a second SAS formatting program (included in Appendix H) was prepared to analyze the data.

The model indicated by the forward stepwise and maximum R^2 regression procedures was

$$y = \beta_0 + \beta_1x + \beta_{11}x^2, \quad (B-14)$$

where $\beta_0 = 158.80$,
 $\beta_1 = -6.62$, and
 $\beta_{11} = 0.28$,

with the x , y , and z variables as defined previously. The entry and exit risk were both set to 0.095. The outputs of both regression procedures are included in Appendix I. Note that the absence of α terms indicated that, at a risk of 0.095, there was no statistical difference in plasma epinephrine concentrations between the exposure and sham-exposure groups. The estimated resting concentration of plasma epinephrine, 158.8 pg/mL, also agreed well with established values cited in the literature (180 ± 35 pg/mL). This agreement was a further indication of no systematic error within the sampling/assaying procedure.

Epinephrine concentration in the sham-exposure and exposure groups displayed the same type of time dependency found in the norepinephrine concentrations. Since epinephrine and norepinephrine release within the body

are physiologically coupled, this was not a surprising find. Specifically, resting epinephrine values were at their highest value of 181.3 pg/mL at the study onset (week -3). The resting level then gradually declined, reaching its lowest point of 119.4 pg/mL at week 12 of the study. Epinephrine concentration slowly rose beyond that point to a value of 133.9 pg/mL at week 19, the last week for which data were taken. All of the just mentioned values are typical of resting epinephrine concentrations in normal, unstressed rats. It did not appear, therefore, that chronic exposure to 435-MHz RFR induced any stress, as measured by the resting concentration of plasma epinephrine, in the exposure group when compared to the sham-exposure group.

The just mentioned conclusions could only be accepted upon verification of the assumptions used in building the model. These assumptions included no model lack-of-fit, $NID(0, \sigma^2)$ residual distribution, and no model multicollinearity.

First, the model was checked for lack-of-fit (Appendix J). The mean square error and mean square pure error were 3359.31 and 3296.69 respectively, yielding sample standard deviation estimates of 57.96 pg/mL and 57.42 pg/mL. Since both of these estimates were rather close to one another, lack-of-fit was probably not significant. The computed lack-of-fit test statistic was then found to be smaller than the critical value. This test confirmed that model lack-of-fit was not present.

The epinephrine data set was then checked for outlier data values before generating residual plots. Three observations at week -3 (animal #53, [epinephrine] = 560 pg/mL; animal #57, [epinephrine] = 806 pg/mL; and animal #62, [epinephrine] = 540 pg/mL) were determined to be outliers and were subsequently removed from the data set. All three points had values of Cook's D greater than 0.05, and thus were overly influential in comparison with other data points from week -3. Once the data set was edited, residual plots were generated to check the assumption that the model errors were distributed $NID(0, \sigma^2)$. Appendix K contains the epinephrine residual plots. Examination of the plots yielded no obvious patterns or problems, thereby indicating that the residuals were normally distributed with mean 0 and variance σ^2 .

However, independence among the residuals was not assured. Often, residuals produced from a regression modelling data taken in time series show a degree of autocorrelation from one week to the next. To adequately address this problem, it became necessary to perform an autoregression on the regression

model, and determine the extent of autocorrelation and the effects of the autocorrelation on the hypothesis tests.

Results of the autoregression (not included in text) indicated a significant amount of correlation between data at one week to data at the previous week (lag-1 autocorrelation). The autoregression also detected a smaller amount of lag-3 correlation stemming from a presently unknown source. The lag-1 correlation indicated that the best predictor for an animal's epinephrine concentration was more the last known epinephrine concentration rather than the time into the study. If the study purpose were to determine a predictive model of epinephrine concentration versus time, this would be a significant find. However, since the study purpose was to determine the effects of RFR on epinephrine concentration, this finding did not significantly change any of the significance tests on the parameters. To adjust for the presence of lag-1 correlation on the parameter tests, a qualitative measure would be to increase the α risk of the conclusion drawn. Since the probability that each epinephrine parameter's F statistic is greater than F_C was better than 0.0001, then this adjustment of α risk would have no practical effect on the conclusion. Thus, although the model had nonindependent characteristics, they were of such a nature as to not affect the final conclusion taken from the model.

To complete the analysis, diagnostics to check for model multicollinearity and correlation between the terms were used. Examination of the listed condition numbers and matrix eigenvalues (being provided under separate cover) detected no troublesome values. This review indicated that the model did not display a significant degree of multicollinearity. Similarly, examination of the correlation matrix showed that correlation between the estimated values of 3 were all within tolerable limits. The highest degree of correlation was between the x and the x^2 term, which often occurs when using a polynomial model in linear regression.

For future reference, and for the sake of completeness, tables listing animal case number, observations (if taken) at each week, predicted value of epinephrine concentration, standardized error of prediction, 95% confidence intervals on the mean value of the epinephrine concentration, and residuals were prepared, as were tables containing animal case number, regular and studentized residual values, a graphical display of student residual values, and influence statistics (such as Cook's D). These tables were used to detect both outliers and influential data points in the epinephrine data set.

To arrive at a conservative estimate of the minimum change due to RFR in resting epinephrine concentrations which this protocol was capable of detecting, the value of the operating curve parameter ϕ_B corresponding to the RFR factor (B) discussed at the beginning of the statistical methodology was calculated. This parameter was given by

$$\phi_B^2 = \frac{naD^2}{2b\sigma^2} \quad (B-15)$$

where n = number of replications per cell = 40,

a = number of levels of factor A = 12,

b = number of levels of factor B = 2,

σ^2 = population variance, and

D^2 = detection threshold.

Substituting in values for a , b , n , and the MS_{pe} as an estimate of σ^2 , provided an operating curve parameter of

$$\phi_B = 0.1908 D. \quad (B-16)$$

To obtain a value of ϕ from the operating curve, the type I risk α and type II risk β were set to 0.05 and 0.10, respectively. Then, the value of ϕ was read from the fixed effects ANOVA curve with $\nu_1 = 1$ and $\nu_2 = 936$. This value was

$$\phi_B = 2.4. \quad (B-17)$$

Degrees of freedom in both numerator and denominator were calculated in the same manner as those in the norepinephrine analysis. Note that the 40 replications in the protocol were not replications in the truest sense of the word (since a single animal was not put through the study 40 times). Since Sprague-Dawley rats represented a very homogeneous population, this difference would have only minor effects on the rigor of this calculation.

The detection level was therefore

$$D_B = 12.58 \text{ pg/mL}. \quad (B-18)$$

Thus, this protocol conservatively was able to detect an increase in resting plasma epinephrine concentrations of 12.58 pg/mL about 90% of the time.

Plasma Dopamine Statistical Analysis.

Upon examining the scatter diagrams of Figures 10 and 11 and the mean dopamine concentration versus time plot of Figure 12, it did not appear that resting dopamine levels in the exposure group were higher than resting dopamine levels in the sham-exposure group. Therefore, the model to test for RFR-induced effects on dopamine concentration was the starting model of the norepinephrine and epinephrine analyses:

$$y = \beta_0 + \beta_1 x + \beta_{11} x^2 + \alpha_0 z + \alpha_1 xz + \alpha_{11} xz^2 \quad (B-19)$$

where y = resting plasma dopamine concentration (in pg/mL),
 x = time (in weeks), and
 z = a categorical variable with value 0 for animals in the sham-exposure group and value 1 for animals in the exposure group.

The significance of the α terms in this model determined whether or not there were any RFR-induced effects; the algebraic sign of the α then determined whether or not the effects tended to increase resting hormone concentrations (indicated by positive α) or decrease resting hormone concentrations (indicated by negative α). Note that these α terms should not be confused with the symbol for statistical significance (risk), which is also an α .

Data from the dopamine spreadsheets (Appendix L) were subsequently put into a new file and a third SAS formatting program (Appendix M) was prepared to analyze the data.

The model indicated by the forward stepwise and maximum R^2 regression procedures was

$$y = \beta_0 + \beta_1 x + \alpha_1 xz + \beta_{11} x^2 \quad (B-20)$$

where

$$\beta_0 = 51.19,$$

$$\beta_1 = -3.14,$$

$$\alpha_1 = -0.92, \text{ and}$$

$$\beta_{11} = 0.13,$$

with the x, y, and z variables defined as previously. The entry and exit risk were both set to 0.10. The outputs of both regression procedures are included in Appendix N. The absence of α_0 indicated that RFR did not produce a detectable effect on the intercept of the model, and therefore did not bias the dopamine concentration of the exposure group when compared to the sham-exposure group. Equivalently, this showed that at the onset of exposure (week 0), both groups displayed comparable resting dopamine levels. This result was not surprising, since the experiment was designed such that the initial resting dopamine levels of both groups would be similar. Additionally, there was no evidence of any RFR-induced effect on the curvature of the exposure group.

The exposure group did differ from the sham-exposure group with regards to overall time response, however. In both groups, dopamine concentration started out somewhat high (61.8 pg/mL sham-exposure group; 64.6 pg/mL exposure group at week -3). After the initiation of radiation, the exposure group's estimated resting dopamine concentration remained below that of the sham-exposure group for the duration of the study. At week 12, estimated resting dopamine concentrations in sham-exposure animals reached a low value of 32.3 pg/mL; the low for exposure animals was attained at week 16 with an estimated dopamine level of 19.6 pg/mL. The dopamine concentration then rose slightly, reaching estimated values of 35.6 pg/mL in sham-exposure animals and 21.1 pg/mL in exposure animals by week 19 (the final week data were collected) of the study. Both ranges (32.3 to 61.8 pg/mL in sham-exposure animals, 19.6 to 64.6 pg/mL in exposure animals) were still well within the normal range of plasma dopamine in nonstressed male Sprague-Dawley rats (85 ± 35 pg/mL). Stress in these animals is reflected in an increased rate of dopamine secretion. Therefore, these results indicated that chronic exposure to 435-MHz RFR did not induce an elevation in resting dopamine concentration in the exposure group.

Once again, it was then necessary to check the validity of the assumptions used in building the dopamine regression. First, a model lack-of-fit test was performed (Appendix O). The mean square error and the mean square pure error were 1235.37 and 814.01 respectively, yielding sample standard deviation estimates of 35.15 and 28.53 pg/mL. The calculated value of F_0 was then about 1.51, while the critical value was about 1.38.

Since F_0 exceeded the critical value, the dopamine model displayed a significant lack-of-fit, thereby deviating from results obtained in plasma norepinephrine and plasma epinephrine. The situation was reminiscent of that

encountered in the analysis of ACTH and corticosterone, and in the analysis of prolactin [2,3]. In those cases, significant lack-of-fit was handled by qualitatively altering the significance levels α to compensate for the model defects. This procedure was preferable to transformation of the dependent or independent variables, since a transformation on the dependent variable y would alter the residual distribution and a transformation on the independent variable x , although theoretically possible, would be time consuming and costly and yield a model with minimally better predictive value.

We then decided to follow this course for the dopamine model. Therefore, model lack-of-fit could be deemed statistically significant but practically insignificant by altering the α risk in the coefficients. Since those coefficients were highly significant to begin with, this alteration of α risk should not change the model in any manner.

Residual plots were then generated for the dopamine data. Since no observations in the original data set had values of Cook's D higher than 0.05, we decided not to reject any values from the data set. The residual plots (Appendix P) therefore displayed no obvious patterns or problems. This supported the assumption that the model errors were normally distributed with a mean of zero and a variance of σ^2 .

As previously mentioned, the lack of patterns within the residual plots did not guarantee independence within the observations because models produced by regression of data taken in time series tend to show some degree of autocorrelation between the ε_i s of each time interval. To adequately address this question, the dopamine data set was reexamined with an autoregressive procedure to determine the extent of residual autocorrelation and its effects on the model's hypothesis tests.

Results of the autoregression (not included in this report) indicated a significant amount of correlation within the data at lags of 1 and 2 weeks (the week 2 autocorrelation was considerably smaller than the week 1 autocorrelation, and stems from a presently unknown source). Once again, this quantitative estimate of autocorrelation was not unexpected, nor practically significant in terms of the conclusions drawn from the model. A further adjustment of the α risk values in the regression would compensate for the lag-1 autocorrelation. Since the probability that each parameter F statistic was greater than the critical F value was better than 0.0003 (for the parameters statistically significant in the dopamine regression), this adjustment of α risk was

inconsequential. Thus, the sheer number of observations taken helped compensate for the model's two main defects: lack-of-fit and nonindependent residuals.

To complete the analysis, diagnostics to check for model multicollinearity and correlation between the terms were used. Examination of the listed condition numbers and matrix eigenvalues (being provided under separate cover) detected no troublesome values and indicated that the model did not display a significant degree of multicollinearity. Similarly, examination of the correlation matrix showed that correlations between the estimated values of β were all within tolerable limits. The highest degree of correlation was between the x and the x^2 term, which often occurs when using a polynomial model in linear regression.

For future reference, and for the sake of completeness, tables listing animal case number, observations (if taken) at each week, predicted value of dopamine concentration, standardized error of prediction, 95% confidence intervals on the mean value of the dopamine concentration, and residuals were prepared, as were tables containing animal case number, regular and studentized residual values, a graphical display of student residual values, and influence statistics (such as Cook's D). These tables were used to detect both outliers and influential data points in the dopamine data set.

To arrive at a conservative estimate of the minimum change due to RFR in resting dopamine concentrations which this protocol was capable of detecting, the value of the operating curve parameter Φ_B corresponding to the RFR factor (B) discussed at the beginning of the statistical methodology was calculated. This parameter was given by

$$\Phi_B^2 = \frac{naD^2}{2b\sigma^2} \quad (B-21)$$

where n = number of replications per cell = 40,
 a = number of levels of factor A = 12,
 b = number of levels of factor B = 2,
 σ^2 = population variance, and
 D^2 = detection threshold.

Substituting in values for a , b , n , and the MS_{pe} as an estimate of σ^2 provided an operating curve parameter of

$$\hat{\beta}_B = 0.3840 D. \quad (B-22)$$

To obtain a value of $\hat{\beta}$ from the operating curve, the type I risk α and type II risk β were set to 0.05 and 0.10, respectively. Then, the value of $\hat{\beta}$ was read from the fixed effects ANOVA curve with $\nu_1 = 1$ and $\nu_2 = 936$. This value was

$$\hat{\beta}_B = 2.4. \quad (B-23)$$

Degrees of freedom in both numerator and denominator were calculated in the same manner as those in the norepinephrine analysis. Once again, the 40 replications in the protocol were not replications in the truest sense (since an individual animal was not put through the study 40 times). However, Sprague-Dawley rats represent a very homogeneous population and thus minimize the between-individual variation of the cell observations.

The detection level was therefore

$$D_B = 6.25 \text{ pg/mL}. \quad (B-24)$$

Thus, the protocol was able to detect an increase in resting plasma dopamine concentrations of 6.25 pg/mL about 90% of the time.

We gratefully acknowledge the assistance of Dr. Russell G. Heikes of Georgia Tech's Department of Industrial and Systems Engineering in developing the statistical methodology of this appendix.

APPENDIX C

NOREPINEPHRINE SAS FORMATTING PROGRAM

NOTE: COPYRIGHT (C) 1984,1986 SAS INSTITUTE INC., CARY, N.C. 27511, U.S.A.
NOTE: CMS SAS RELEASE 5.16 AT GEORGIA INSTITUTE OF TECHNOLOGY (03559001).

NOTE: CPUID VERSION = FF SERIAL = 012242 MODEL = 4381 .

NOTE: SAS OPTIONS SPECIFIED ARE:
LEAVE=0

```

1 DATA TESTN;
2 CMS FILEDEF X DISK NOREPIN DAT A1;
3 CMS FILEDEF 20 DISK NOREPIN0 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
4 CMS FILEDEF 21 DISK NOREPIN1 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
5 CMS FILEDEF 22 DISK NOREPIN2 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
6 CMS FILEDEF 23 DISK NOREPIN3 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
7 CMS FILEDEF 24 DISK NOREPIN4 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
8 CMS FILEDEF 25 DISK NOREPIN5 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
9 CMS FILEDEF 26 DISK NOREPIN6 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
10 CMS FILEDEF 27 DISK NOREPIN7 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
11 CMS FILEDEF 28 DISK NOREPIN8 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
12 ARRAY WEEK {24} WKN3 WKN2 MISSN1 WK0-WK20;
13 KEEP X XSQR Y Z XZ XSQRZ CASE;
14 INFILE X;
15 INPUT CASE 1-3
16         WKN3 5-7
17         WKN2 9-11
18         WK0 13-15
19         WK1 17-19
20         WK2 21-23
21         WK3 25-27
22         WK4 29-31
23         WK5 33-35
24         WK6 37-39
25         WK7 41-43
26         WK8 45-47
27         WK9 49-51
28         WK10 53-55
29         WK11 57-59
30         WK12 61-63
31         WK13 65-67
32         WK14 69-71
33         WK15 73-75
34         WK16 77-79
35         WK17 81-83
36         WK18 85-87
37         WK19 89-91
38         WK20 93-95
39 ;
40 MISSN1=.;
41 MISS25=.;
42 MISS27=.;
43 MISS28=.;
44 IF CASE < 100 THEN Z = 0;
45 IF CASE >= 100 THEN Z = 1;
46 IF Z=1 THEN CASE=CASE-100;
47 DO I = 1 TO 24;
48 X = I-4; XSQR = X*X; XZ = X*Z; XSQRZ = X*X*Z; Y = WEEK {I};OUTPUT;
49 END;

```

NOTE: INFILE X IS FILE NOREPIN DAT A1
 NOTE: 126 LINES WERE READ FROM INFILE X.
 NOTE: DATA SET WORK.TESTN HAS 3024 OBSERVATIONS AND 7 VARIABLES.
 NOTE: THE DATA STATEMENT USED 0.61 SECONDS AND 296K.

50 PROC CONTENTS;
 NOTE: THE PROCEDURE CONTENTS USED 0.19 SECONDS AND 424K AND PRINTED PAGES 1 TO 2.

51 PROC PRINTTO NEW UNIT=20;
 NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

52 PROC SORT OUT=SCTR;
 53 BY Z X Y;
 NOTE: DATA SET WORK.SCTR HAS 3024 OBSERVATIONS AND 7 VARIABLES.
 NOTE: THE PROCEDURE SORT USED 0.72 SECONDS AND 6952K.

54 PROC SUMMARY;
 55 BY Z X;
 56 VAR Y;
 57 OUTPUT OUT=OVLIN MEAN=MEAN;
 NOTE: THE DATA SET WORK.OVLIN HAS 48 OBSERVATIONS AND 5 VARIABLES.
 NOTE: THE PROCEDURE SUMMARY USED 0.54 SECONDS AND 424K.

58 DATA SNOREPIN;
 59 SET SCTR OVLIN;
 60 BY Z;
 NOTE: DATA SET WORK.SNOREPIN HAS 3072 OBSERVATIONS AND 10 VARIABLES.
 NOTE: THE DATA STATEMENT USED 0.52 SECONDS AND 424K.

61 PROC PLOT NOLEGEND DATA=SNOREPIN;
 62 BY Z;
 63 PLOT MEAN*X='X' Y*X='.' / VAXIS=90 TO 450 BY 30 OVERLAY;
 64 TITLE 'NOREPINEPHRINE SCATTER DIAGRAM';
 NOTE: THE PROCEDURE PLOT USED 1.06 SECONDS AND 424K AND PRINTED PAGES 3 TO 4.

65 PROC PRINTTO NEW UNIT=21;
 NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

66 PROC PLOT NOLEGEND DATA=SNOREPIN;
 67 PLOT MEAN*X='X' / VAXIS=90 TO 450 BY 30;
 68 TITLE 'Mean Norepinephrine Concentration Versus Time';
 NOTE: THE PROCEDURE PLOT USED 0.81 SECONDS AND 424K AND PRINTED PAGE 5.

69 PROC PRINTTO NEW UNIT=22;
 70 TITLE 'CATECHOLAMINE ANALYSIS: Norepinephrine';
 NOTE: THE PROCEDURE PRINTTO USED 0.03 SECONDS AND 424K.

71 PROC DATASETS;
 72
 LIST OF MEMBERS BEFORE UPDATE OF DIRECTORY.

NAME	MEMTYPE	OBS	TRACKS	PROT
OVLIN	DATA	48	1	
SCTR	DATA	3024	1	

```

SNOREPIN/DATA          3072      1
TESTN  /DATA           3024      1

```

```

72      DELETE SCTR;
73      DELETE OVLMN;

```

LIST OF MEMBERS AFTER UPDATE OF DIRECTORY.

```

NAME  MEMTYPE          OBS  TRACKS  PROT
SNOREPIN/DATA          3072      1
TESTN  /DATA           3024      1

```

NOTE: THE PROCEDURE DATASETS USED 0.12 SECONDS AND 424K.

74 PROC STEPWISE;

```

75      MODEL Y = X XSQR Z XZ XSQRZ /SLENTY=0.10 SLSTAY=0.10 STEPWISE MAXR;

```

NOTE: THE PROCEDURE STEPWISE USED 0.63 SECONDS AND 424K AND PRINTED PAGES 6 TO 8.

76 PROC PRINTTO NEW UNIT=23;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

77 PROC REG;

```

78      MODEL Y = X XSQR / PARTIAL;
79      ID CASE;

```

NOTE: ACOV AND SPEC OPTION ONLY VALID WITH RAWDATA

NOTE: THE PROCEDURE REG USED 1.46 SECONDS AND 744K AND PRINTED PAGES 9 TO 12.

80 PROC PRINTTO NEW UNIT=24;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

81 PROC GLM;

```

82      CLASS X Z;
83      MODEL Y = X X*X X*Z;

```

NOTE: THE PROCEDURE GLM USED 3.36 SECONDS AND 1128K AND PRINTED PAGES 13 TO 14.

84 PROC PRINTTO NEW UNIT=25;

```

85  -----*
86  *
87  *      to obtain tables listing the variance inflation factors,      *
88  *      influence statistics, and tolerances, the following SAS      *
89  *      statements were used in this partition:                      *
90  *
91  *      PROC REG;
92  *          MODEL Y = X XSQR / TOL VIF INFLUENCE;                      *
93  *          ID CASE;
94  *          OUTPUT OUT=RNOREPIN P=PREDICT R=RESID STUDENT=STUDENT;      *
95  *
96  -----*

```

NOTE: THE PROCEDURE PRINTTO USED 0.04 SECONDS AND 424K.

97 PROC REG;

```

98      MODEL Y = X XSQR / I SS1 SS2 STB COVB CORR SEQB COLLIN
99      COLLINOINT ACOV P R CLM;

```

100 ID CASE;

101 OUTPUT OUT=RNOREPIN P=PREDICT R=RESID STUDENT=STUDENT;

NOTE: THE DATA SET WORK.RNOREPIN HAS 3072 OBSERVATIONS AND 13 VARIABLES.

NOTE: THE PROCEDURE REG USED 6.76 SECONDS AND 744K AND PRINTED PAGES 15 TO 80.

102 PROC PRINTTO NEW UNIT=26;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

```
103 PROC PLOT DATA=RNOREPIN;  
104     PLOT RESID*X='*' / VAXIS=-200 TO 200 BY 50;  
105     PLOT RESID*PREDICT='*' / HAXIS=220 TO 300 BY 5 VAXIS=-200 TO 200 BY 50;  
106     PLOT STUDENT*X='*' / VAXIS=-3 TO 3 BY 0.5;  
107     PLOT STUDENT*PREDICT='*' / HAXIS=220 TO 300 BY 5 VAXIS=-3 TO 3 BY 0.5;  
108     TITLE 'NOREPINEPHRINE RESIDUAL PLOTS';
```

NOTE: THE PROCEDURE PLOT USED 1.34 SECONDS AND 424K AND PRINTED PAGES 81 TO 84.

```
109 PROC PRINTTO NEW UNIT=27;
```

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

```
110 PROC PLOT DATA=RNOREPIN;  
111     BY Z;  
112     PLOT RESID*CASE='*' / VAXIS=-200 TO 200 BY 50 HAXIS=0 TO 65 BY 5;  
113     PLOT STUDENT*CASE='*' / VAXIS=-3 TO 3 BY 0.5 HAXIS=0 TO 65 BY 5;  
114     TITLE 'NOREPINEPHRINE RESIDUAL PLOTS';
```

NOTE: THE PROCEDURE PLOT USED 0.74 SECONDS AND 424K AND PRINTED PAGES 85 TO 88.

```
115 PROC PRINTTO NEW UNIT=28;
```

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 424K.

```
116 PROC AUTOREG;  
117     TITLE 'Norepinephrine Autoregressive Models';  
118     MODEL Y = X XSQR / COEF CORRB COVB BACKSTEP;  
119     MODEL Y = X XSQR / NLAG=1 COEF CORRB COVB BACKSTEP;  
120     MODEL Y = X XSQR / NLAG=2 COEF CORRB COVB BACKSTEP;  
121     MODEL Y = X XSQR / NLAG=3 COEF CORRB COVB BACKSTEP;  
122     MODEL Y = X XSQR / NLAG=4 COEF CORRB COVB BACKSTEP;
```

NOTE: THE PROCEDURE AUTOREG USED 6.64 SECONDS AND 424K AND PRINTED PAGES 89 TO 101.

NOTE: SAS USED 6952K MEMORY.

NOTE: SAS INSTITUTE INC.

SAS CIRCLE

PO BOX 8000

CARY, N.C. 27511-8000

APPENDIX D

STEPWISE AND MAXIMUM R^2 REGRESSION
PROCEDURES USED TO BUILD NOREPINEPHRINE MODEL

9:33 WEDNESDAY, JULY 15, 1987

CATECHOLAMINE ANALYSIS: Norepinephrine

STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

WARNING: 2409 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.1149742 C(P) = 28.24332231

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
1	393988.32358118	393988.32358118	85.47	0.0001
661	3047035.38079288	4609.73582571		
662	3441023.70437406			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 272.49852493 0.36602307 393988.32358118 85.47 0.0001

X -3.38385787

BOUNDS ON CONDITION NUMBER: 1. 1

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.14406933 C(P) = 7.29239822

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
2	495745.99146390	247872.99573195	55.55	0.0001
660	2945277.71291016	4462.54198926		
662	3441023.70437406			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 272.83919523 0.99008634 276104.88323894 61.87 0.0001

X -7.78787472 0.06215566 101757.66788272 22.80 0.0001

XSQR 0.29680630

BOUNDS ON CONDITION NUMBER: 7.55828. 30.23312

NO OTHER VARIABLES MET THE 0.1000 SIGNIFICANCE LEVEL FOR ENTRY INTO THE MODEL.

SUMMARY OF STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

STEP	VARIABLE ENTERED	VARIABLE REMOVED	NUMBER IN	PARTIAL R ²	MODEL R ²	C(P)	F	PROB>F
1	X		1	0.1145	0.1145	28.2433	85.4687	0.0001
2	XSQR		2	0.0296	0.1441	7.2924	22.8026	0.0001

CATECHOLAMINE ANALYSIS: Norepinephrine

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

WARNING: 2409 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.1149742 C(P) = 28.24332231

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
1	393988.32358118	393988.32358118	85.47	0.0001
131	3047035.38079288	4609.73582571		
132	3441023.70437406			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 272.19852493 393988.32358118 85.47 0.0001

X -3.8385787 0.36602307 393988.32358118 85.47 0.0001

BOUNDS ON CONDITION NUMBER: 1. 1

THE ABOVE MODEL IS THE BEST 1 VARIABLE MODEL FOUND.

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.14406933 C(P) = 7.29239822

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
2	495745.99146390	247872.99573195	55.55	0.0001
660	2945277.71291016	4462.54198926		
662	3441023.70437406			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 272.83919523 276104.88323894 61.87 0.0001

X -7.78787472 0.99008634 101757.66788272 22.80 0.0001

XSQR 0.29680630 0.06215566

BOUNDS ON CONDITION NUMBER: 7.55828, 30.23312

THE ABOVE MODEL IS THE BEST 2 VARIABLE MODEL FOUND.

STEP 3 VARIABLE XZ ENTERED R SQUARE = 0.14522127 C(P) = 8.39837088

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
3	499709.84651081	166569.94883694	37.32	0.0001
659	2941313.85786325	4463.29872210		
662	3441023.70437406			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 272.79906534 243230.01739869 54.50 0.0001

X -7.54772938 1.0243501 102791.24459014 23.03 0.0001

XSQR 0.29842352 0.06218462 3963.85504691 0.89 0.3463

XZ -0.52163781 0.55352617

BOUNDS ON CONDITION NUMBER: 8.058878, 51.68796

CATECHOLAMINE ANALYSIS: Norepinephrine

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

THE ABOVE MODEL IS THE BEST 3 VARIABLE MODEL FOUND.

STEP 4 VARIABLE Z ENTERED		R SQUARE = 0.15031078		C(P) = 6.44837554	
DF		SUM OF SQUARES	MEAN SQUARE	F	PROB>F
4	REGRESSION	517222.96765114	129305.74191278	29.10	0.0001
658	ERROR	2923800.73672292	4443.46616523		
662	TOTAL	3441023.70437406			
B VALUE		STD ERROR	TYPE II SS	F	PROB>F
266.08355576	INTERCEPT				
-7.04498095	X	1.05112228	199606.66641284	44.92	0.0001
0.29589589	XSQR	0.06205937	101014.81865341	22.73	0.0001
13.38690058	Z	6.74309380	17513.12114033	3.94	0.0475
-1.43505798	XZ	0.71883196	17709.48871269	3.99	0.0463

BOUNDS ON CONDITION NUMBER: 8.555467, 82.15935

THE ABOVE MODEL IS THE BEST 4 VARIABLE MODEL FOUND.

STEP 5 VARIABLE XSQRZ ENTERED		R SQUARE = 0.15346548		C(P) = 6.00000000	
DF		SUM OF SQUARES	MEAN SQUARE	F	PROB>F
5	REGRESSION	528078.34690860	105615.66938172	23.82	0.0001
657	ERROR	2912945.35746546	4433.70678457		
662	TOTAL	3441023.70437406			
B VALUE		STD ERROR	TYPE II SS	F	PROB>F
265.85805427	INTERCEPT				
-5.55978297	X	1.41540121	68410.61872420	15.43	0.0001
0.19548465	XSQR	0.08922393	21282.84253430	4.80	0.0288
13.61396198	Z	6.73724761	18103.85312935	4.08	0.0437
-4.31499343	XZ	1.97563869	21150.08915658	4.77	0.0293
0.19411466	XSQRZ	0.12405644	10855.37925747	2.45	0.1181

BOUNDS ON CONDITION NUMBER: 20.60071, 367.9338

THE ABOVE MODEL IS THE BEST 5 VARIABLE MODEL FOUND.

APPENDIX E

NOREPINEPHRINE LACK-OF-FIT TEST

CATECHOLAMINE ANALYSIS: Norepinephrine
GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: Y

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE
MODEL	37	664106.63087876	17948.82786159	4.04	0.0001	0.192997
ERROR	625	2776917.07349530	4443.06731759			
CORRECTED TOTAL	662	3441023.70437406				

ROOT MSE
66.65633742

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE III SS	F VALUE
X	19	565422.75758651	6.70	0.0001	19	531882.23868000	6.30
X*Z	18	98683.87329225	1.23	0.2274	18	98683.87329225	1.23

this term is solely a measure of sum-of-squares pure error.

CATECHOLAMINE ANALYSIS: Norepinephrine

ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB > F
MODEL	2	495745.99	247873.00	55.545	0.0001
ERROR	660	2945277.71	4462.54199		
C TOTAL	662	3441023.70			
ROOT MSE		66.80226	R-SQUARE	0.1441	
DEP MEAN		252.175	ADJ R-SQ	0.1415	
C.V.		26.49044			

PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR HO: PARAMETER=0	PROB > T
INTERCEP	1	272.83920	3.37851093	80.757	0.0001
X	1	-7.78787472	0.99008634	-7.866	0.0001
XSQR	1	0.29680630	0.06215566	4.775	0.0001

$$F_0 = \frac{MS_{\text{lof}}}{MS_{\text{pe}}} = 1.0827$$

$$F_{0.10, 35, 625} \sim 1.38$$

this term contains both sum-of-squares pure error and sum-of-squares lack-of-fit.

Partitioning SS_E into SS_{pe} and SS_{lof}

$$SS_E = 2945277.71 \quad df = 660$$

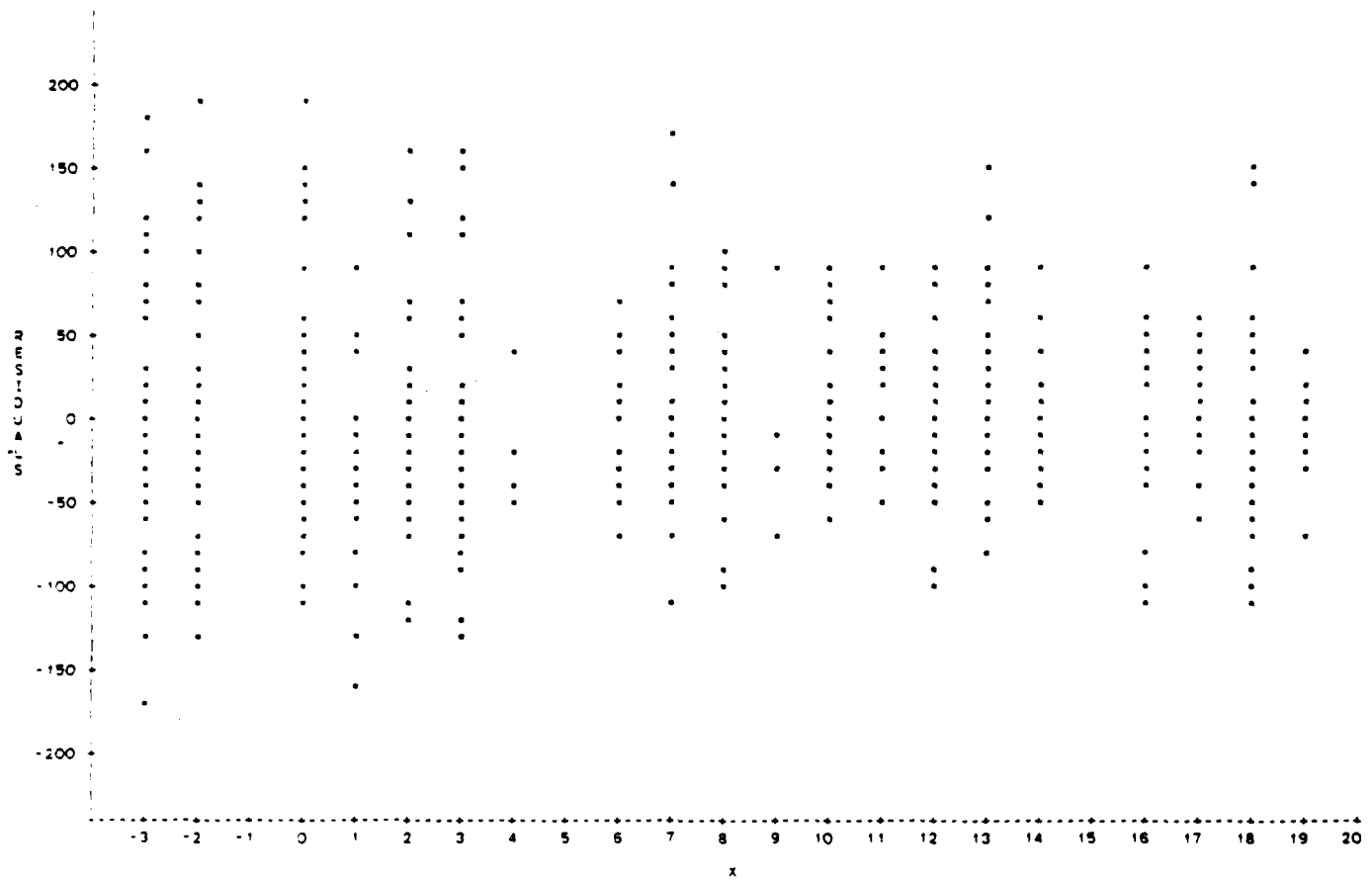
$$SS_{\text{pe}} = 2776917.07 \quad df = 625$$

$$SS_{\text{lof}} = 168360.64 \quad df = 35$$

$$MS_{\text{lof}} = 4810.30$$

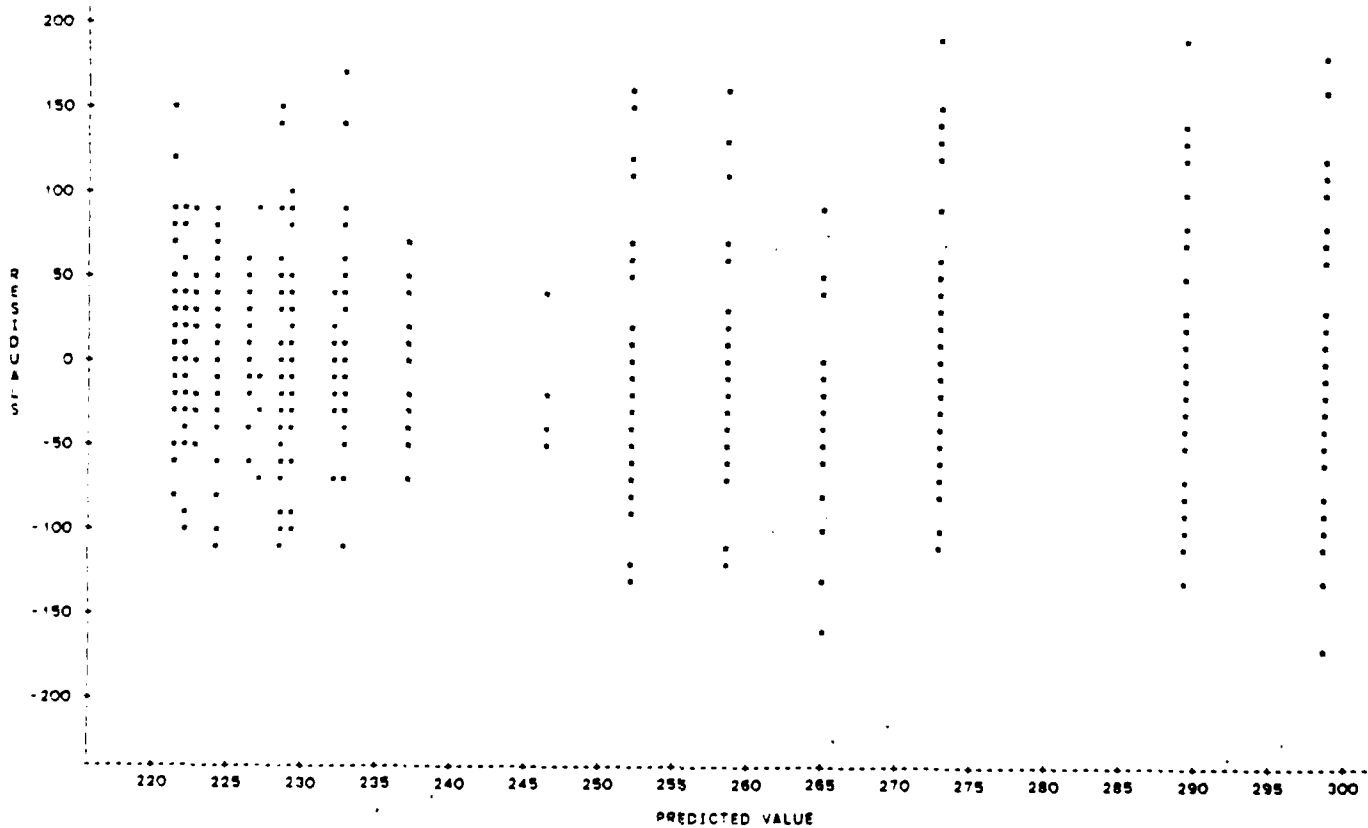
$$MS_{\text{pe}} = 4443.07$$

APPENDIX F
NOREPINEPHRINE RESIDUAL PLOTS



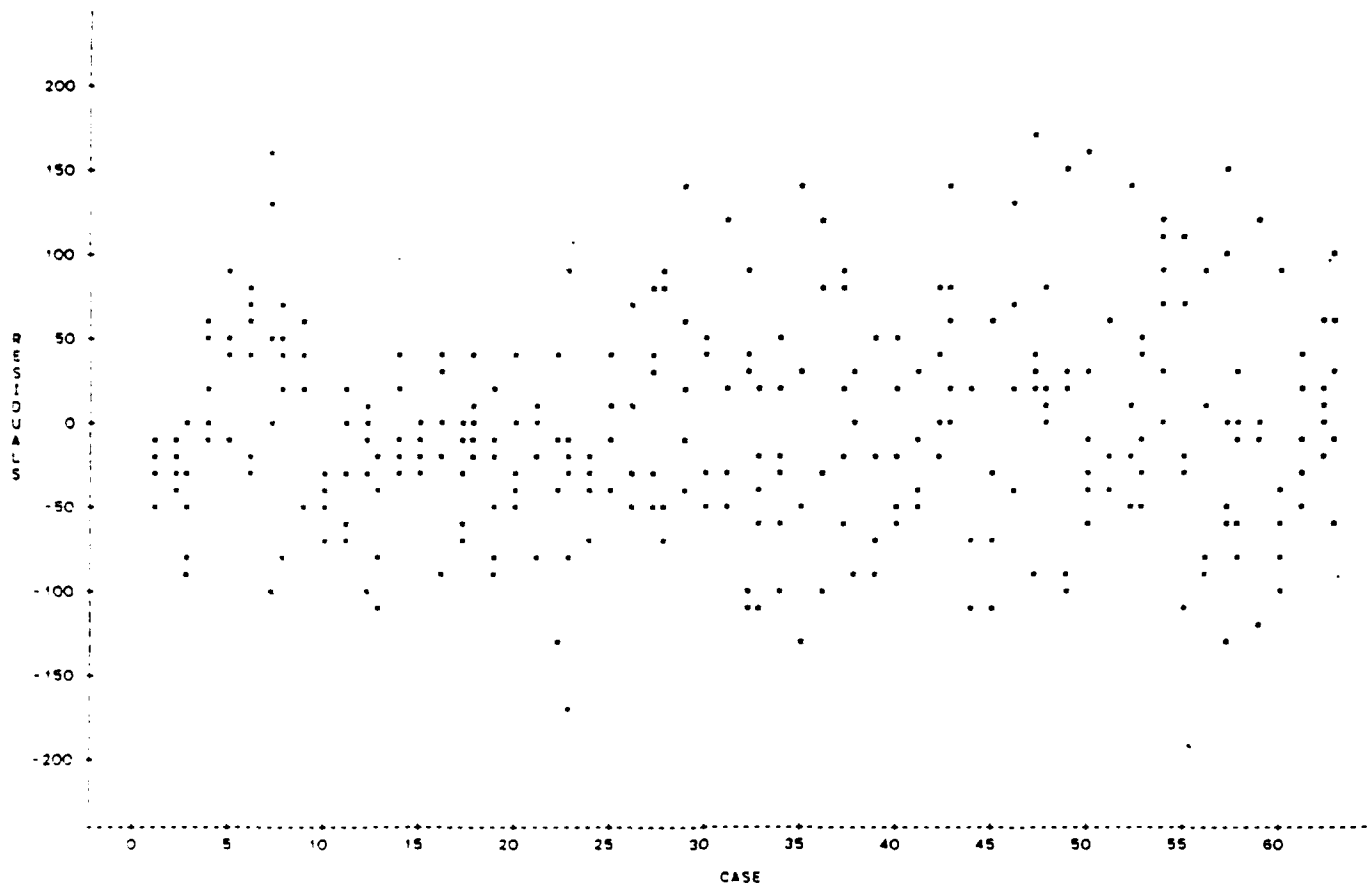
NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 364 OBS HIDDEN

Residuals versus time.



NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 364 OBS HIDDEN

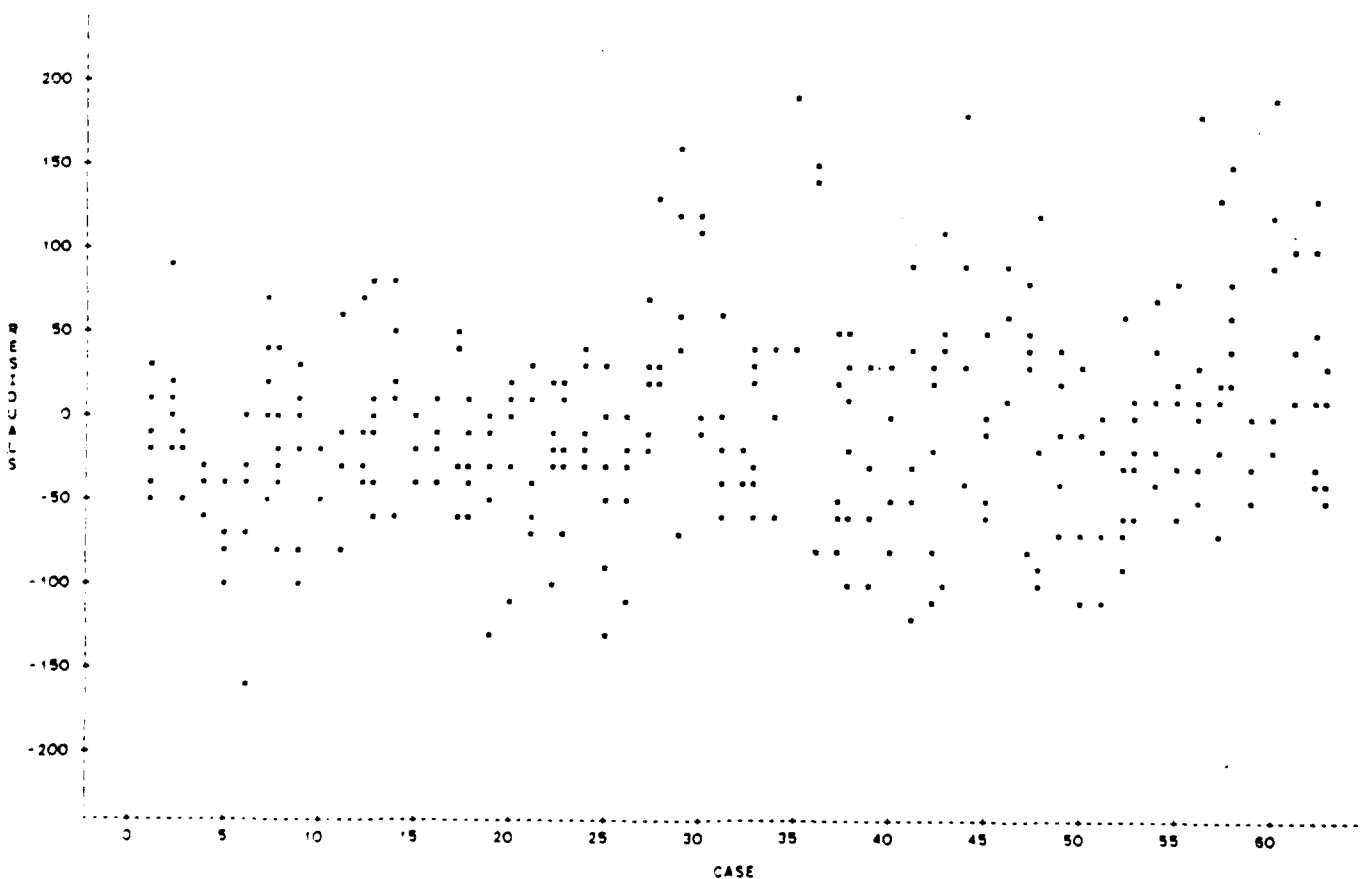
Residuals versus predicted value of plasma norepinephrine concentration.



NOTE 1201 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

45 OBS HIDDEN

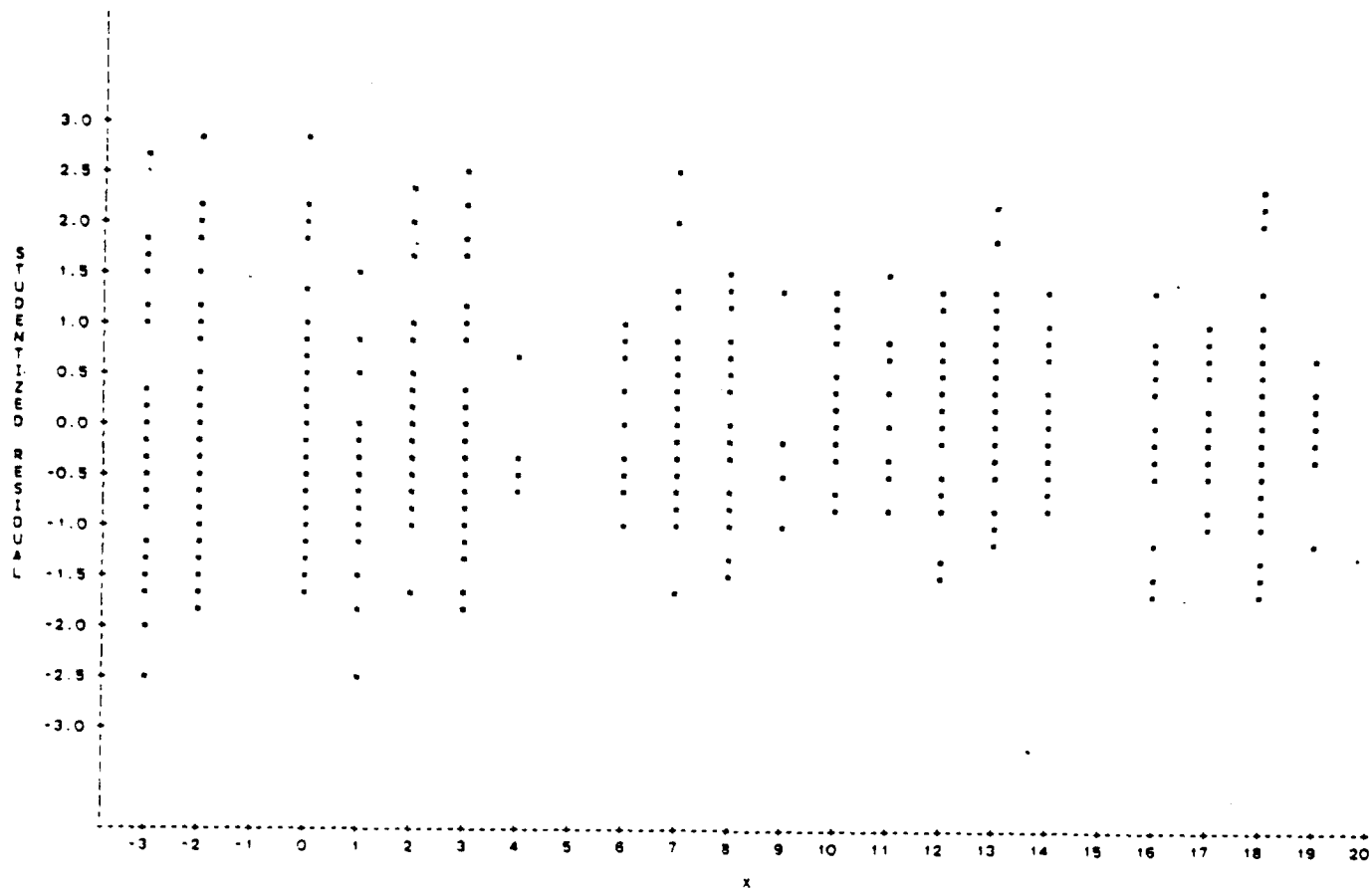
Residuals versus animal ID number (sham-exposure group).



NOTE 1215 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

37 OBS HIDDEN

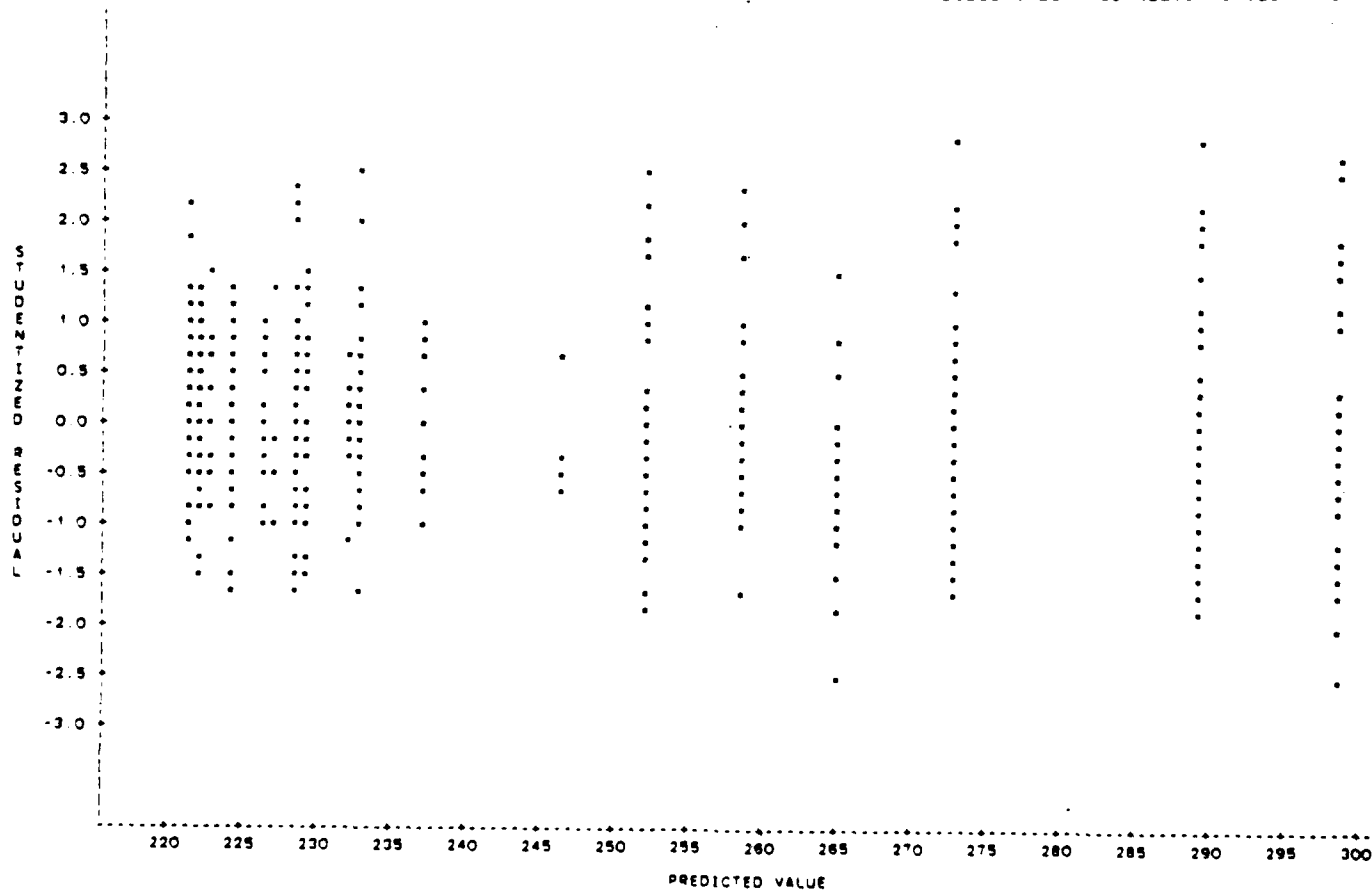
Residuals versus animal ID number (exposure group).



NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

378 OBS HIDDEN

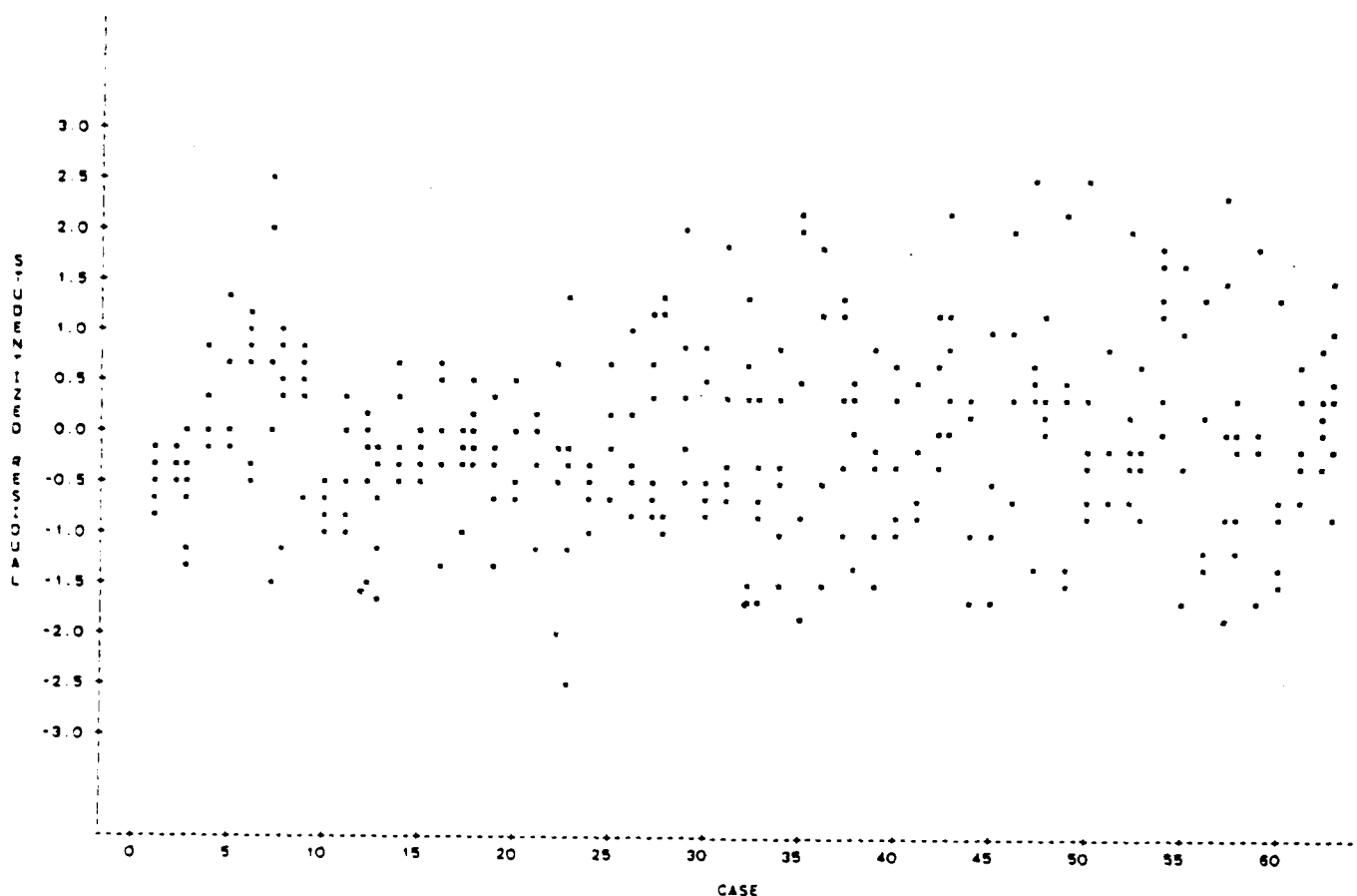
Studentized residuals versus time.



NOTE 2416 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

395 OBS HIDDEN

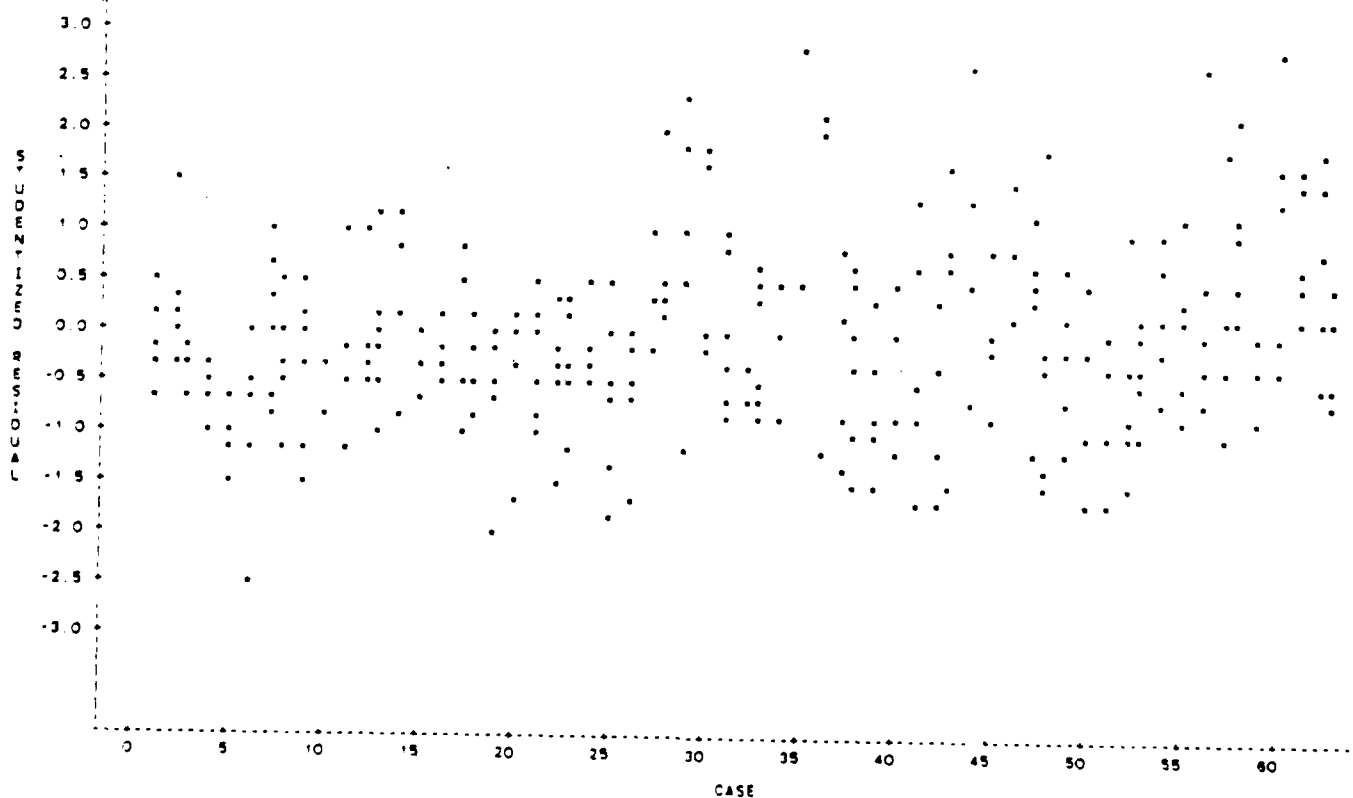
Studentized residuals versus predicted value of plasma norepinephrine concentration.



NOTE 1201 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

40 OBS HIDDEN

Studentized residuals versus animal ID number (sham-exposure group).



NOTE 1215 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

43 OBS HIDDEN

Studentized residuals versus animal ID number (exposure group).

APPENDIX G

RAW EPINEPHRINE DATA SPREADSHEETS

EPI (pg/ml) Control I

Box #	Group	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd	24th	25th	26th	27th	28th	29th	30th	31st	32nd	33rd	34th	35th	36th	37th	38th	39th	40th	41st	42nd	43rd	44th	45th	46th	47th	48th	49th	50th																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																								
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EPI- (pg/ml) Control II

[illegible]

EPi (pg/ml) control III

[illegible]

EP1 (pg/ml) Control IV

[illegible]

EPI (29 / ml) Control V

[illegible]

EPI (~~pg~~/mc) MWI

[illegible]

EPI (pg/ml) MW II

[illegible]

EPL (pg/ml) MW III

[illegible]

EP1 (pg/ml) MW IV

Box #	Group	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd	24th	25th	26th	27th	28th	29th	30th	31st	32nd	33rd	34th	35th	36th	37th	38th	39th	40th	41st	42nd	43rd	44th	45th	46th	47th	48th	49th	50th	51st	52nd	53rd	54th	55th	56th	57th	58th	59th	60th	61st	62nd	63rd	64th	65th	66th	67th	68th	69th	70th	71st	72nd	73rd	74th	75th	76th	77th	78th	79th	80th	81st	82nd	83rd	84th	85th	86th	87th	88th	89th	90th	91st	92nd	93rd	94th	95th	96th	97th	98th	99th	100th	101st	102nd	103rd	104th	105th	106th	107th	108th	109th	110th	111st	112nd	113rd	114th	115th	116th	117th	118th	119th	120th	121st	122nd	123rd	124th	125th	126th	127th	128th	129th	130th	131st	132nd	133rd	134th	135th	136th	137th	138th	139th	140th	141st	142nd	143rd	144th	145th	146th	147th	148th	149th	150th	151st	152nd	153rd	154th	155th	156th	157th	158th	159th	160th	161st	162nd	163rd	164th	165th	166th	167th	168th	169th	170th	171st	172nd	173rd	174th	175th	176th	177th	178th	179th	180th	181st	182nd	183rd	184th	185th	186th	187th	188th	189th	190th	191st	192nd	193rd	194th	195th	196th	197th	198th	199th	200th	201st	202nd	203rd	204th	205th	206th	207th	208th	209th	210th	211st	212nd	213rd	214th	215th	216th	217th	218th	219th	220th	221st	222nd	223rd	224th	225th	226th	227th	228th	229th	230th	231st	232nd	233rd	234th	235th	236th	237th	238th	239th	240th	241st	242nd	243rd	244th	245th	246th	247th	248th	249th	250th	251st	252nd	253rd	254th	255th	256th	257th	258th	259th	260th	261st	262nd	263rd	264th	265th	266th	267th	268th	269th	270th	271st	272nd	273rd	274th	275th	276th	277th	278th	279th	280th	281st	282nd	283rd	284th	285th	286th	287th	288th	289th	290th	291st	292nd	293rd	294th	295th	296th	297th	298th	299th	300th	301st	302nd	303rd	304th	305th	306th	307th	308th	309th	310th	311st	312nd	313rd	314th	315th	316th	317th	318th	319th	320th	321st	322nd	323rd	324th	325th	326th	327th	328th	329th	330th	331st	332nd	333rd	334th	335th	336th	337th	338th	339th	340th	341st	342nd	343rd	344th	345th	346th	347th	348th	349th	350th	351st	352nd	353rd	354th	355th	356th	357th	358th	359th	360th	361st	362nd	363rd	364th	365th	366th	367th	368th	369th	370th	371st	372nd	373rd	374th	375th	376th	377th	378th	379th	380th	381st	382nd	383rd	384th	385th	386th	387th	388th	389th	390th	391st	392nd	393rd	394th	395th	396th	397th	398th	399th	400th	401st	402nd	403rd	404th	405th	406th	407th	408th	409th	410th	411st	412nd	413rd	414th	415th	416th	417th	418th	419th	420th	421st	422nd	423rd	424th	425th	426th	427th	428th	429th	430th	431st	432nd	433rd	434th	435th	436th	437th	438th	439th	440th	441st	442nd	443rd	444th	445th	446th	447th	448th	449th	450th	451st	452nd	453rd	454th	455th	456th	457th	458th	459th	460th	461st	462nd	463rd	464th	465th	466th	467th	468th	469th	470th	471st	472nd	473rd	474th	475th	476th	477th	478th	479th	480th	481st	482nd	483rd	484th	485th	486th	487th	488th	489th	490th	491st	492nd	493rd	494th	495th	496th	497th	498th	499th	500th	501st	502nd	503rd	504th	505th	506th	507th	508th	509th	510th	511st	512nd	513rd	514th	515th	516th	517th	518th	519th	520th	521st	522nd	523rd	524th	525th	526th	527th	528th	529th	530th	531st	532nd	533rd	534th	535th	536th	537th	538th	539th	540th	541st	542nd	543rd	544th	545th	546th	547th	548th	549th	550th	551st	552nd	553rd	554th	555th	556th	557th	558th	559th	560th	561st	562nd	563rd	564th	565th	566th	567th	568th	569th	570th	571st	572nd	573rd	574th	575th	576th	577th	578th	579th	580th	581st	582nd	583rd	584th	585th	586th	587th	588th	589th	590th	591st	592nd	593rd	594th	595th	596th	597th	598th	599th	600th	601st	602nd	603rd	604th	605th	606th	607th	608th	609th	610th	611st	612nd	613rd	614th	615th	616th	617th	618th	619th	620th	621st	622nd	623rd	624th	625th	626th	627th	628th	629th	630th	631st	632nd	633rd	634th	635th	636th	637th	638th	639th	640th	641st	642nd	643rd	644th	645th	646th	647th	648th	649th	650th	651st	652nd	653rd	654th	655th	656th	657th	658th	659th	660th	661st	662nd	663rd	664th	665th	666th	667th	668th	669th	670th	671st	672nd	673rd	674th	675th	676th	677th	678th	679th	680th	681st	682nd	683rd	684th	685th	686th	687th	688th	689th	690th	691st	692nd	693rd	694th	695th	696th	697th	698th	699th	700th	701st	702nd	703rd	704th	705th	706th	707th	708th	709th	710th	711st	712nd	713rd	714th	715th	716th	717th	718th	719th	720th	721st	722nd	723rd	724th	725th	726th	727th	728th	729th	730th	731st	732nd	733rd	734th	735th	736th	737th	738th	739th	740th	741st	742nd	743rd	744th	745th	746th	747th	748th	749th	750th	751st	752nd	753rd	754th	755th	756th	757th	758th	759th	760th	761st	762nd	763rd	764th	765th	766th	767th	768th	769th	770th	771st	772nd	773rd	774th	775th	776th	777th	778th	779th	780th	781st	782nd	783rd	784th	785th	786th	787th	788th	789th	790th	791st	792nd	793rd	794th	795th	796th	797th	798th	799th	800th	801st	802nd	803rd	804th	805th	806th	807th	808th	809th	810th	811st	812nd	813rd	814th	815th	816th	817th	818th	819th	820th	821st	822nd	823rd	824th	825th	826th	827th	828th	829th	830th	831st	832nd	833rd	834th	835th	836th	837th	838th	839th	840th	841st	842nd	843rd	844th	845th	846th	847th	848th	849th	850th	851st	852nd	853rd	854th	855th	856th	857th	858th	859th	860th	861st	862nd	863rd	864th	865th	866th	867th	868th	869th	870th	871st	872nd	873rd	874th	875th	876th	877th	878th	879th	880th	881st	882nd	883rd	884th	885th	886th	887th	888th	889th	890th	891st	892nd	893rd	894th	895th	896th	897th	898th	899th	900th	901st	902nd	903rd	904th	905th	906th	907th	908th	909th	910th	911st	912nd	913rd	914th	915th	916th	917th	918th	919th	920th	921st	922nd	923rd	924th	925th	926th	927th	928th	929th	930th	931st	932nd	933rd	934th	935th	936th	937th	938th	939th	940th	941st	942nd	943rd	944th	945th	946th	947th	948th	949th	950th	951st	952nd	953rd	954th	955th	956th	957th	958th	959th	960th	961st	962nd	963rd	964th	965th	966th	967th	968th	969th	970th	971st	972nd	973rd	974th	975th	976th	977th	978th	979th	980th	981st	982nd	983rd	984th	985th	986th	987th	988th	989th	990th	991st	992nd	993rd	994th	995th	996th	997th	998th	999th	1000th	1001st	1002nd	1003rd	1004th	1005th	1006th	1007th	1008th	1009th	1010th	1011st	1012nd	1013rd	1014th	1015th	1016th	1017th	1018th	1019th	1020th	1021st	1022nd	1023rd	1024th	1025th	1026th	1027th	1028th	1029th	1030th	1031st	1032nd	1033rd	1034th	1035th	1036th	1037th	1038th	1039th	1040th	1041st	1042nd	1043rd	1044th	1045th	1046th	1047th	1048th	1049th	1050th	1051st	1052nd	1053rd	1054th	1055th	1056th	1057th	1058th	1059th	1060th	1061st	1062nd	1063rd	1064th	1065th	1066th	1067th	1068th	1069th	1070th	1071st	1072nd	1073rd	1074th	1075th	1076th	1077th	1078th	1079th	1080th	1081st	1082nd	1083rd	1084th	1085th	1086th	1087th	1088th	1089th	1090th	1091st	1092nd	1093rd	1094th	1095th	1096th	1097th	1098th	1099th	1100th	1101st	1102nd	1103rd	1104th	1105th	1106th	1107th	1108th	1109th	1110th	1111st	1112nd	1113rd	1114th	1115th	1116th	1117th	1118th	1119th	1120th	1121st	1122nd	1123rd	1124th	1125th	1126th	1127th	1128th	1129th	1130th	1131st	1132nd	1133rd	1134th	1135th	1136th	1137th	1138th	1139th	1140th	1141st	1142nd	1143rd	1144th	1145th	1146th	1147th	1148th	1149th	1150th	1151st	1152nd	1153rd	1154th	1155th	1156th	1157th	1158th	1159th	1160th	1161st	1162nd	1163rd	1164th	1165th	1166th	1167th	1168th	1169th	1170th	1171st	1172nd	1173rd	1174th	1175th	1176th	1177th	1178th	1179th	1180th	1181st	1182nd	1183rd	1184th	1185th	1186th	1187th	1188th	1189th	1190th	1191st	1192nd	1193rd	1194th	1195th	1196th	1197th	1198th	1199th	1200th	1201st	1202nd	1203rd	1204th	1205th	1206th	1207th	1208th	1209th	1210th	1211st	1212nd	1213rd	1214th	1215th	1216th	1217th	1218th	1219th	1220th	1221st	1222nd	1223rd	1224th	1225th	1226th	1227th	1228th	1229th	1230th	1231st	1232nd	1233rd	1234th	1235th	1236th	1237th	1238th	1239th	1240th	1241st	1242nd	1243rd	1244th	1245th	1246th	1247th	1248th	1249th	1250th	1251st	1252nd	1253rd	1254th	1255th	1256th	1257th	1258th	1259th	1260th	1261st	1262nd	1263rd	1264th	1265th	1266th	1267th	1268th	1269th	1270th	1271st	1272nd	1273rd	1274th	1275th	1276th	1277th	1278th	1279th	1280th	1281st	1282nd	1283rd	1284th	1285th	1286th	1287th	1288th	1289th	1290th	1291st	1292nd	1293rd	1294th	1295th	1296th	1297th	1298th	1299th	1300th	1301st	1302nd	1303rd	1304th	1305th	1306th	1307th	1308th	1309th	1310th	1311st	1312nd	1313rd	1314th	1315th	1316th	1317th	1318th	1319th	1320th	1321st	1322nd	1323rd	1324th	1325th	1326th	1327th	1328th	1329th	1330th	1331st	1332nd	1333rd	1334th	1335th	1336th	1337th	1338th	1339th	1340th	1341st	1342nd	1343rd	1344th	1345th	1346th	1347th	13
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EPI (pg/ml) MW V

[illegible]

APPENDIX H
EPINEPHRINE SAS FORMATTING PROGRAM

NOTE: COPYRIGHT (C) 1984,1986 SAS INSTITUTE INC., CARY, N.C. 27511, U.S.A.
NOTE: CMS SAS RELEASE 5.16 AT GEORGIA INSTITUTE OF TECHNOLOGY (03559001).

NOTE: CPUID VERSION = FF SERIAL = 012242 MODEL = 4381 .

NOTE: SAS OPTIONS SPECIFIED ARE:
LEAVE=0

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1 DATA TESTE;
2 CMS FILEDEF X DISK EPIN DAT A1;
3 CMS FILEDEF 20 DISK EPIN0 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
4 CMS FILEDEF 21 DISK EPIN1 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
5 CMS FILEDEF 22 DISK EPIN2 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
6 CMS FILEDEF 23 DISK EPIN3 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
7 CMS FILEDEF 24 DISK EPIN4 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
8 CMS FILEDEF 25 DISK EPIN5 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
9 CMS FILEDEF 26 DISK EPIN6 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
10 CMS FILEDEF 27 DISK EPIN7 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
11 CMS FILEDEF 28 DISK EPIN8 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
12 ARRAY WEEK {24} WKN3 WKN2 MISSN1 WK0-WK20;
13 KEEP X XSQR Y Z XZ XSQRZ CASE;
14 INFILE X;
15 INPUT CASE 1-3
16         WKN3 5-7
17         WKN2 9-11
18         WK0 13-15
19         WK1 17-19
20         WK2 21-23
21         WK3 25-27
22         WK4 29-31
23         WK5 33-35
24         WK6 37-39
25         WK7 41-43
26         WK8 45-47
27         WK9 49-51
28         WK10 53-55
29         WK11 57-59
30         WK12 61-63
31         WK13 65-67
32         WK14 69-71
33         WK15 73-75
34         WK16 77-79
35         WK17 81-83
36         WK18 85-87
37         WK19 89-91
38         WK20 93-95
39 ;
40 MISSN1=.;
41 IF CASE < 100 THEN Z = 0;
42 IF CASE >= 100 THEN Z = 1;
43 IF Z=1 THEN CASE=CASE-100;
44 DO I = 1 TO 24;
45 X = I-4; XSQR = X*X; XZ = X*Z; XSQRZ = X*X*Z; Y = WEEK {I};OUTPUT;
46 END;

```

NOTE: INFILE X IS FILE EPIN DAT A1
NOTE: 129 LINES WERE READ FROM INFILE X.

NOTE: DATA SET WORK.TESTE HAS 3096 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.59 SECONDS AND 208K.

47 PROC CONTENTS;
NOTE: THE PROCEDURE CONTENTS USED 0.20 SECONDS AND 464K AND PRINTED PAGES 1 TO 2.

48 PROC PRINTTO NEW UNIT=20;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

49 PROC SORT OUT=SCTR;
50 BY Z X Y;

NOTE: DATA SET WORK.SCTR HAS 3096 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE PROCEDURE SORT USED 0.76 SECONDS AND 6928K.

51 PROC SUMMARY;
52 BY Z X;
53 VAR Y;
54 OUTPUT OUT=OVLN MEAN=MEAN;
NOTE: THE DATA SET WORK.OVLN HAS 48 OBSERVATIONS AND 5 VARIABLES.
NOTE: THE PROCEDURE SUMMARY USED 0.56 SECONDS AND 464K.

55 DATA SEPIN;
56 SET SCTR OVLN;
57 BY Z;

NOTE: DATA SET WORK.SEPIN HAS 3144 OBSERVATIONS AND 10 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.67 SECONDS AND 336K.

58 PROC PLOT NOLEGEND DATA=SEPIN;
59 BY Z;
60 PLOT MEAN*X='X' Y*X='.' / HAXIS=-3 TO 20 BY 1 VAXIS=50 TO 250 BY 25 OVERLAY
61 ;
62 TITLE 'EPINEPHRINE SCATTER DIAGRAM';
NOTE: THE PROCEDURE PLOT USED 0.65 SECONDS AND 464K AND PRINTED PAGES 3 TO 4.

63 PROC PRINTTO NEW UNIT=21;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

64 PROC PLOT NOLEGEND DATA=SEPIN;
65 PLOT MEAN*X='X' / HAXIS=-3 TO 20 BY 1 VAXIS=50 TO 250 BY 25;
66 TITLE 'Mean Epinephrine Concentration Versus Time';
NOTE: THE PROCEDURE PLOT USED 0.46 SECONDS AND 464K AND PRINTED PAGE 5.

67 PROC PRINTTO NEW UNIT=22;
68 TITLE 'CATECHOLAMINE ANALYSIS: Epinephrine';

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

69 PROC DATASETS;
70
LIST OF MEMBERS BEFORE UPDATE OF DIRECTORY.

NAME	MEMTYPE	OBS	TRACKS	PROT
OVLN	DATA	48	1	
SCTR	DATA	3096	1	
SEPIN	DATA	3144	1	

TESTE /DATA 3096 1

70 DELETE SCTR;
71 DELETE OVLMN;

LIST OF MEMBERS AFTER UPDATE OF DIRECTORY.

NAME	MEMTYPE	OBS	TRACKS	PROT
SEPIN	/DATA	3144	1	
TESTE	/DATA	3096	1	

NOTE: THE PROCEDURE DATASETS USED 0.12 SECONDS AND 464K.

72 PROC STEPWISE;

73 MODEL Y = X XSQR Z XZ XSQRZ / SLENTRY=0.095 SLSTAY=0.095 STEPWISE MAXR;

NOTE: THE PROCEDURE STEPWISE USED 0.57 SECONDS AND 464K AND PRINTED PAGES 6 TO 8.

74 PROC PRINTTO NEW UNIT=23;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

75 PROC REG;

76 MODEL Y = X XSQR / PARTIAL;

77 ID CASE;

NOTE: ACOV AND SPEC OPTION ONLY VALID WITH RAWDATA

NOTE: THE PROCEDURE REG USED 1.76 SECONDS AND 656K AND PRINTED PAGES 9 TO 12.

78 PROC PRINTTO NEW UNIT=24;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

79 PROC GLM;

80 CLASS X Z;

81 MODEL Y = X X*X X*Z;

NOTE: THE PROCEDURE GLM USED 3.10 SECONDS AND 1040K AND PRINTED PAGES 13 TO 14.

82 PROC PRINTTO NEW UNIT=25;

```

83 *-----*
84 *
85 *   to obtain tables listing the variance inflation factors,
86 *   influence statistics, and tolerances, the following SAS
87 *   statements were used in this partition:
88 *
89 *   PROC REG;
90 *       MODEL Y = X XSQR / TOL VIF INFLUENCE;
91 *       ID CASE;
92 *       OUTPUT OUT=REPIN P=PREDICT R=RESID STUDENT=STUDENT;
93 *
94 *-----*

```

NOTE: THE PROCEDURE PRINTTO USED 0.04 SECONDS AND 336K.

85 PROC REG;

86 MODEL Y = X XSQR / I SS1 SS2 STB COVB CORRB SEQB COLLIN
87 COLLINOINT ACOV P R CLM;

88 ID CASE;

89 OUTPUT OUT=REPIN P=PREDICT R=RESID STUDENT=STUDENT;

90 THE DATA SET WORK.REPIN HAS 3144 OBSERVATIONS AND 13 VARIABLES.

91 THE PROCEDURE REG USED 6.93 SECONDS AND 656K AND PRINTED PAGES 15 TO 82.

92 PROC PRINTTO NEW UNIT=26;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

```
101 PROC PLOT DATA=REPIN;  
102     PLOT RESID*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-150 TO 150 BY 25;  
103     PLOT RESID*PREDICT='*' / HAXIS=115 TO 185 BY 5 VAXIS=-150 TO 150 BY 25;  
104     PLOT STUDENT*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-4 TO 5 BY 0.5;  
105     PLOT STUDENT*PREDICT='*' / HAXIS=115 TO 185 BY 5 VAXIS=-4 TO 5 BY 0.5;  
106     TITLE 'EPINEPHRINE RESIDUAL PLOTS';
```

NOTE: THE PROCEDURE PLOT USED 0.95 SECONDS AND 464K AND PRINTED PAGES 83 TO 86.

```
107 PROC PRINTTO NEW UNIT=27;
```

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

```
108 PROC PLOT DATA=REPIN;  
109     BY Z;  
110     PLOT RESID*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-150 TO 150 BY 25;  
111     PLOT STUDENT*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-4 TO 5 BY 0.5;  
112     TITLE 'EPINEPHRINE RESIDUAL PLOTS';
```

NOTE: THE PROCEDURE PLOT USED 0.79 SECONDS AND 464K AND PRINTED PAGES 87 TO 90.

```
113 PROC PRINTTO NEW UNIT=28;
```

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 336K.

```
114 PROC AUTOREG;  
115     TITLE 'Epinephrine Autoregressive Models';  
116     MODEL Y = X XSQR / COEF CORRB COVB BACKSTEP;  
117     MODEL Y = X XSQR / NLAG=1 COEF CORRB COVB BACKSTEP;  
118     MODEL Y = X XSQR / NLAG=2 COEF CORRB COVB BACKSTEP;  
119     MODEL Y = X XSQR / NLAG=3 COEF CORRB COVB BACKSTEP;  
120     MODEL Y = X XSQR / NLAG=4 COEF CORRB COVB BACKSTEP;
```

NOTE: THE PROCEDURE AUTOREG USED 6.92 SECONDS AND 464K AND PRINTED PAGES 91 TO 103.

NOTE: SAS USED 6928K MEMORY.

NOTE: SAS INSTITUTE INC.
SAS CIRCLE
PO BOX 8000
CARY, N.C. 27511-8000

APPENDIX I

STEPWISE AND MAXIMUM R^2 REGRESSION
PROCEDURES USED TO BUILD EPINEPHRINE MODEL

9:41 WEDNESDAY, JULY 15, 1987

CATECHOLAMINE ANALYSIS: Epinephrine

STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

WARNING: 2550 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1	VARIABLE X ENTERED	R SQUARE = 0.08730405	C(P) = 35.09383984
	DF	SUM OF SQUARES	MEAN SQUARE
REGRESSION	1	197141.55027836	197141.55027836
ERROR	592	2060961.61470481	3481.35407889
TOTAL	593	2258103.16498316	
	B VALUE	STD ERROR	TYPE II SS
INTERCEPT	158.81632525		
X	-2.55984031	0.34017147	197141.55027836
			56.63
			0.0001

BOUNDS ON CONDITION NUMBER: 1, 1

STEP 2	VARIABLE XSQR ENTERED	R SQUARE = 0.12078896	C(P) = 14.16045333
	DF	SUM OF SQUARES	MEAN SQUARE
REGRESSION	2	272753.92439253	136376.96219626
ERROR	591	1985349.24059064	3359.30497562
TOTAL	593	2258103.16498316	
	B VALUE	STD ERROR	TYPE II SS
INTERCEPT	158.79893544		
X	-6.66208019	0.92698997	173507.82846438
XSQR	0.28169664	0.05937586	75612.37411417
			51.65
			22.51
			0.0001
			0.0001

BOUNDS ON CONDITION NUMBER: 7.695787, 30.78315

NO OTHER VARIABLES MET THE 0.0950 SIGNIFICANCE LEVEL FOR ENTRY INTO THE MODEL.

SUMMARY OF STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

STEP	VARIABLE ENTERED	VARIABLE REMOVED	NUMBER IN	PARTIAL R ²	MODEL R ²	C(P)	F	PROB>F
1	X		1	0.0873	0.0873	35.0938	56.6278	0.0001
2	XSQR		2	0.0335	0.1208	14.1605	22.5083	0.0001

CATECHOLAMINE ANALYSIS: Epinephrine

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

WARNING: 2550 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1	VARIABLE X ENTERED	R SQUARE = 0.08730405	C(P) = 35.09383984
REGRESSION	DF	SUM OF SQUARES	MEAN SQUARE
ERROR	1	197141.55027836	197141.55027836
TOTAL	592	2060961.61470481	3481.35407889
	593	2258103.16498316	56.63
			0.0001
INTERCEPT	B VALUE	STD ERROR	TYPE II SS
X	158.81632525		F
	-2.55984031	0.34017147	56.63
		197141.55027836	0.0001
BOUNDS ON CONDITION NUMBER:	1.	1	

THE ABOVE MODEL IS THE BEST 1 VARIABLE MODEL FOUND.

STEP 2	VARIABLE XSQR ENTERED	R SQUARE = 0.12078896	C(P) = 14.16045333
REGRESSION	DF	SUM OF SQUARES	MEAN SQUARE
ERROR	2	272753.92439253	136376.96219626
TOTAL	591	1985349.24059064	3359.30497562
	593	2258103.16498316	40.60
			0.0001
INTERCEPT	B VALUE	STD ERROR	TYPE II SS
X	158.79893544		F
	-6.66208019	0.92698997	51.65
XSQR	0.28169664	0.05937586	22.51
		173507.82846438	0.0001
		75612.37411417	0.0001
BOUNDS ON CONDITION NUMBER:	7.695787,	30.78315	

THE ABOVE MODEL IS THE BEST 2 VARIABLE MODEL FOUND.

STEP 3	VARIABLE Z ENTERED	R SQUARE = 0.12483461	C(P) = 13.38963753
REGRESSION	DF	SUM OF SQUARES	MEAN SQUARE
ERROR	3	281889.42478648	93963.14159549
TOTAL	590	1976213.74019668	3349.51481389
	593	2258103.16498316	28.05
			0.0001
INTERCEPT	B VALUE	STD ERROR	TYPE II SS
X	154.93778668		F
	-6.63711697	0.92576161	51.40
XSQR	0.27971980	0.05930136	22.25
Z	7.84556183	4.75060400	2.73
		9135.50039395	0.0992
BOUNDS ON CONDITION NUMBER:	7.698924,	49.19166	

CATECHOLAMINE ANALYSIS: Epinephrine

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

THE ABOVE MODEL IS THE BEST 3 VARIABLE MODEL FOUND.

STEP 4	VARIABLE XZ ENTERED	DF	B VALUE	SUM OF SQUARES	R SQUARE = 0.14101088	C(P) = 4.31071813	F	PROB>F
REGRESSION		4		318417.10455811	79604.27613953		24.17	0.0001
ERROR		589		1939686.06042506	3293.18516201			
TOTAL		593		2258103.16498316				
		B VALUE	STD ERROR	TYPE II SS	F	PROB>F		
INTERCEPT		148.62241564		99820.52761921	30.31	0.0001		
X		-5.43217501	0.98666994	71099.68782579	21.59	0.0001		
XSQR		0.27336090	0.05883160	37751.60148760	11.46	0.0008		
Z		20.47384481	6.04699754	36527.67977163	11.09	0.0009		
XZ		-2.20506461	0.66209202					

BOUNDS ON CONDITION NUMBER: 8.893651, 83.71208

THE ABOVE MODEL IS THE BEST 4 VARIABLE MODEL FOUND.

STEP 5	VARIABLE XSQRZ ENTERED	DF	B VALUE	SUM OF SQUARES	R SQUARE = 0.14146455	C(P) = 6.00000000	F	PROB>F
REGRESSION		5		319441.55576601	63888.31115320		19.38	0.0001
ERROR		588		1938661.60921715	3297.04355309			
TOTAL		593		2258103.16498316				
		B VALUE	STD ERROR	TYPE II SS	F	PROB>F		
INTERCEPT		148.67993274		67481.07929095	20.47	0.0001		
X		-5.90883059	1.30608930	45121.59874017	13.69	0.0002		
XSQR		0.3058514	0.08263127	37776.13355382	11.46	0.0008		
Z		20.48053628	6.05055083	1523.45896043	0.46	0.4969		
XZ		-1.24939073	1.83799887	1024.45120791	0.31	0.5775		
XSQRZ		-0.06563374	0.11774537					

BOUNDS ON CONDITION NUMBER: 20.6184, 363.4548

THE ABOVE MODEL IS THE BEST 5 VARIABLE MODEL FOUND.

APPENDIX J
EPINEPHRINE LACK-OF-FIT TEST

9:41 WEDNESDAY, JULY 15, 1987

CATECHOLAMINE ANALYSIS: Epinephrine
GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: Y

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE
MODEL	37	425141.48629790	11490.31044048	3.49	0.0001	0.188274
ERROR	556	1832961.67868527	3296.69366670			
CORRECTED TOTAL	593	2258103.16498317				

SOURCE	DF	TYPE I SS	F VALUE	PR > F	DF	TYPE III SS	F VALUE
X	19	348054.66052419	5.56	0.0001	19	328774.50250746	5.25
X*Z	18	77086.82577371	1.30	0.1818	18	77086.82577371	1.30

ROOT MSE
57.41684132

this term is solely a measure of sum-of-squares pure error.

CATECHOLAMINE ANALYSIS: Epinephrine

ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB>F
MODEL	2	272753.92	136376.96	40.597	0.0001
ERROR	591	1985349.24	3359.30498		
C TOTAL	593	2258103.16			

ROOT MSE 57.95951
DEP MEAN 144.1684
C.V. 40.20266

PARAMETER ESTIMATES

VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR HO: PARAMETER=0	PROB > T
INTERCEP	1	158.79894	3.05148810	52.040	0.0001
X	1	-6.66208019	0.92698997	-7.187	0.0001
XSOR	1	0.28169564	0.05937586	4.744	0.0001

this term contains both sum-of-squares pure error and sum-of-squares lack-of-fit.

Partitioning SS_E into SS_{pe} and SS_{lof}

$$SS_E = 1985349.24 \quad df = 591$$

$$SS_{pe} = 1832961.68 \quad df = 556$$

$$SS_{lof} = 152387.56 \quad df = 35$$

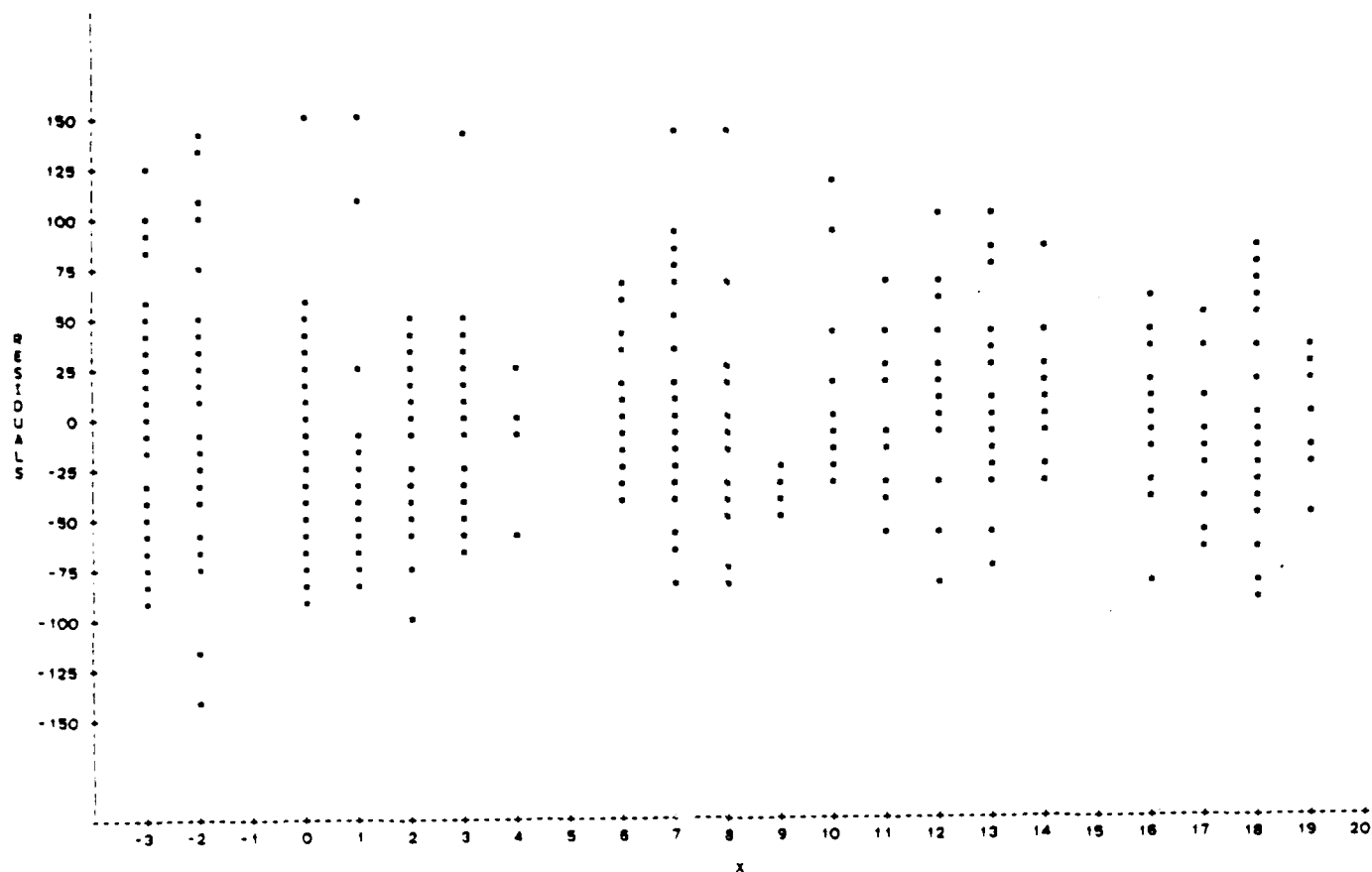
$$MS_{lof} = 4353.93$$

$$MS_{pe} = 3296.69$$

$$F_0 = \frac{MS_{lof}}{MS_{pe}} = 1.3207$$

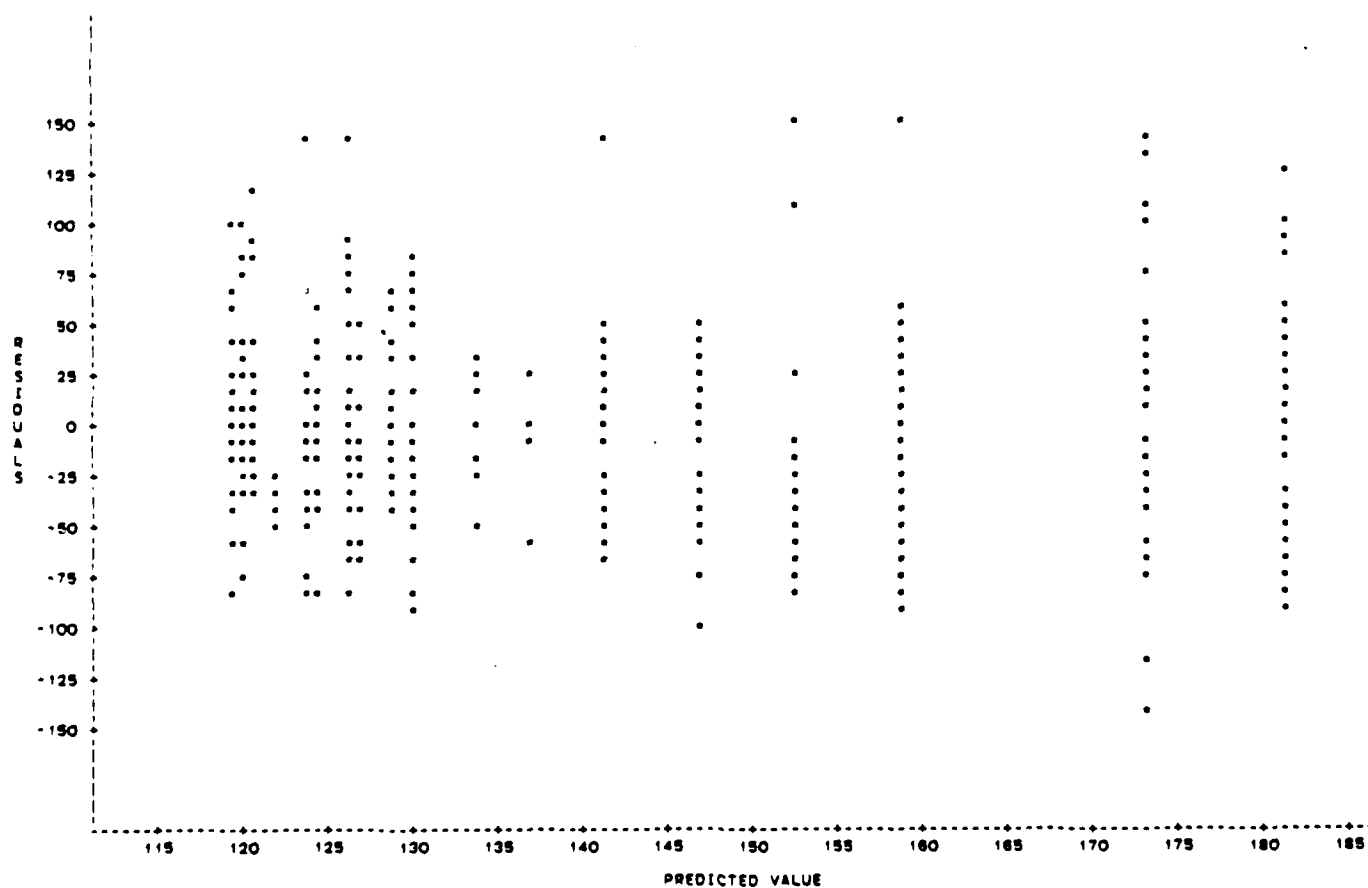
$$F_{0.10, 35, 556} \sim 1.38$$

APPENDIX K
EPINEPHRINE RESIDUAL PLOTS



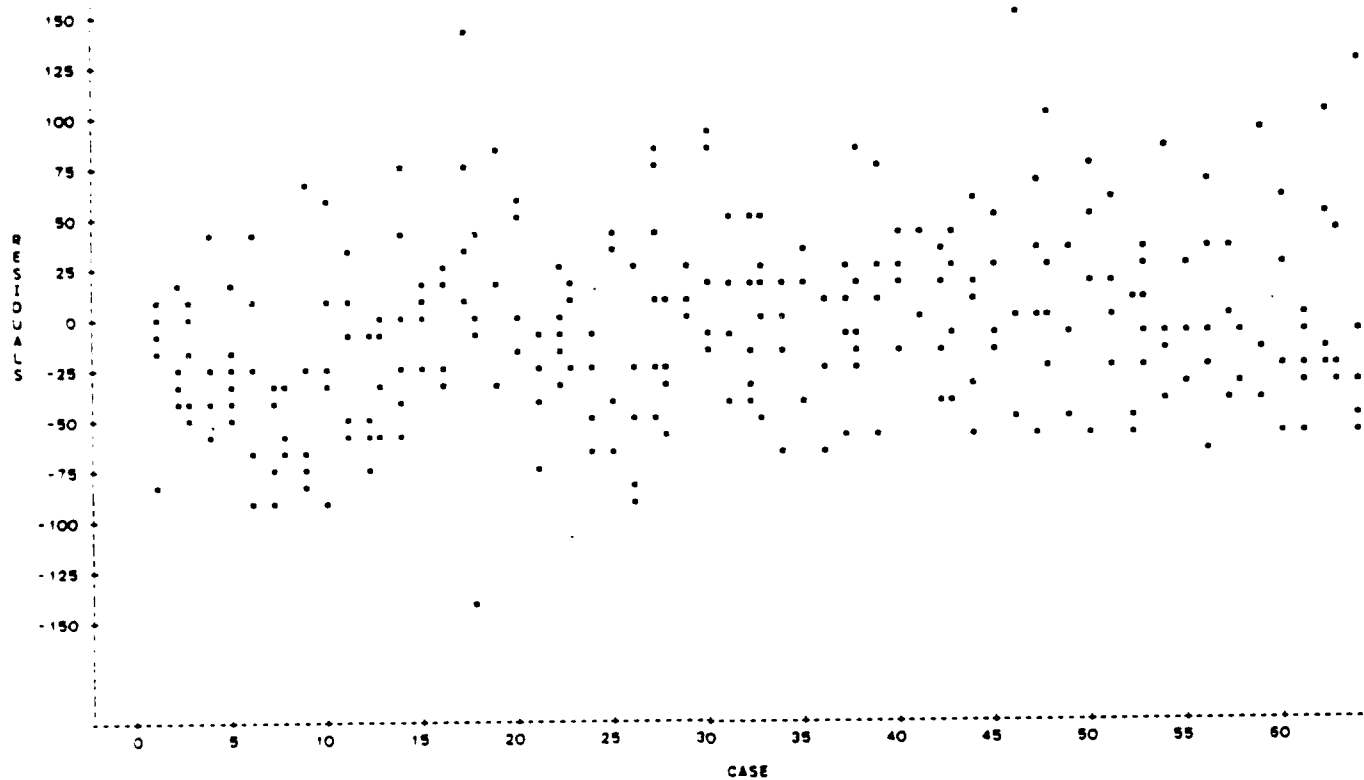
NOTE 2562 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 329 OBS HIDDEN

Residuals versus time.



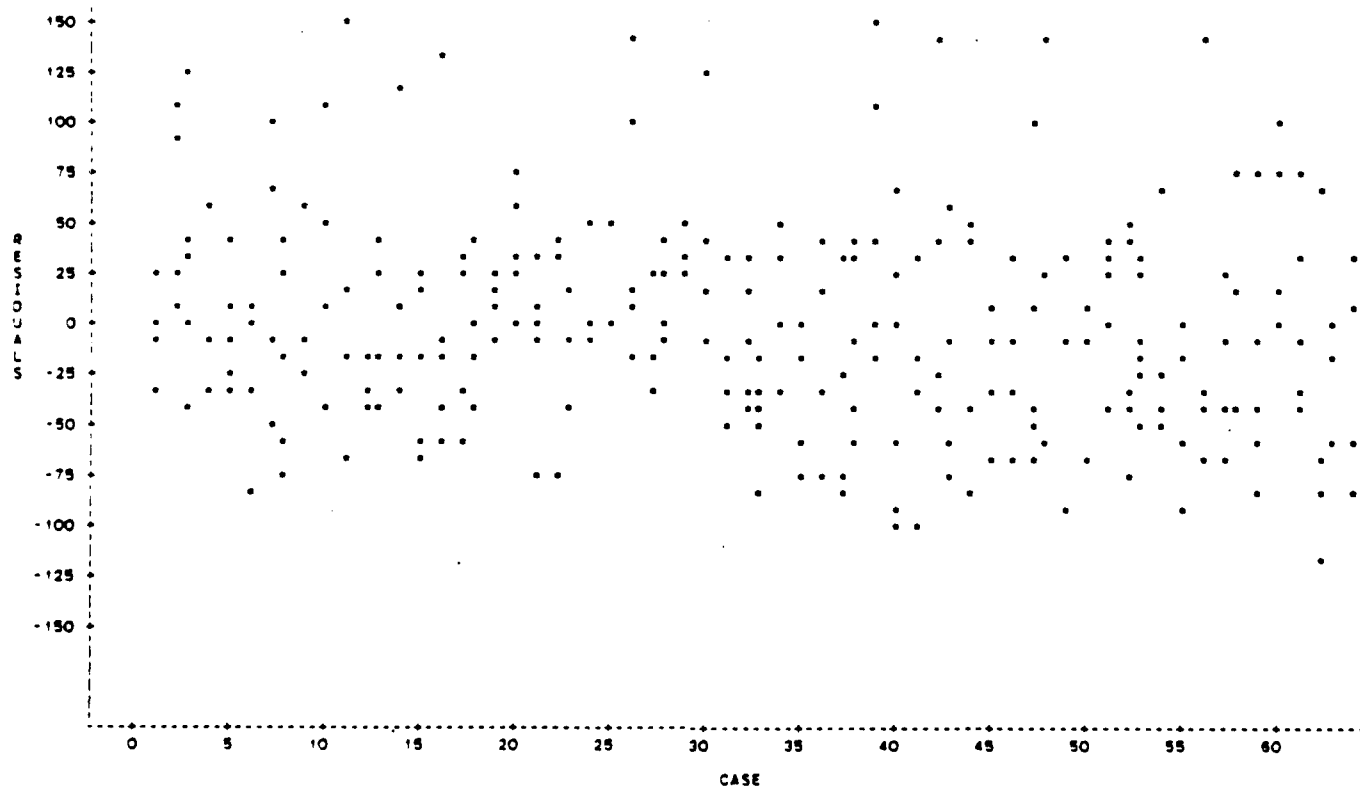
NOTE: 2562 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 342 OBS HIDDEN

Residuals versus predicted value of plasma epinephrine concentration.



NOTE 1265 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

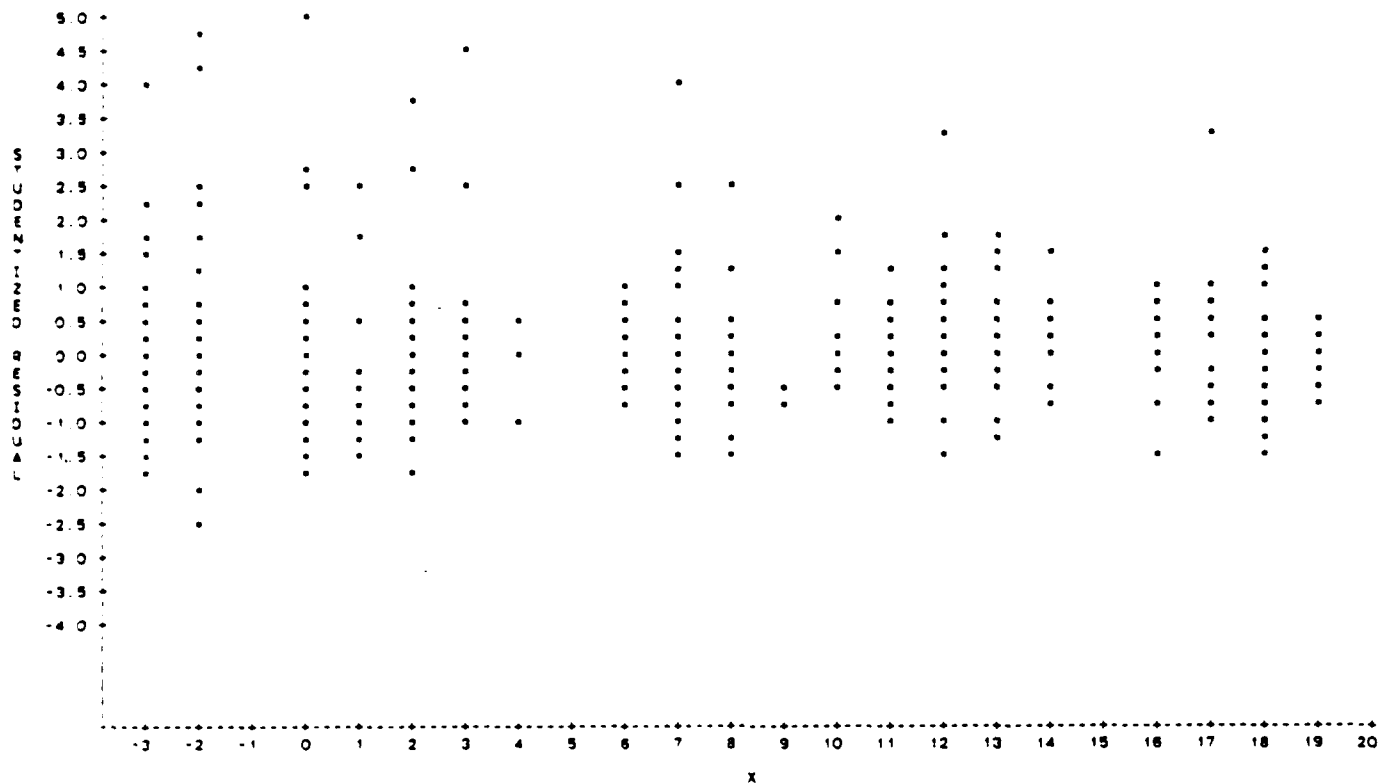
33 OBS HIDDEN

Residuals versus animal ID number
(sham-exposure group).

NOTE 1297 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

20 OBS HIDDEN

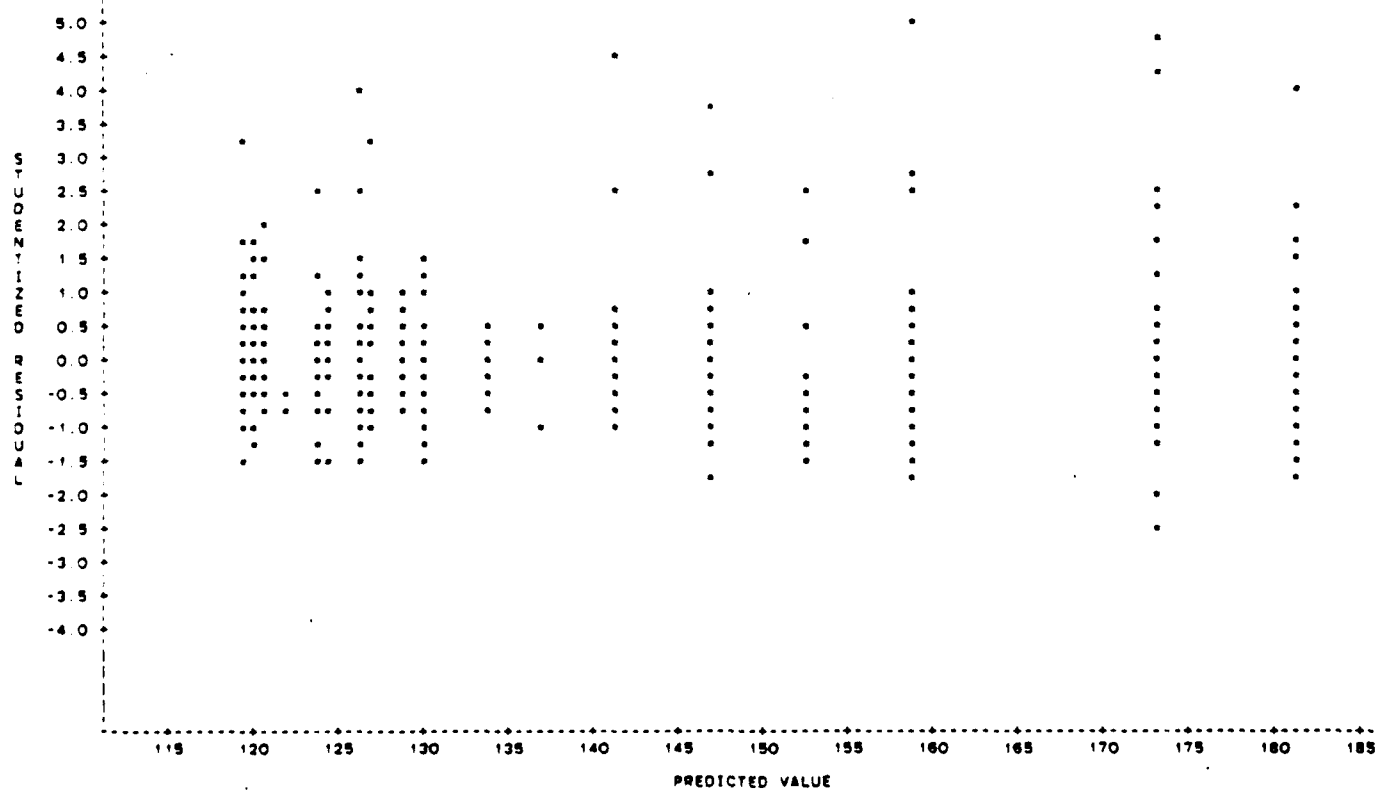
Residuals versus animal ID number
(exposure group).



NOTE 2550 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

396 OBS HIDDEN

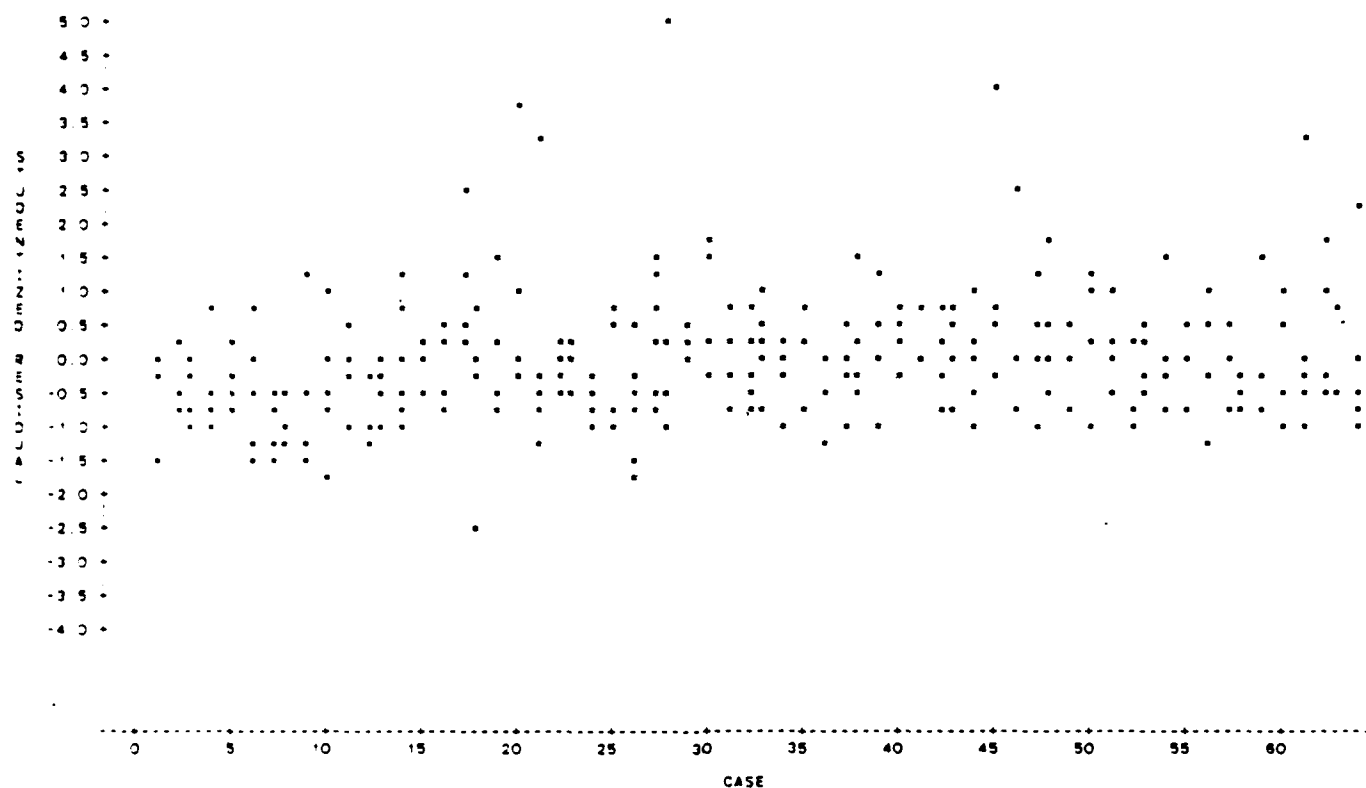
Studentized residuals versus time.



NOTE 2550 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

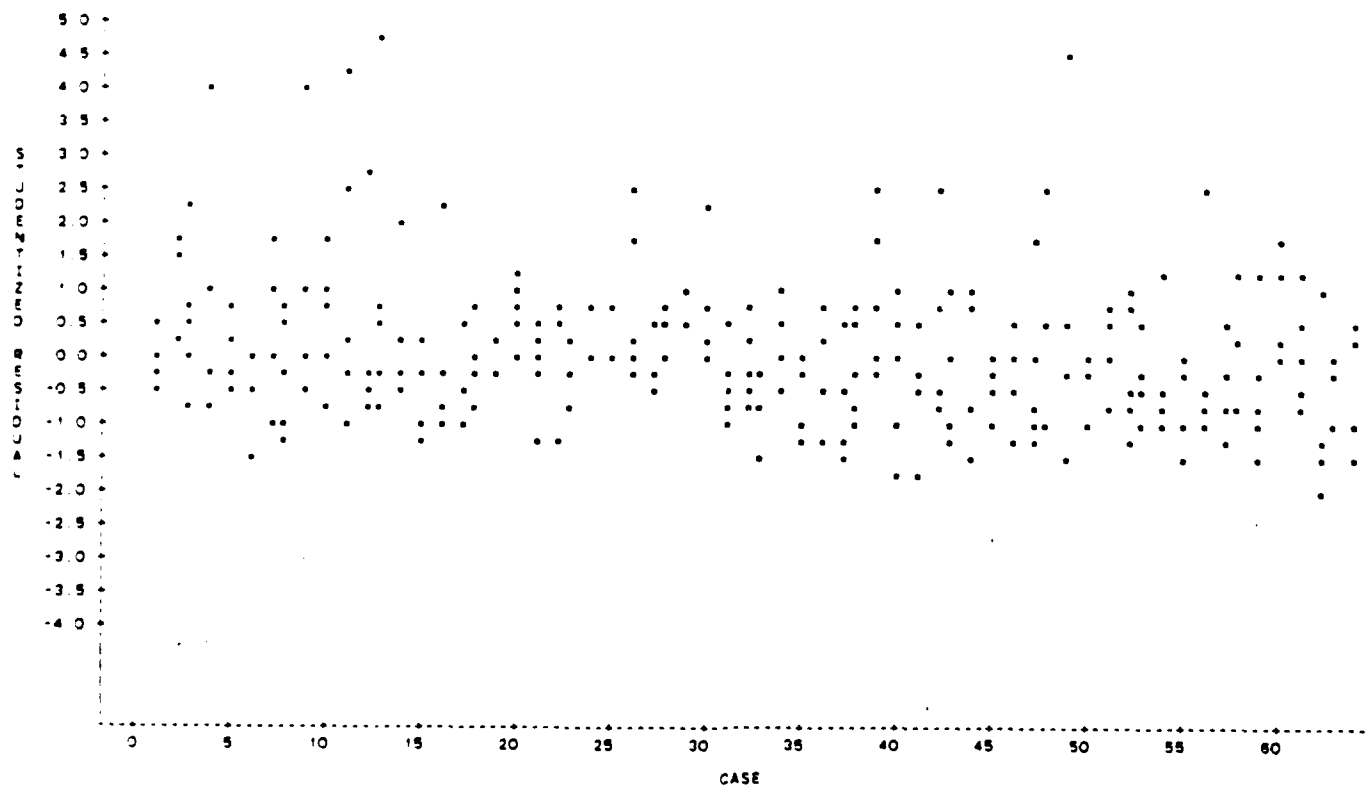
409 OBS HIDDEN

Studentized residuals versus predicted
value of plasma epinephrine concentration.



NOTE 1260 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

50 OBS HIDDEN

Studentized residuals versus animal ID
number (sham-exposure group).

NOTE 1290 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

37 OBS HIDDEN

Studentized residuals versus animal ID
number (exposure group).

APPENDIX L

RAW DOPAMINE DATA SPREADSHEETS

AD-A188 255

LONG-TERM BIOEFFECTS OF 435-MHZ RADIOFREQUENCY
RADIATION ON SELECTED BLOOD (U) GEORGIA TECH RESEARCH
INST ATLANTA V P POPOVIC ET AL AUG 87

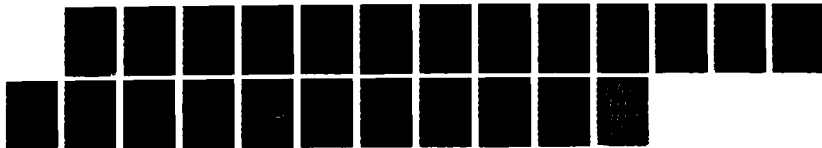
2/2

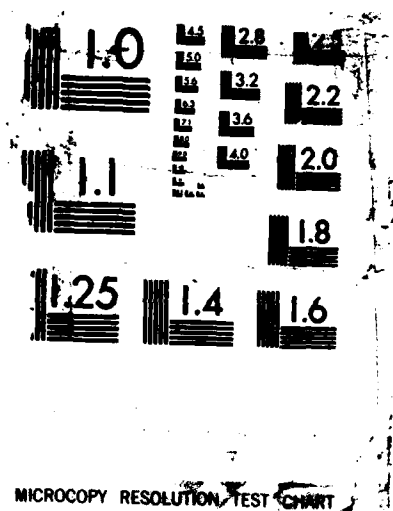
UNCLASSIFIED

USAFSAM-TR-87-11 F33615-83-K-0600

F/G 6/5

NL





DA control I

Set #	Group	TIME	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd	24th	25
1	31	65	58					18			57						30										
2	107	161	102					16			-						81										
3	-	64	22					4			-						37										
4	103	81	19					27			14						14										
5	160	71	159					-			59						19										
6	18	44	5					34			-						15										
7	86	120	46					6			59						24										
8	21	101	113					10			-						44										
9	16	42	61					-					47				10										
10	-	6	-					27			-						24										
11	61	41	18					27			-						15										
12	32	19	-					19			59						22										
13	84	23	27					36					31				37										

DA control II

Set #	Group	TIME	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th	21st	22nd	23rd	24th	25
14		160	34	18				19				160					91										
15		56	79	40				41				-					70										
16		43	-	31				37				20					21										
17		71	-	22				19				-					55										
18		95	60	22				-				13					62										
19	29	35	-					16				-					14										
20	-	35	19					14				28					20										
21	201	60	41					113				19					11										
22	18	84		-						20				-			7										
23	102	-		23						22				25			38										
24	48	61		20						-				-			21										
25	42	29		-						26				122			65										
26	26	18		18						19				12			20										

DA control III

Bat #	Group	TIME																								Σ	s
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
27		44	81		32		34								17												
28		27	49		61		24								-					49							
29		61	-		27		40								31					27							
30		18	38		44		61								-					14							
31		41	39		24		7								44					8							
32		44	47		-		68							31						12							
33		29	-		38		27							-						-							
34		-	44	62						9				22						16							
35		-	64	6						40				-						44							
36		81	-	18						50				31						70							
37		56	59	42						-				42						11							
38		-	40	8						31				-						14							
39		44	61	35						31				-						-							

DA control IV

Bat #	Group	TIME																								Σ	s
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24		
40		-	61		113					24			24							49							
41		-	38		-					41			-							14							
42		61	114		61					-			24							-							
43		44	91		9					15			-							27							
44		-	26		-					43			36							18							
45		34	-		4					64			41							-							
46		29	113		-					21			41							25							
47		61	-		31					12			-							15							
48		-	75		70					43			-							13							
49		38	61		-					86			95							20							
50		42	48		29					-			41							44							
51		27	92		-					-			31							20							
52		-	48		18					29			-							41							

DA control $\bar{V}$

[illegible]

DA MWI

[illegible]

DA MIV II

[illegible]

DA ^{MIN} ~~CHARTER~~ II

[illegible]

DA ~~14W~~ IV

[illegible]

DA ^{MW} ~~control~~ V

Set #	Group	TIME																Σ	s
		JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE	JUNE			
53		411	70		-				21				31			21			
54		17	24		18				-				31			20			
55		-	58		-				6				-			-			
56		28	-		21				23				73			18			
57		-	38		-				23				-			24			
58		14	38		36				48				21			-			
59		55	-		8				12				24			18			
60		-	48		12				-				16			-			
61		40	50		-				22				-			25			
62		37	60		31				18				21			18			
63		50	-		26				34				11			23			
64		-	41		28				12				19			11			

APPENDIX M
DOPAMINE SAS FORMATTING PROGRAM

NOTE: COPYRIGHT (C) 1984,1986 SAS INSTITUTE INC., CARY, N.C. 27511, U.S.A.
NOTE: CMS SAS RELEASE 5.16 AT GEORGIA INSTITUTE OF TECHNOLOGY (03559001).

NOTE: CPUID VERSION = FF SERIAL = 012242 MODEL = 4381 .

NOTE: SAS OPTIONS SPECIFIED ARE:
LEAVE=0

```

1 DATA TESTD;
2 CMS FILEDEF X DISK DOPAMIN DAT A1;
3 CMS FILEDEF 20 DISK DOPAMIN0 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
4 CMS FILEDEF 21 DISK DOPAMIN1 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
5 CMS FILEDEF 22 DISK DOPAMIN2 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
6 CMS FILEDEF 23 DISK DOPAMIN3 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
7 CMS FILEDEF 24 DISK DOPAMIN4 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
8 CMS FILEDEF 25 DISK DOPAMIN5 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
9 CMS FILEDEF 26 DISK DOPAMIN6 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
10 CMS FILEDEF 27 DISK DOPAMIN7 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
11 CMS FILEDEF 28 DISK DOPAMIN8 LISTING A1 ( BLKSIZE 141 RECFM VBA LRECL 133;
12 ARRAY WEEK {24} WKN3 WKN2 MISSN1 WK0-WK20;
13 KEEP X XSQR Y Z XZ XSQRZ CASE;
14 INFILE X;
15 INPUT CASE 1-3
16      WKN3 5-7
17      WKN2 9-11
18      WK0 13-15
19      WK1 17-19
20      WK2 21-23
21      WK3 25-27
22      WK4 29-31
23      WK5 33-35
24      WK6 37-39
25      WK7 41-43
26      WK8 45-47
27      WK9 49-51
28      WK10 53-55
29      WK11 57-59
30      WK12 61-63
31      WK13 65-67
32      WK14 69-71
33      WK15 73-75
34      WK16 77-79
35      WK17 81-83
36      WK18 85-87
37      WK19 89-91
38      WK20 93-95
39 ;
40 MISSN1=.;
41 IF CASE < 100 THEN Z = 0;
42 IF CASE >= 100 THEN Z = 1;
43 IF Z=1 THEN CASE=CASE-100;
44 DO I = 1 TO 24;
45 X = I-4; XSQR = X*X; XZ = X*Z; XSQRZ = X*X*Z; Y = WEEK {I};OUTPUT;
46 END;

```

NOTE: INFILE X IS FILE DOPAMIN DAT A1
NOTE: 128 LINES WERE READ FROM INFILE X.

NOTE: DATA SET WORK.TESTD HAS 3072 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.58 SECONDS AND 252K.

47 PROC CONTENTS;
NOTE: THE PROCEDURE CONTENTS USED 0.20 SECONDS AND 316K AND PRINTED PAGES 1 TO 2.

48 PROC PRINTTO NEW UNIT=20;
NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

49 PROC SORT OUT=SCTR;
50 BY Z X Y;
NOTE: DATA SET WORK.SCTR HAS 3072 OBSERVATIONS AND 7 VARIABLES.
NOTE: THE PROCEDURE SORT USED 0.78 SECONDS AND 6908K.

51 PROC SUMMARY;
52 BY Z X;
53 VAR Y;
54 OUTPUT OUT=OVL MN MEAN=MEAN;
NOTE: THE DATA SET WORK.OVL MN HAS 48 OBSERVATIONS AND 5 VARIABLES.
NOTE: THE PROCEDURE SUMMARY USED 0.57 SECONDS AND 444K.

55 DATA SDOPAMIN;
56 SET SCTR OVL MN;
57 BY Z;
NOTE: DATA SET WORK.SDOPAMIN HAS 3120 OBSERVATIONS AND 10 VARIABLES.
NOTE: THE DATA STATEMENT USED 0.57 SECONDS AND 316K.

58 PROC PLOT NOLEGEND DATA=SDOPAMIN;
59 BY Z;
60 PLOT MEAN*X='X' Y*X='.' / HAXIS=-3 TO 20 BY 1 VAXIS=0 TO 100 BY 10 OVERLAY;
61 TITLE 'DOPAMINE SCATTER DIAGRAM';
NOTE: THE PROCEDURE PLOT USED 0.66 SECONDS AND 444K AND PRINTED PAGES 3 TO 4.

62 PROC PRINTTO NEW UNIT=21;
NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

63 PROC PLOT NOLEGEND DATA=SDOPAMIN;
64 PLOT MEAN*X='X' / HAXIS=-3 TO 20 BY 1 VAXIS=0 TO 100 BY 10;
65 TITLE 'Mean Dopamine Concentration Versus Time';
NOTE: THE PROCEDURE PLOT USED 0.47 SECONDS AND 444K AND PRINTED PAGE 5.

66 PROC PRINTTO NEW UNIT=22;
67 TITLE 'CATECHOLAMINE ANALYSIS: Dopamine';
NOTE: THE PROCEDURE PRINTTO USED 0.03 SECONDS AND 316K.

68 PROC DATASETS;
69
LIST OF MEMBERS BEFORE UPDATE OF DIRECTORY.
NAME MEMTYPE OBS TRACKS PROT
OVL MN /DATA 48 1
SCTR /DATA 3072 1
SDOPAMIN/DATA 3120 1
TESTD /DATA 3072 1

69 DELETE SCTR;
70 DELETE OVLMN;

LIST OF MEMBERS AFTER UPDATE OF DIRECTORY.

NAME	MEMTYPE	OBS	TRACKS	PROT
SDOPAMIN/DATA		3120	1	
TESTD /DATA		3072	1	

NOTE: THE PROCEDURE DATASETS USED 0.12 SECONDS AND 444K.

71 PROC STEPWISE;

72 MODEL Y = X XSQR Z XZ XSQRZ / SLENTY=0.10 SLSTAY=0.10 STEPWISE MAXR;

NOTE: THE PROCEDURE STEPWISE USED 0.60 SECONDS AND 444K AND PRINTED PAGES 6 TO 9.

73 PROC PRINTTO NEW UNIT=23;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

74 PROC REG;

75 MODEL Y = X XSQR XZ / PARTIAL;

76 ID CASE;

NOTE: ACOV AND SPEC OPTION ONLY VALID WITH RAWDATA

NOTE: THE PROCEDURE REG USED 1.64 SECONDS AND 636K AND PRINTED PAGES 10 TO 14.

77 PROC PRINTTO NEW UNIT=24;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

78 PROC GLM;

79 CLASS X Z;

80 MODEL Y = X X*X X*Z;

NOTE: THE PROCEDURE GLM USED 3.20 SECONDS AND 1020K AND PRINTED PAGES 15 TO 16.

81 PROC PRINTTO NEW UNIT=25;

```

82 *-----*
83 *
84 *   to obtain tables listing the variance inflation factors,
85 *   influence statistics, and tolerances, the following SAS
86 *   statements were used in this partition:
87 *
88 *   PROC REG;
89 *       MODEL Y = X XSQR XZ / TOL VIF INFLUENCE;
90 *       ID CASE;
91 *       OUTPUT OUT=RDOPAMIN P=PREDICT R=RESID STUDENT=STUDENT;
92 *
93 *-----*

```

NOTE: THE PROCEDURE PRINTTO USED 0.04 SECONDS AND 316K.

94 PROC REG;

95 MODEL Y = X XSQR XZ / I SS1 SS2 STB COVB CORR B SEQB COLLIN

96 COLLINOINT ACOV P R CLM;

97 ID CASE;

98 OUTPUT OUT=RDOPAMIN P=PREDICT R=RESID STUDENT=STUDENT;

NOTE: THE DATA SET WORK.RDOPAMIN HAS 3120 OBSERVATIONS AND 13 VARIABLES.

NOTE: THE PROCEDURE REG USED 7.33 SECONDS AND 636K AND PRINTED PAGES 17 TO 83.

99 PROC PRINTTO NEW UNIT=26;

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

```
100 PROC PLOT DATA=RDOPAMIN;
101     PLOT RESID*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-125 TO 125 BY 25;
102     PLOT RESID*PREDICT='*' / HAXIS=15 TO 65 BY 5 VAXIS=-125 TO 125 BY 25;
103     PLOT STUDENT*X='*' / HAXIS=-3 TO 20 BY 1 VAXIS=-2 TO 6 BY 0.5;
104     PLOT STUDENT*PREDICT='*' / HAXIS=15 TO 65 BY 5 VAXIS=-2 TO 6 BY 0.5;
105     TITLE 'DOPAMINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 0.96 SECONDS AND 444K AND PRINTED PAGES 84 TO 87.
```

```
106 PROC PRINTTO NEW UNIT=27;
```

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

```
107 PROC PLOT DATA=RDOPAMIN;
108     BY Z;
109     PLOT RESID*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-125 TO 125 BY 25;
110     PLOT STUDENT*CASE='*' / HAXIS=0 TO 65 BY 5 VAXIS=-2 TO 6 BY 0.5;
111     TITLE 'DOPAMINE RESIDUAL PLOTS';
NOTE: THE PROCEDURE PLOT USED 0.79 SECONDS AND 444K AND PRINTED PAGES 88 TO 91.
```

```
112 PROC PRINTTO NEW UNIT=28;
```

NOTE: THE PROCEDURE PRINTTO USED 0.02 SECONDS AND 316K.

```
113 PROC AUTOREG;
114     TITLE 'Dopamine Autoregressive Models';
115     MODEL Y = X XSQR XZ / COEF CORRB COVB BACKSTEP;
116     MODEL Y = X XSQR XZ / NLAG=1 COEF CORRB COVB BACKSTEP;
117     MODEL Y = X XSQR XZ / NLAG=2 COEF CORRB COVB BACKSTEP;
118     MODEL Y = X XSQR XZ / NLAG=3 COEF CORRB COVB BACKSTEP;
119     MODEL Y = X XSQR XZ / NLAG=4 COEF CORRB COVB BACKSTEP;
NOTE: THE PROCEDURE AUTOREG USED 6.82 SECONDS AND 444K AND PRINTED PAGES 92 TO 104.
NOTE: SAS USED 6908K MEMORY.
```

NOTE: SAS INSTITUTE INC.
SAS CIRCLE
PO BOX 8000
CARY, N.C. 27511-8000

APPENDIX N

STEPWISE AND MAXIMUM R^2 REGRESSION
PROCEDURES USED TO BUILD DOPAMINE MODEL

CATECHOLAMINE ANALYSIS: Dopamine

STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

WARNING: 2540 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.1383387 C(P) = 35.64759543

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
1	79084.01924111	79084.01924111	89.31	0.0001
578	511827.81524165	885.51525128		
579	590911.83448276			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 50.88462452 0.17040093 79084.01924111 89.31 0.0001
X -1.61034271

BOUNDS ON CONDITION NUMBER: 1. 1

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.16378089 C(P) = 16.50035676

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
2	96780.06684698	48390.03342349	56.51	0.0001
577	494131.76763578	856.38087978		
579	590911.83448276			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 51.16621035 0.47015576 50410.47786297 58.86 0.0001
X -3.60718727 0.02910352 17696.04760587 20.66 0.0001
XSQR 0.13229708

BOUNDS ON CONDITION NUMBER: 7.871703, 31.48681

STEP 3 VARIABLE XZ ENTERED R SQUARE = 0.18228629 C(P) = 5.43267906

DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
3	107715.12320433	35905.04106811	42.80	0.0001
576	483196.71127843	838.88317930		
579	590911.83448276			

REGRESSION
ERROR
TOTAL

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 51.19300509 0.48288295 35502.28830246 42.32 0.0001
X -3.14137153 0.02880945 17186.75431622 20.49 0.0001
XSQR 0.13040108 0.25504253 10935.05635735 13.04 0.0003
XZ -0.92081500

BOUNDS ON CONDITION NUMBER: 8.476848, 53.65372

NO OTHER VARIABLES MET THE 0.1000 SIGNIFICANCE LEVEL FOR ENTRY INTO THE MODEL.

9:42 WEDNESDAY, JULY 15, 1987

CATECHOLAMINE ANALYSIS: Dopamine

SUMMARY OF STEPWISE REGRESSION PROCEDURE FOR DEPENDENT VARIABLE Y

STEP	ENTERED	VARIABLE REMOVED	NUMBER IN	PARTIAL R ²	MODEL R ²	C(P)	F	PROB>F
1	X		1	0.1338	0.1338	35.6476	89.3085	0.0001
2	XSQR		2	0.0299	0.1638	16.5004	20.6638	0.0001
3	XZ		3	0.0185	0.1823	5.4327	13.0353	0.0003

CATECHOLAMINE ANALYSIS: Dopamine

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

WARNING: 2540 OBSERVATIONS DELETED DUE TO MISSING VALUES.

STEP 1 VARIABLE X ENTERED R SQUARE = 0.13383387 C(P) = 35.64759543

REGRESSION	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
ERROR	1	79084.01924111	79084.01924111	89.31	0.0001
TOTAL	578	511827.81524165	885.51525128		
	579	590911.83448276			

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 50.88462452 0.17040093 79084.01924111 89.31 0.0001

X -1.61034271

BOUNDS ON CONDITION NUMBER: 1. 1

THE ABOVE MODEL IS THE BEST 1 VARIABLE MODEL FOUND.

STEP 2 VARIABLE XSQR ENTERED R SQUARE = 0.16378089 C(P) = 16.50035676

REGRESSION	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
ERROR	2	96780.06684698	48390.03342349	56.51	0.0001
TOTAL	577	494131.76763578	856.38087978		
	579	590911.83448276			

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 51.16621035 0.47015576 50410.47786297 58.86 0.0001

X -3.60718727 0.02910352 17696.04760587 20.66 0.0001

XSQR 0.13229708

BOUNDS ON CONDITION NUMBER: 7.871703, 31.48681

THE ABOVE MODEL IS THE BEST 2 VARIABLE MODEL FOUND.

STEP 3 VARIABLE XZ ENTERED R SQUARE = 0.18228629 C(P) = 5.43267906

REGRESSION	DF	SUM OF SQUARES	MEAN SQUARE	F	PROB>F
ERROR	3	107715.12320433	35905.04106811	42.80	0.0001
TOTAL	576	483196.71127843	838.88317930		
	579	590911.83448276			

B VALUE STD ERROR TYPE II SS F PROB>F

INTERCEPT 51.19300509 0.48288295 35502.28830246 42.32 0.0001

X -3.14137153 0.02880945 17186.75431622 20.49 0.0001

XSQR 0.13040108 0.25504253 10935.05635735 13.04 0.0003

XZ -0.92081500

BOUNDS ON CONDITION NUMBER: 8.476848, 53.65372

CATECHOLAMINE ANALYSIS: Dopamine

MAXIMUM R-SQUARE IMPROVEMENT FOR DEPENDENT VARIABLE Y

THE ABOVE MODEL IS THE BEST 3 VARIABLE MODEL FOUND.

STEP 4	VARIABLE Z ENTERED	DF	SUM OF SQUARES	R SQUARE = 0.18561951	C(P) = 5.07890681	F	PROB>F
REGRESSION		4	109684.76408667	27421.19102167		32.76	0.0001
ERROR		575	481227.07039609	836.91664417			
TOTAL		579	590911.83448276				
	B VALUE	STD ERROR	TYPE II SS	F	PROB>F		
INTERCEPT	53.46801950		37438.63316655	44.73	0.0001		
X	-3.29252492	0.49227772	17147.85500401	20.49	0.0001		
XSQR	0.13025415	0.02877582	1969.64088234	2.35	0.1256		
Z	-4.80630860	3.13299159	2687.09295880	3.21	0.0737		
XZ	-0.59459324	0.33183311					

BOUNDS ON CONDITION NUMBER: 8.830601, 84.0164

THE ABOVE MODEL IS THE BEST 4 VARIABLE MODEL FOUND.

STEP 5	VARIABLE XSQRZ ENTERED	DF	SUM OF SQUARES	R SQUARE = 0.18714737	C(P) = 6.00000000	F	PROB>F
REGRESSION		5	110587.59525974	22117.51905195		26.43	0.0001
ERROR		574	480324.23922302	836.80181049			
TOTAL		579	590911.83448276				
	B VALUE		STD ERROR	TYPE II SS		F	PROB>F
INTERCEPT	53.41128854						
X	-2.85185028		0.64984281	16116.08025819		19.26	0.0001
XSQR	0.10118340		0.04014020	5317.18959525		6.35	0.0120
Z	-4.67847901		3.13519295	1863.38859502		2.23	0.1362
XZ	-1.49685016		0.92985381	2168.45252801		2.59	0.1080
XSQRZ	0.05979800		0.05756979	902.83117307		1.08	0.2994

BOUNDS ON CONDITION NUMBER: 20.43339, 361.1462

THE ABOVE MODEL IS THE BEST 5 VARIABLE MODEL FOUND.

APPENDIX O
DOPAMINE LACK-OF-FIT TEST

CATECHOLAMINE ANALYSIS: Dopamine
GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: Y							
SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE	
MODEL	37	149717.57206551	4046.42086664	4.97	0.0001	0.253367	
ERROR	542	441194.26241725	814.01155428				ROOT MSE
CORRECTED TOTAL	579	590911.83448276					28.53088772
SOURCE	DF	TYPE III SS	F VALUE	PR > F	DF	TYPE III SS	F VALUE
X	19	128211.55135535	8.29	0.0001	19	124070.95712755	8.02
X*X	18	21506.02071016	1.47	0.0958	18	21506.02071016	1.47

this term is solely a measure of sum-of-squares pure error.

CATECHOLAMINE ANALYSIS: Dopamine

ANALYSIS OF VARIANCE

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PROB > F
MODEL	3	107715.12	35905.04107	42.801	0.0001
ERROR	576	483196.71	838.88318		
C TOTAL	579	590911.83			
ROOT MSE		28.96348	R-SQUARE	0.1823	
DEP MEAN		41.14483	ADJ R-SQ	0.1780	
C.V.		70.39398			

PARAMETER ESTIMATES

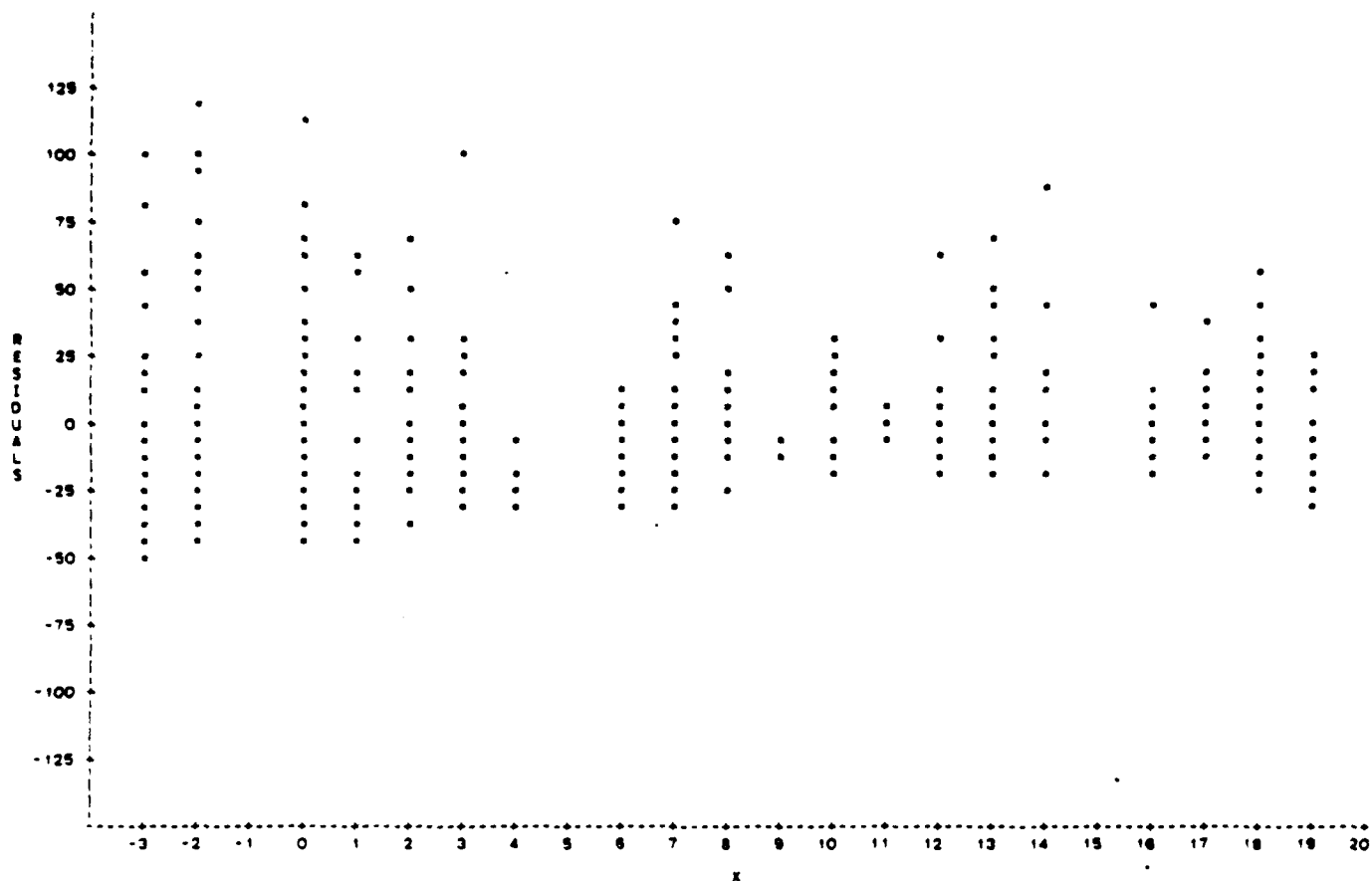
VARIABLE	DF	PARAMETER ESTIMATE	STANDARD ERROR	T FOR H0: PARAMETER=0	PROB > T
INTERCEP	1	51.19300509	1.56730010	32.663	0.0001
X	1	-3.14137153	0.48288295	-6.505	0.0001
XSQR	1	0.13040108	0.02880945	4.526	0.0001
XZ	1	-0.92081500	0.25504253	-3.610	0.0003

$$F_0 = \frac{MS_{\text{lof}}}{MS_{\text{pe}}} = 1.5176$$

$$F_{0.10, 34, 542} \sim 1.38$$

this term contains both sum-of-squares pure error and sum-of-squares lack-of-fit.

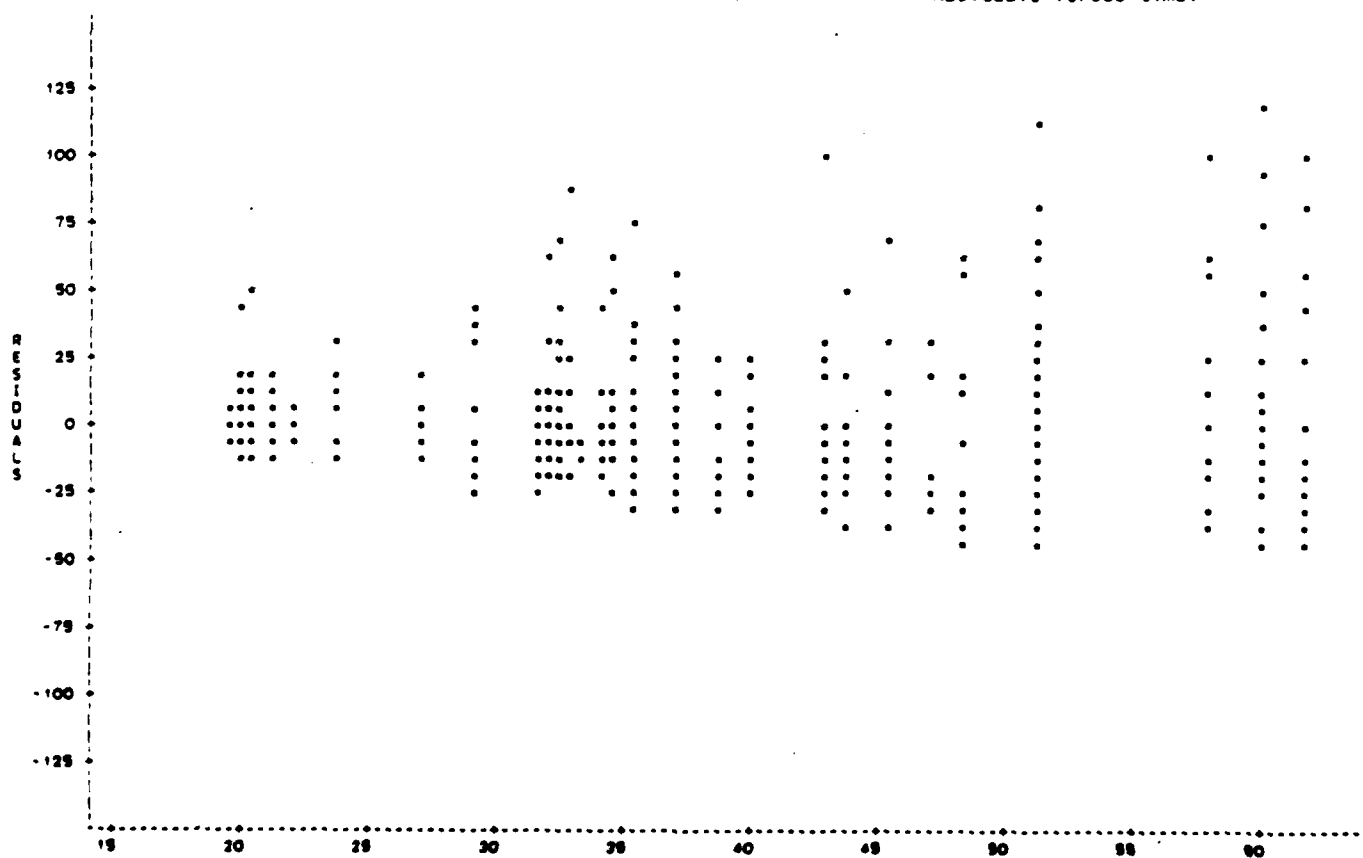
APPENDIX P
DOPAMINE RESIDUAL PLOTS



NOTE: 2544 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

381 OBS HIDDEN

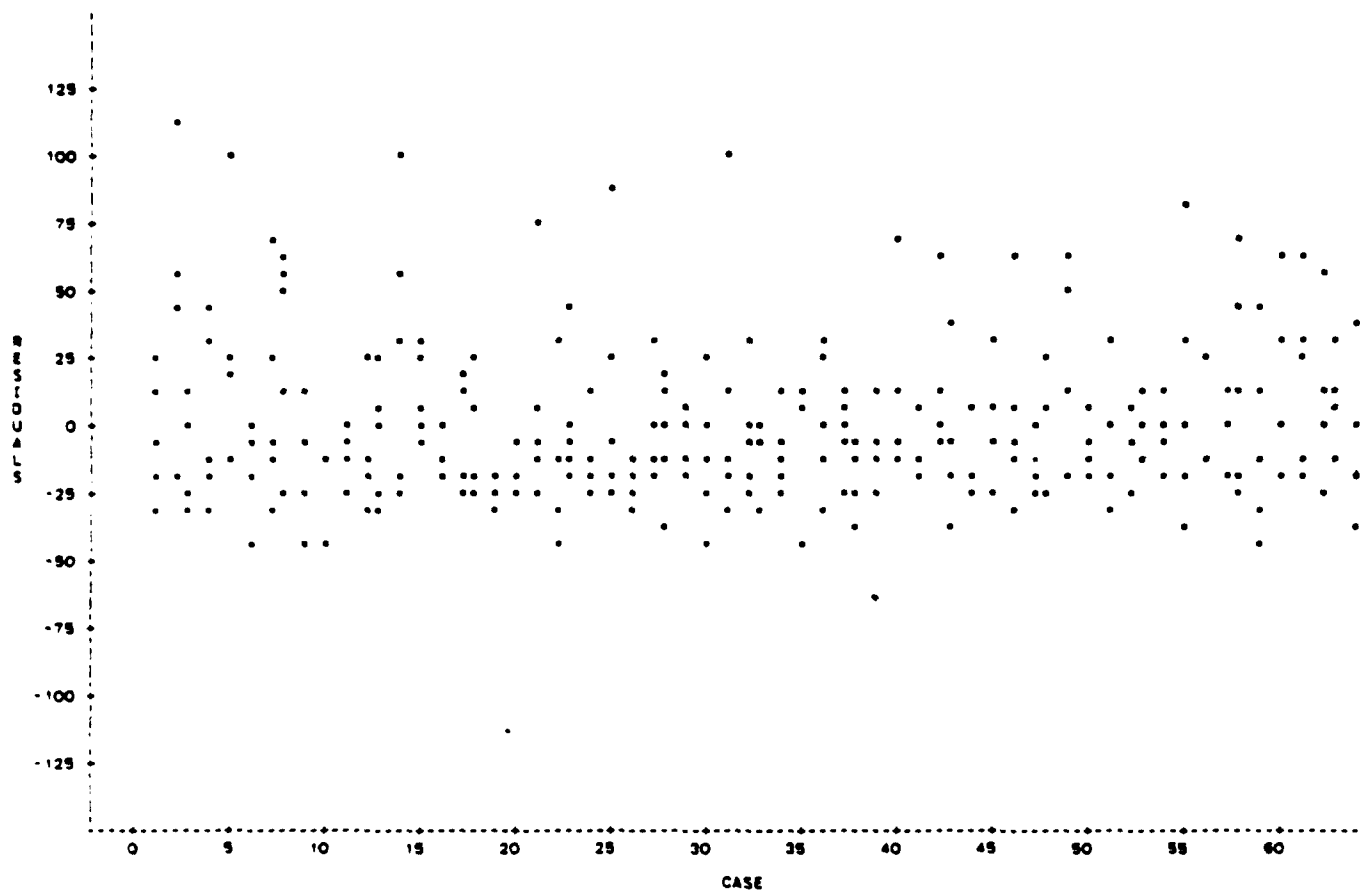
Residuals versus time.



NOTE: 2544 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

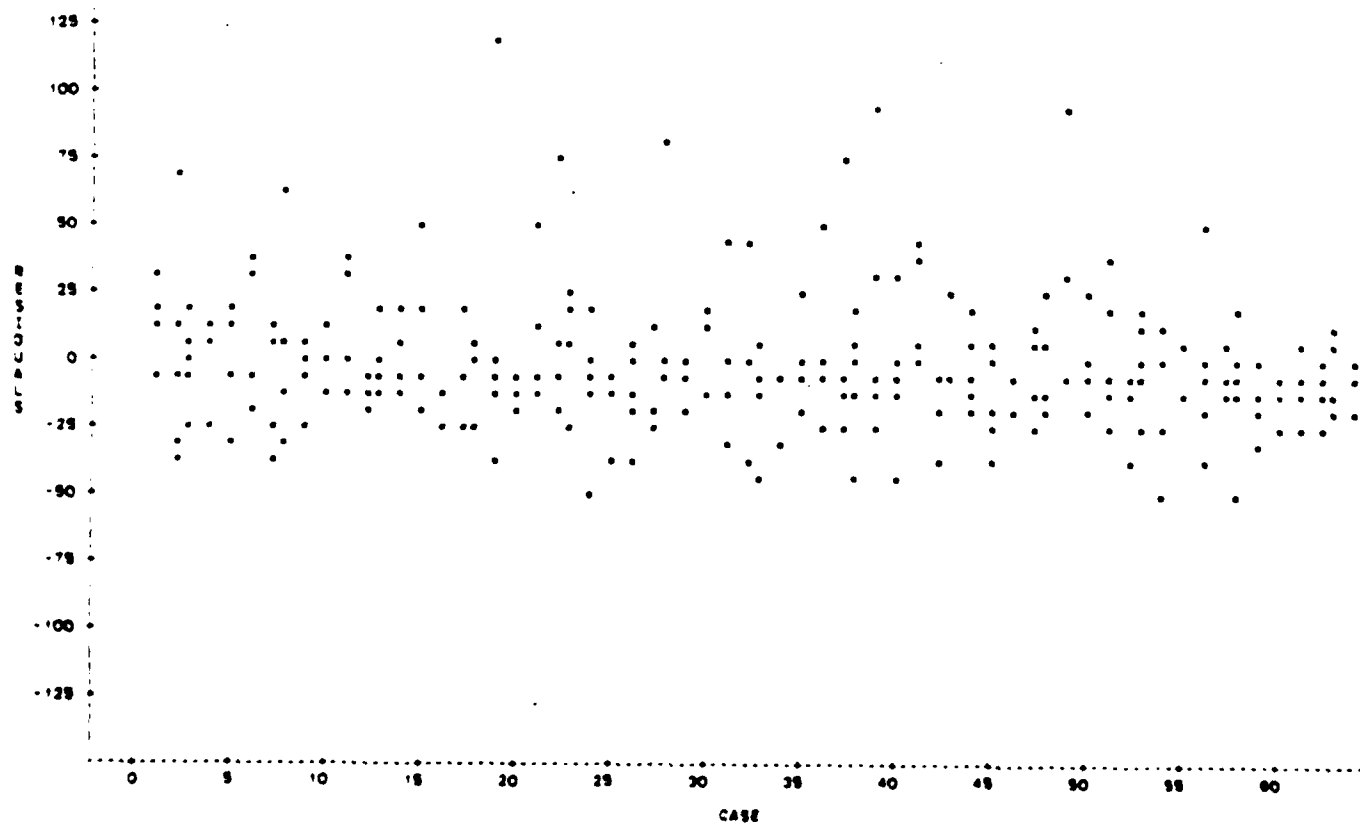
336 OBS HIDDEN

Residuals versus predicted value of
plasma dopamine concentration.



NOTE 1260 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

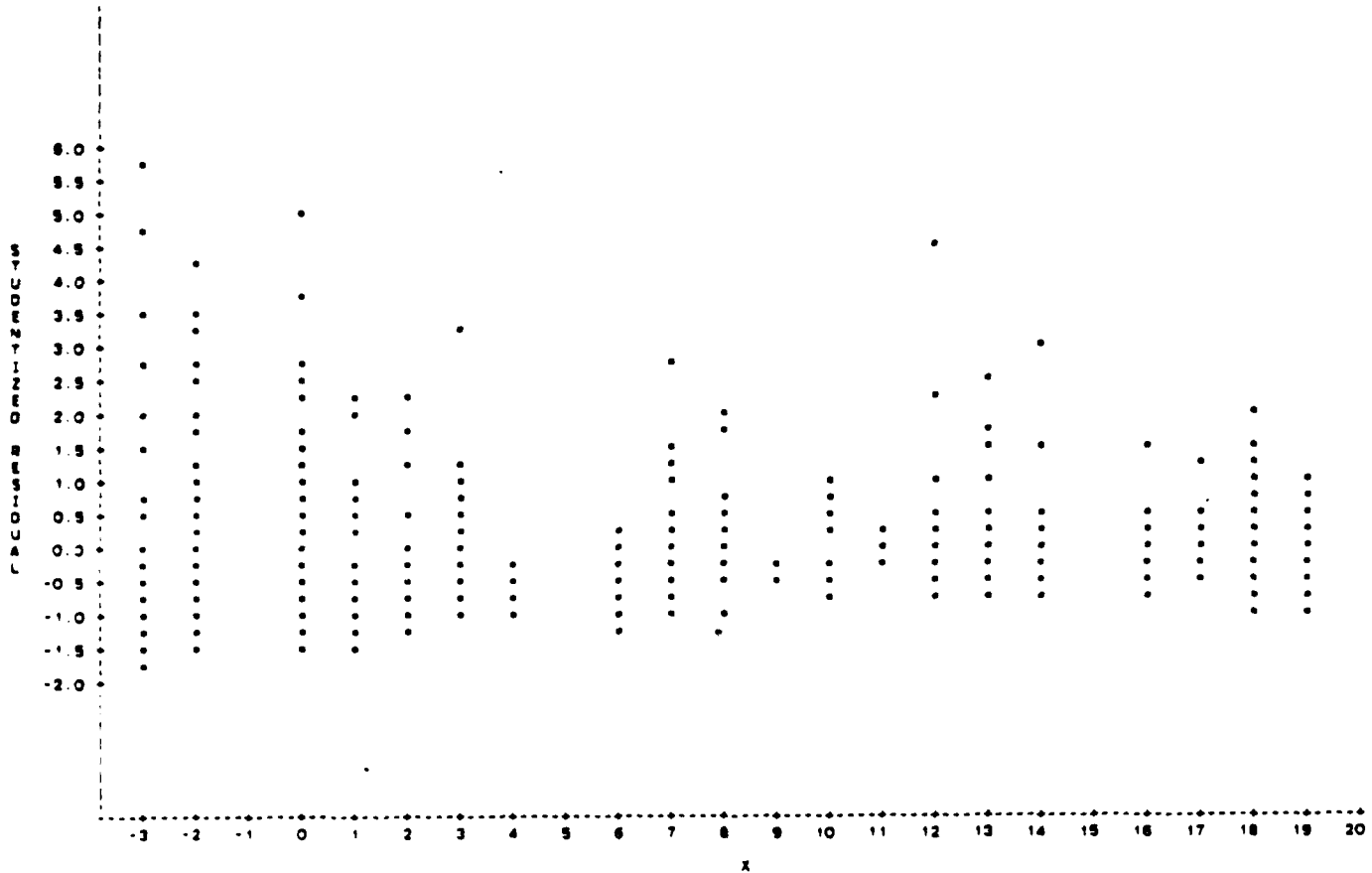
37 OBS HIDDEN

Residuals versus animal ID number
(sham-exposure group).

NOTE 1264 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

34 OBS HIDDEN

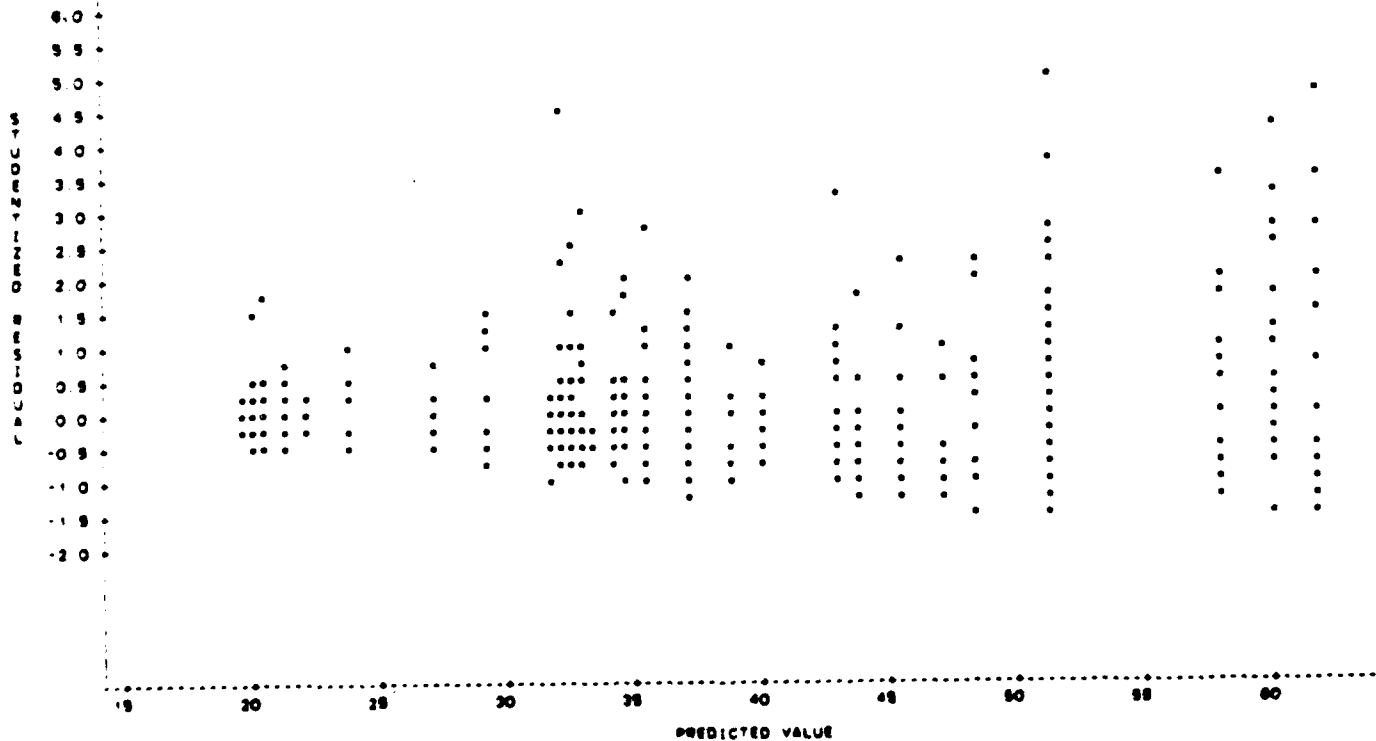
Residuals versus animal ID number
(exposure group).



NOTE 2940 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

389 OBS HIDDEN

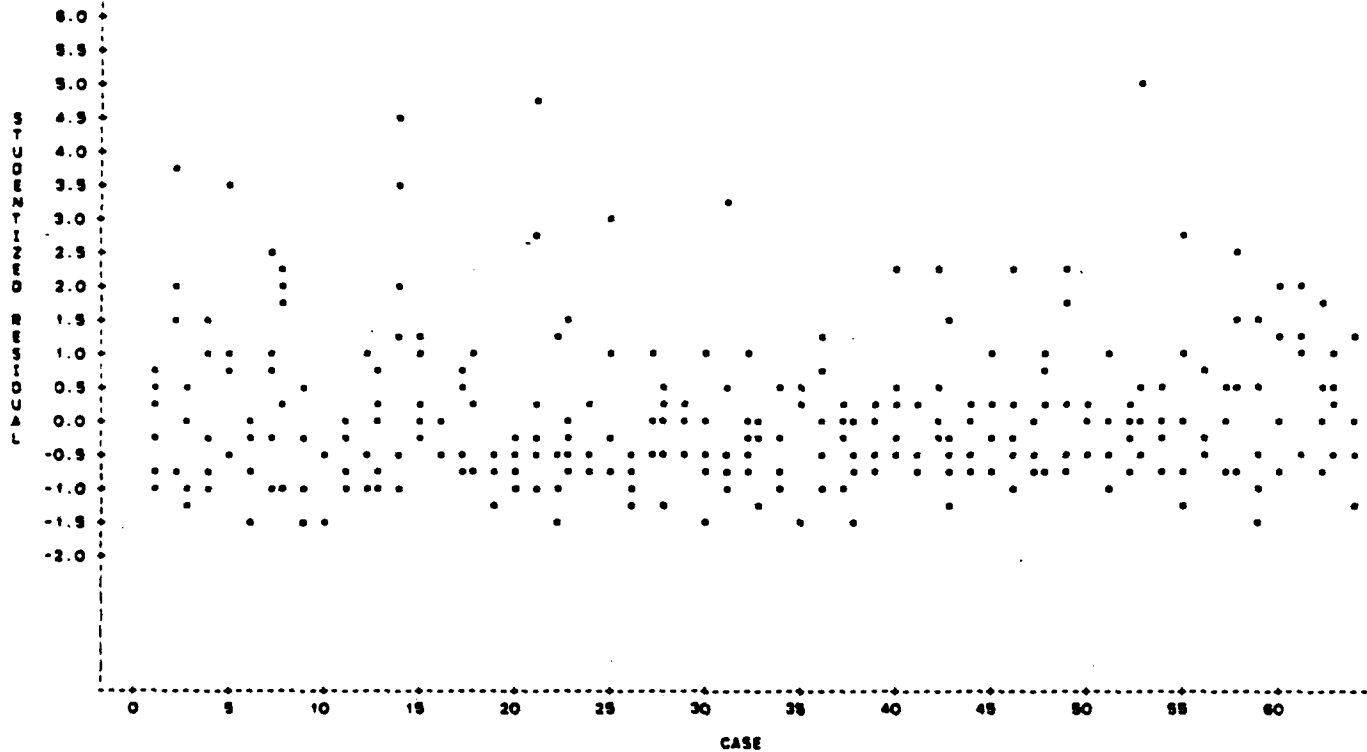
Studentized residuals versus time.



NOTE 2940 OBS HAD MISSING VALUES OR WERE OUT OF RANGE

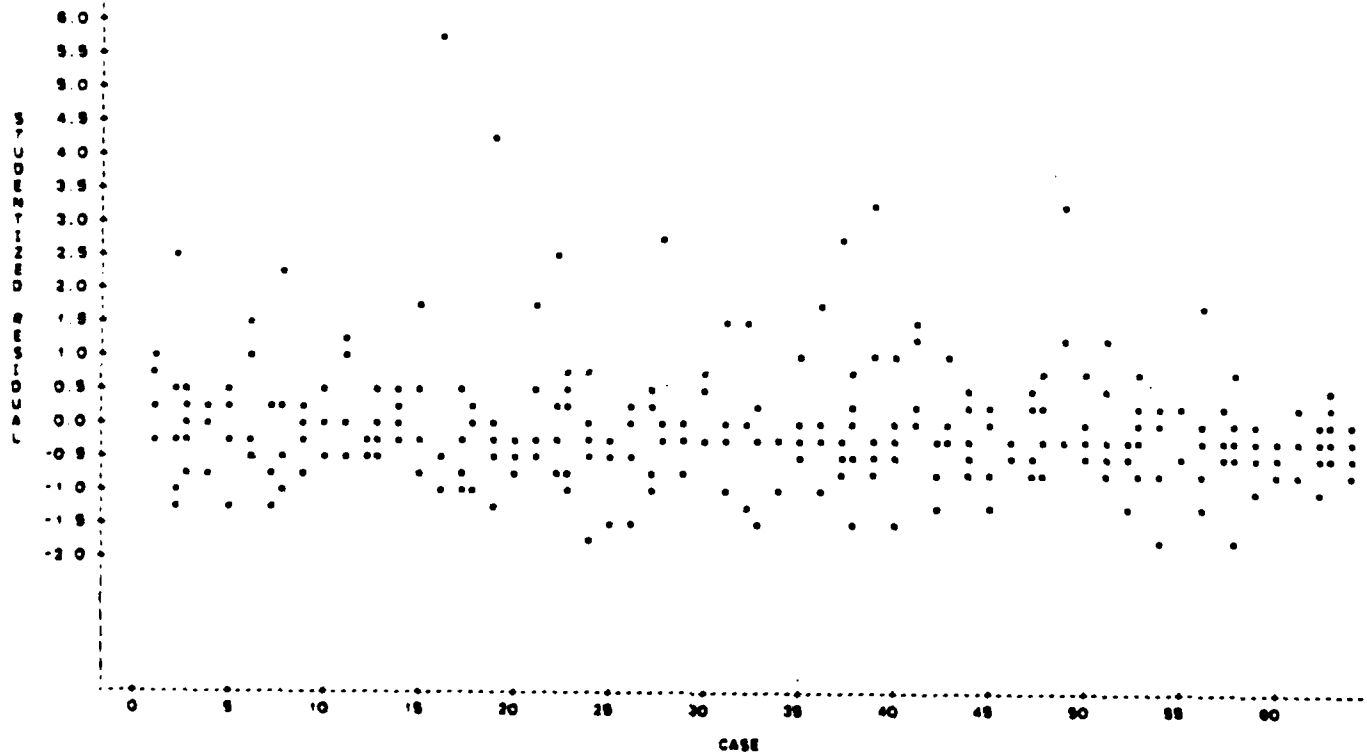
389 OBS HIDDEN

Studentized residuals versus predicted
value of plasma dopamine concentration.



NOTE 1257 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 41 OBS HIDDEN

Studentized residuals versus animal ID number (sham-exposure group).



NOTE 1293 OBS HAD MISSING VALUES OR WERE OUT OF RANGE 34 OBS HIDDEN

Studentized residuals versus animal ID number (exposure group).

END

FEB.

1988

DTic