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WASHTON, Arnold Marvin, 1947-
PAVLOVIAN CONDITIONING OF HEART RATE IN MACACA MULATTA: AUTONOMIC AND STIMULUS CONTROL OF CARDIAC RESPONDING AS A FUNCTION OF CS-US INTERVAL.

City University of New York,
Ph.D., 1978
Psychology, psychobiology

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PAVLOVIAN CONDITIONING OF HEART RATE IN *MACACA MULATTA*: AUTONOMIC AND STIMULUS CONTROL OF CARDIAC RESPONDING AS A FUNCTION OF CS-US INTERVAL

by

Arnold M. Washton

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1978

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

January 30, 1978
date

Wm. Schoenfeld
William N. Schoenfeld, Ph.D.
Chairman of the Examining Committee

January 30, 1978
date

Florence L. Denmark
Florence L. Denmark, Ph.D.
Executive Officer

Examining Committee: William N. Schoenfeld, Ph.D.
Brett K. Cole, Ph.D.
Thom Verhave, Ph.D.
Ronald M. Kadden, Ph.D.
Richard S. Kestenbaum, Ph.D.
Daniel M. Sussman, Ph.D.

The City University of New York

Abstract

PAVLOVIAN CONDITIONING OF HEART RATE IN MACACA MULATTA: AUTONOMIC AND STIMULUS CONTROL OF CARDIAC RESPONDING AS A FUNCTION OF CS-US INTERVAL

by

Arnold M. Washton

Adviser: Professor William N. Schoenfeld

Heart rate (HR) conditioning was studied in six chair-restrained rhesus monkeys under systematic manipulation of the variable of CS-US interval duration in a Pavlovian delay conditioning procedure involving a visual conditional stimulus (CS) paired with an electric-shock unconditional stimulus (US). The underlying autonomic nervous system (ANS) contributions to conditional HR changes were examined through the use of selective pharmacological blocking agents.

A longitudinal experimental design was employed in which each subject was exposed to all experimental conditions. This design involved eight different CS-US interval values, measured from CS onset to US onset, of 2, 4, 6, 10, 20, 40, 60, and 120 sec, presented in that order for eight sessions each to all subjects. Subsequently, all subjects were re-exposed to the 20-sec and then the 2-sec CS-US interval conditions. During every trial, cardiac interbeat time values were recorded in successive 2-sec time periods beginning 2 sec before CS onset and continuing throughout CS. Measures of cardiac conditional response (CR) magnitude, latency, and waveform were based on average interbeat time values for the successive 2-sec recording periods.

At each CS-US interval, pharmacological blocking agents were administered to assess the relative sympathetic and parasympathetic ANS contributions to observed cardiac rate CRs. The substances used were propranolol, a sympathetic blocking agent, and atropine sulfate, a parasympathetic blocking agent, injected intravenously at a dose of .16 mg/kg each. During re-exposure to the 20-sec CS-US interval, subjects were tested under several dosages of propranolol, atropine, and the ganglionic blocking agent, chlorisondamine. During this phase of the experiment, cardiac data were recorded not only during the CS-US interval, but after US delivery as well, so that the underlying ANS contributions to cardiac rate CRs and URs could be compared.

Results of the CS-US interval manipulations, with respect to the waveform, latency, and magnitude of observed cardiac CRs were as follows. Cardiac CR waveforms were least consistent at the first three CS-US intervals from 2-6 sec, where instances of accelerative, decelerative, and biphasic HR patterns were found during CS, both within and among subjects, with the direction of response varying with the level of HR just prior to CS onset. By contrast, at CS-US intervals from 10-120 sec, a stable biphasic HR pattern consisting of initial acceleration followed by deceleration was uniformly observed during CS, despite continued wide fluctuations in pre-CS heart rate. Latency to peak HR in the biphasic CR function increased with CS-US intervals from 10-40 sec, and then decreased at the two longest CS-US intervals of 60 and 120 sec. The rate of cardiac deceleration from the preceding peak of acceleration was inversely related to the duration of the CS-US interval: the longer the interval the slower the decline in HR from maximum to minimum within

CS. The magnitude of peak HR change during CS increased as the CS-US interval increased from 2-20 sec and remained essentially unchanged thereafter despite further lengthening of the CS-US interval to 120 sec.

Results of the pharmacological manipulations were: (a) parasympathetic blockade raised pre-CS heart rate and significantly reduced both accelerative and decelerative HR changes in the CS-US interval; (b) sympathetic blockade lowered pre-CS heart rate, variably affected CR acceleration, and facilitated CR deceleration; and, (c) combined sympathetic and parasympathetic blockade lowered pre-CS heart rate and eliminated conditional HR changes almost entirely. These effects were similar across CS-US intervals from 2-120 sec, and whether the entire pre-drug CR form was monophasic or biphasic. During re-exposure to the 20-sec CS-US interval, higher dosages of propranolol (1.0 mg/kg) significantly reduced the initial accelerative component of the biphasic CR and enhanced the decelerative component, while ganglionic blockade eliminated the CR entirely. Drug effects on the biphasic UR were similar to those for the CR, although the UR tended to be less suppressed by the drugs.

The present findings suggested that: (a) a CS-US interval of at least 10 sec is critical for obtaining large and consistent cardiac rate CRs; (b) the CS-US interval is a powerful variable in determining the temporal distribution of cardiac rate changes during CS; and, (c) the initial accelerative and subsequent decelerative components of the biphasic CR and UR are mediated by both branches of the ANS.

Acknowledgements

There are many individuals whose help I am pleased to acknowledge: I am grateful to my teachers, Dr. William N. Schoenfeld and Dr. Ronald M. Kadden, for providing the advice and guidance that made this study possible, and, for their helpful editorial revisions of the manuscript. I also wish to thank Mr. Curtis E. Best for assisting enthusiastically in caring for the animals. Special thanks to Drs. Herbert Nechin, Richard B. Resnick, and Richard S. Kestenbaum, for their personal advice and support.

I am particularly grateful to my wife, Nannette, for her unfailing support and encouragement, and for the many sacrifices she made during the course of my graduate training. I am also grateful to my daughter, Tala, a continuous source of inspiration and joy. It is to both Nannette and Tala that I dedicate this dissertation.

TABLE OF CONTENTS

List of Figures

List of Tables

Introduction

The interest in cardiovascular responses during Pavlovian conditioning procedures stems, in part, from the traditional association of heart rate (HR) changes with "emotional" and "motivational" states of the organism. It has been said, for example, that HR changes reflect "fear" (e.g., Cannon, 1923; Rescorla & Solomon, 1967), "anxiety" (e.g., Zeaman & Smith, 1965), "anticipation" (e.g., Dronsejko, 1972; Hastings & Obrist, 1967), and "uncertainty" (e.g., Miller & Caul, 1969; Niemela, 1969). Conditioned cardiac activity has also been of interest as a result of theoretical formulations concerning the role of autonomic responses in mediating learned instrumental behavior (e.g., Mowrer, 1960; Rescorla & Solomon, 1967; Schoenfeld, 1950). Additionally, the demonstration of cardiac conditionability has attracted the attention of investigators concerned with the etiology and treatment of cardiovascular abnormalities such as arrhythmia and hypertension (e.g., Engel & Bleeker, 1974; Forsyth, 1974; Smith & Stebbins, 1965).

Cardiac conditioning under Pavlovian procedures has been demonstrated in a variety of organisms including dogs (e.g., Gantt, 1960), monkeys (e.g., Snapper, Pomerleau, & Schoenfeld, 1969), rats (e.g., Fitzgerald & Martin, 1971), rabbits (e.g., Schneiderman, 1972), cats (e.g., Hein, 1969), pigeons (e.g., Cohen & Pitts, 1968), and humans (e.g., Notterman, Schoenfeld, & Bersh, 1952). Most studies in this area have used procedures involving an auditory or visual CS paired with an

electric-shock US, and a CS-US interval often in the range of 5-10 sec. The cardiac conditional response (cardiac CR) is usually measured during the CS-US interval, although in some cases it is measured only on "test" trials where US is omitted. The cardiac CR is defined as whatever HR changes occur following the onset of CS as compared with cardiac activity just prior to CS onset.

The use of HR changes as a dependent variable in Pavlovian procedures raises problems of response definition and measurement. Cardiac activity is a continuous physiological process that exhibits substantial moment-to-moment variability, unlike the more punctate response effectors (e.g., leg flexion and eyeblink) whose basal activity level tends to be very low. For example, a leg flexion response is seldom emitted in the absence of appropriate stimulation, making it fairly easy to identify the occurrence of a CR (cf. Gantt, 1960). By contrast, basal heart rate is continuous and also acutely sensitive to extraneous stimulation. Thus, conditional cardiac activity must be evaluated by comparing HR changes during the CS-US interval against baseline measures taken prior to CS onset. Relative to such baseline (pre-CS) measures, heart rate might accelerate or decelerate significantly during the CS-US interval, or, remain essentially unchanged. In this regard, one of the problems in evaluating the conditioned cardiac effect is that heart rate responsiveness to stimulation changes with the pre-stimulation level of cardiac activity, a phenomenon known in the psychophysiological literature (for HR and other autonomic measures) as the "law of initial value" or LIV (Wilder, 1957).

In surveying the massive literature on cardiac conditioning, one is confronted with a confusing array of findings concerning the conditioned response of the heart. At least some of this confusion can be attributed to the different measures of the cardiac CR that have been used. For instance, some workers have focused primarily on cardiac CR magnitude, defined as the difference between pre-CS and post-CS HR averages (e.g., Black & Black, 1967; Notterman, Schoenfeld, & Bersh, 1952; Van Dercar & Schneiderman, 1967), while others have focused on the time course of HR changes across the CS-US interval; i.e., the "form" of the cardiac CR (e.g., Dronsejko, 1972; Snapper, Pomerleau, & Schoenfeld, 1969). Confusion also arises from the multiplicity of techniques used to collect and analyze cardiac response data. Thus, investigators interested in cardiac CR magnitude sometimes define it as the difference between average HR for the entire CS-US interval and average pre-CS rate (e.g., Black & Black, 1967), or, as the difference between peak CS heart rate and pre-CS rate (e.g., Deane, 1965). Those interested in the form of the cardiac CR record time intervals either between successive heart beats (e.g., Newton & Perez-Cruet, 1967), or, blocks of four or five heart beats (e.g., Kazis, Milligan, & Powell, 1973; Wilson, 1969), while still others count the number of heart beats within specified time periods (e.g., Miller & Caul, 1969; Ramsay, 1970). Occasionally, interbeat times are recorded and then transformed into a rate measure such as beats per minute (e.g., Dronsejko, 1972; Geer, 1964; Zeaman & Smith, 1965). It has been shown that this non-linear transformation, reflecting the reciprocal relationship between measures of period and rate, alters the statistical properties of the frequency

distribution of raw interbeat time values and, therefore, may distort the reported outcome of a given experiment (Black, 1965; Jennings, Stringfellow, & Graham, 1974; Khachturian, Kerr, Kruger, & Schachter, 1972).

It has long been recognized, for HR and other autonomic measures, that the duration of the CS-US interval is an important variable in determining the effects of a CS. Pavlov himself noted that the latency of salivary responding during CS depended on the duration of the CS-US interval. He found that at short CS-US intervals (e.g., 1-5 sec), the salivary response almost immediately followed the onset of CS, whereas at much longer CS-US intervals (e.g., 1-3 min) the latency of the response was considerably delayed and proportional to the duration of the CS-US interval (Pavlov, 1927). Pavlov called this phenomenon "inhibition of delay," attributing it to inhibitory properties acquired by the early segments of a long CS from lack of reinforcement by US. Additionally, he found that the formation of a conditioned salivary response at long CS-US intervals was difficult if not impossible to achieve without preliminary training at much shorter CS-US values, and he therefore often began long-interval conditioning by training his subjects at a CS-US interval of 1-5 sec, subsequently lengthening the interval over successive days. Pavlov also noted that long-interval conditioning was facilitated by procedures in which CS remained on throughout the entire CS-US interval ("delay"), as compared with those in whch CS terminated prior to US onset ("trace"). Based on these observations, Pavlov (1927) was led to remark that the duration of the CS-US interval was of "fundamental importance" since it seemed to determine "the eventual character of every conditioned reflex" (p. 88).

Since Pavlov's work, the major focus of research on the CS-US variable has been to identify an "optimal" interval value which results in the largest magnitude of conditional responses within the CS-US interval. In a review of the literature on optimal CS-US intervals for a variety of non-cardiac response measures, Jones (1962) concluded that no single CS-US interval is "optimal" for all conditioning situations, but rather that the magnitude of CRs in Pavlovian procedures depends upon a number of factors such as the length of training and latency characteristics of the particular response system examined.

Among the many cardiac conditioning studies in recent years, a number have explored the variable of CS-US interval length as a determiner of cardiac CR magnitude. However, apart from the general observation that HR can be conditioned at more extended CS-US intervals than short-latency punctate responses such as nictitating membrane or eyeblink (cf. Gormezano & Moore, 1971; Schneiderman, 1972), there are conflicting reports as to which CS-US interval is "optimal" for producing the largest cardiac CRs. Most studies in this area have used across-groups manipulations of the CS-US interval, comparing two or three CS-US values in the relatively narrow range of 0 to 20 sec. A brief summary of the reported findings is presented below.

An early study by McAllister, Farber, and Taylor (1954), in human subjects, found no differences between the magnitude of cardiac CRs at CS-US intervals of .5 and 5.0 sec, and Church and Black (1958) obtained a similar finding in dogs at CS-US intervals of 5 and 20 sec. Other investigators, however, have observed significant differences in the magnitude of cardiac CRs across CS-US intervals. For example, Hastings

and Obrist (1967), also using humans, found that the magnitude of cardiac CRs increased with CS-US intervals ranging from .8 to 13 sec, and Fitzgerald and Martin (1971) found that the magnitude of CRs in rats increased with CS-US intervals from 0 to 6 sec. Some investigators have found optimal HR conditioning at an intermediate CS-US interval within the range of values employed. Van Dercar and Schneiderman (1967), for example, found that the cardiac CR of rabbits was larger at a CS-US interval of 2.25 sec, relative to other intervals in the range of .25 to 6.75 sec. Moreover, in several species optimal conditioning was found at a CS-US interval of 5 sec, when intervals in the range of .5 to 10 sec were compared (for rabbits, Deane, 1965; Lockhart & Steinbrecher, 1970; for rats, Black & Black, 1967; for humans, Wilson, 1969).

The studies summarized above present a rather confusing picture of CS-US interval effects on the magnitude of cardiac CRs, although at least some of this confusion arises from differences among studies in the range and spacing of CS-US intervals employed. Among studies which have focused, not on the magnitude, but on the form of the cardiac CR in Pavlovian procedures, conflicting findings have also been obtained. That is, investigators have reported the cardiac CR form as either: (a) a monophasic HR acceleration across the entire CS-US interval (e.g., Miller & Caul, 1969; Obrist & Webb, 1967); (b) a monophasic HR deceleration across the CS-US interval (e.g., Notterman et al., 1952; Van Dercar & Schneiderman, 1967); (c) a biphasic HR pattern of initial acceleration followed by deceleration within the CS-US interval (e.g., Ramsay, 1970; Snapper et al., 1969); (d) a biphasic HR pattern of initial deceleration followed by acceleration (e.g., Deane, 1965; Fredericks et al., 1974);

or, (e) a polyphasic HR pattern involving more than one cycle of acceleration and deceleration within the CS-US interval (e.g., Bowers, 1971; Newton & Perez-Cruet, 1967). Such discrepancies in findings have led some authors to discount heart rate as a useful dependent variable in Pavlovian conditioning procedures (e.g., Obrist, Howard, Lawler, Galosy, Meyers, & Gaebelin, 1974; Rescorla & Solomon, 1967; Smith, 1966). However, at least some of the variability in cardiac CR forms can be attributed to the different ways in which cardiac response data have been reported. For example, biphasic HR changes are sometimes observed during the CS-US interval, but the cardiac CR is reported as either accelerative or decelerative, based on a belief by the authors that one or the other of these phasic HR changes is not part of the CR. Wood and Obrist (1964), for instance, regarded the initial accelerative component of human biphasic CRs as an artifact of respiratory changes, and the subsequent decelerative component as the "true" conditioned response. Fitzgerald and Walloch (1966), on the other hand, described the cardiac CR of their subjects (dogs) as purely accelerative, dismissing the subsequent decrease in HR toward the end of the CS-US interval as "simple recovery from preceding acceleration." Another group of investigators (Klose, Augenstein, Schneiderman, Manas, Abrams, & Bloom, 1975), obtained biphasic CRs in rhesus monkeys, but reported the CR form as accelerative.

Diversity of cardiac CR forms in the literature can also be traced to species differences. For example, cardiac CRs of monophasic acceleration are often found in dogs and pigeons (e.g., Cohen & Durkovic, 1966; Cohen & Pitts, 1968; Obrist & Webb, 1967), whereas CRs of monophasic deceleration are more characteristic of rats, rabbits, and cats (e.g.,

Fitzgerald & Martin, 1971; Hein, 1969; Schneiderman, 1972). Biphasic CRs of initial acceleration followed by deceleration, are most commonly found in primates (e.g., for humans, Dronsejko, 1972; Geer, 1964; Zeaman & Smith, 1965; for monkeys, Ramsay, 1970; Smith & Stebbins, 1965; Snapper et al., 1969).

It also seems possible that diversity in cardiac CR forms reflects the diversity of experimental conditions, procedures, and values of temporal and intensity parameters employed. It has been shown, in this regard, that cardiac CRs can assume differing forms depending upon: (a) the duration of the CS-US interval (e.g., Brown & Peters, 1967; Dronsejko, 1972); (b) the intensity and modality of CS and US (e.g., Fitzgerald & Teyler, 1970; Zeaman & Smith, 1965); (c) the probability that US will follow CS (e.g., Miller & Caul, 1969; Niemela, 1969); (d) the length of training (e.g., Black & Black, 1967; Fehr & Stern, 1965); (e) whether a trace or delay procedure is employed (e.g., Black, Carlson, & Solomon, 1962; Manning, Schneiderman, & Lordahl, 1969); (f) whether a simple or discriminative conditioning procedure is employed (e.g., Kadden, Washton, McMillan, & Schoenfeld, 1975; Ramsay, 1971); and, (g) whether CRs are examined within the CS-US interval or on test trials where US is omitted (e.g., Borgealt, Donahoe, & Weinstein, 1972; Fitzgerald & Teyler, 1970). Additionally, several physiological parameters have been found to affect the form of the heart rate CR. For example, the cardiac CR form can depend upon the level of heart rate just prior to CS onset (e.g., Black, 1965; Ramsay, 1970), and, upon the nature of concomitant changes in blood pressure (e.g., Schneiderman, 1972), respiratory activity (e.g., Westcott & Huttenlocher, 1961; Wood &

Obrist, 1964), or somatic muscle activity (e.g., Obrist et al., 1974; Randall & Smith, 1974).

The temporal variable of CS-US interval length, in particular, seems to have contributed to the reporting of diverse cardiac CR forms, both within and among species. For instance, when the literature is organized by increasing CS-US interval length, it can be seen that many of the species which displayed monophasic HR acceleration or deceleration at CS-US intervals of approximately 6 sec or less, often showed biphasic CR forms in studies using longer CS-US intervals (e.g., for humans, Dronsejko, 1972; Hastings & Obrist, 1965; for dogs, Brown & Peters, 1967; Newton & Perez-Cruet, 1967; for rabbits, Deane, 1965; Lockhart & Steinbrecher, 1970; for rats, Fehr & Stern, 1965; Roberts & Young, 1971). This general observation suggests that CS-US intervals less than about 6 sec may be too short to show a biphasic waveform.

A study by Dronsejko (1972), in human subjects, demonstrates one way that cardiac CR forms can change as a function of CS-US interval length. Dronsejko examined HR response patterning during CS while increasing the CS-US interval (in steps of .5 sec every two trials) from 4 to 12 sec, within single subjects. She found that an initially monophasic HR acceleration at CS-US intervals from 4-6 sec, developed into a biphasic CR pattern of initial acceleration followed by deceleration at intervals from 8-12 sec. Additionally, she noted that the initial accelerative component of the biphasic response was "bound to the CS and time-locked" since it peaked consistently at 5 sec after CS onset, irrespective of CS-US interval length. Dronsejko concluded

that the long CS-US intervals allowed time for the complete biphasic response to occur, whereas intervals shorter than 6 sec truncated the response. Results similar to Dronsejko's were reported by Brown and Peters (1967), who used dogs and CS-US intervals of 5, 15, and 30 sec. These workers found that the biphasic HR response (acceleration followed by deceleration) which peaked consistently at 15 sec into the 30-sec interval, was truncated by US onset at the shorter intervals, leaving a CR pattern of monophasic acceleration across the whole of CS.

The findings of Dronsejko (1972) and Brown and Peters (1967) suggest that the temporal patterning of HR changes within the CS-US interval is not under control of the variable of CS-US interval length. However, there are many other reports in the literature, for various species, showing that measures of HR temporal patterning differ markedly among subjects trained at different values of CS-US intervals. For example, Church and Black (1958) found that the latency of peak HR in the biphasic CR of dogs increased with the duration of the CS-US interval, and similar findings have been reported in humans (e.g., Hastings & Obrist, 1967; Wilson, 1969), monkeys (e.g., Snapper et al., 1969), rabbits (e.g., Deane, 1965; Lockhart & Steinbrecher, 1970), and rats (e.g., Fitzgerald & Martin, 1971). Some authors have noted that the rate of HR change within the CS-US interval depends upon the duration of the CS-US interval. Laird and Fenz (1971), for example, found that the rate of cardiac deceleration from the preceding peak of acceleration in human biphasic CRs was inversely related to CS-US intervals in the range of 8-16 sec; i.e., the longer the interval the slower the decline in heart rate from peak acceleration to peak deceleration within the

interval. Similar observations have been reported by Wilson (1969), also in humans, and by Church and Black (1958) in dogs.

The only reported study of CS-US interval effects on the cardiac CR of rhesus, was conducted by Snapper, Pomerleau, and Schoenfeld (1969), but with equivocal results. These investigators examined the CR waveform of two subjects, at CS-US intervals of 12, 30, and 60 sec. Both subjects displayed a biphasic waveform consisting of initial acceleration followed by deceleration over the course of CS, at all three interval durations. However, for one subject, HR patterning during the 12-sec CS-US interval was identical to that of the first 12 sec of the 30- and 60-sec intervals, with peak acceleration occurring consistently at 4 sec after CS onset (cf., for humans, Dronsejko, 1972; for dogs, Brown & Peters, 1967). For the other subject, peak acceleration occurred at a later point in the 30- and 60-sec CS-US intervals than in the 12-sec interval (cf., for dogs, Church & Black, 1958; for rabbits, Deane, 1965). On the basis of these results, it is unclear whether temporal patterning of conditional HR changes in rhesus can be expected to change as a function of CS-US interval length.

The cardiac rate CR of rhesus monkeys has almost always been reported as biphasic, involving initial acceleration followed by deceleration within the CS-US interval (e.g., Kadden et al., 1975; Nathan & Smith, 1968; Randall & Smith, 1974; Snapper et al., 1969). It can be noted, however, that studies examining HR conditioning in rhesus have employed relatively long CS-US intervals, usually in the range of 10-60 sec. No data are currently available on the cardiac CR form of rhesus during CS-US intervals shorter than approximately 10 sec, and there appears to be

only one report of rhesus CR forms during CS-US intervals longer than 60 sec, but that study (Brady, Kelly, & Plumlee, 1969), which used a 3-min CS-US interval, presented data for 1-min HR averages, leaving unspecified the detailed time course of the cardiac CR.

Thus, the literature appears to indicate that although the CS-US interval has received much experimental attention as a variable determining conditioned cardiac effects, something less than a consistent account of findings has emerged. With respect to CR magnitude, for instance, there is little agreement as to what CS-US interval, if any, is "optimal" for producing the largest cardiac CRs, or, whether cardiac CR magnitudes can be expected to change at all under differing interval values (e.g., Church & Black, 1958; McAllister, Farber, & Taylor, 1954). With respect to HR patterning, the results of some studies demonstrate a degree of independence between the CS-US interval duration and the time course of HR changes during CS (e.g., Brown & Peters, 1967; Dronsejko, 1972), while others show significant control by the CS-US variable over HR response patterning during CS (e.g., Church & Black, 1958; Laird & Fenz, 1971; Manning et al., 1969). To some extent, differences in the range and spacing of CS-US intervals employed by different studies have contributed to conflicting findings. Moreover, most studies have used group designs, comparing only two or three CS-US intervals in the relatively narrow range of 0 to 20 sec, with a different group of subjects at each interval.

The many conflicts and confusions which seem to characterize research in cardiac conditioning led Harris and Brady (1974) to remark, in a review of the literature, that despite the wealth of research over

the past decade, the data appear to justify few generalizations about autonomic conditioning and "contribute more to the complexity of the process than to its clarification." However, this state of affairs does not seem surprising when one takes into account the many important differences among studies with respect to methodology, species variables, data treatments, and the like, even among studies which appear to address themselves to the same problem. Indeed, investigators of cardiac conditioning have often stated that the very inconsistency of results, both within and among species, suggests that heart rate is extremely sensitive to slight variations in experimental procedures, and that further systematic study of relevant variables, coupled with more uniform data analysis techniques, may help to reduce variability in findings and elucidate lawful relationships (e.g., Black, 1965; Miller & Caul, 1969; Shearn, 1961; Wilson, 1969).

The present study examined HR conditioning in rhesus monkeys under systematic manipulation of the CS-US interval, a variable that has been of interest to experimenters since Pavlov's work on salivary responses of dogs, through more recent studies on several response systems in a wide variety of organisms (cf. Dykman, 1967; Gormezano & Moore, 1971; Kimble, 1961). The importance of the CS-US variable in conditioning is evidenced not only by the experimental attention it has received, but also by its role in traditional theorizing about the learning process (e.g., Hull, 1943; Pavlov, 1927; Skinner, 1938), and, in more recent attempts to integrate experimental procedures and their behavioral effects through parametric manipulation of the temporal relationships among stimuli in both Pavlovian and operant conditioning paradigms

(e.g., Farmer & Schoenfeld, 1966; Kadden, Washton, McMillan, & Schoenfeld, 1975; Schoenfeld & Cole, 1972).

A longitudinal experimental design was employed in which each subject was exposed to eight different CS-US intervals ranging from 2 to 120 sec. This design afforded examination of the cardiac rate CR of individual organisms across a 60-fold change in CS-US interval length. A delay procedure was employed, based on evidence in the literature that delay is superior to trace conditioning, with respect to the magnitude and stability of cardiac CRs, especially at long CS-US intervals (e.g., Black, Carlson, & Solomon, 1962; Fitzgerald & Teyler, 1970; Manning, Schneiderman, & Lordahl, 1969). Also, CS-US intervals were manipulated proceeding from short to long values because, as noted earlier, Pavlov (1927) found that long-interval conditioning was difficult to achieve unless preceded by training at much shorter CS-US intervals. The present study also examined the recoverability of cardiac CR forms by re-exposing each subject to selected CS-US intervals, such as the 2-sec interval where the experiment had begun.

By examining the cardiac rate CR of individual organisms, across a wide range of CS-US intervals, the present study may help to clarify the role of the CS-US variable in determining conditioned cardiac effects. As stated earlier, most studies of rhesus cardiac CRs have used a CS-US interval in the range of 10-60 sec. Thus, of particular interest in the present study, was the form of the rhesus HR CR at CS-US intervals shorter than 10 sec, and at intervals longer than 60 sec.

The law of initial value

It has long been recognized that the degree of responsiveness to stimulation of the heart and other organs depends on the pre-stimulation level of organ activity. This relationship was described by Wilder (1950, 1957) when he formulated the now well-known "law of initial value" (LIV), pointing out its generality in numerous fields of research (e.g., physiology, pharmacology, and medicine). Essentially the LIV states that the magnitude of response to a stimulus is inversely related to the pre-stimulus (initial) level of response system activity; i.e., the amount of stimulus-induced change from initial level has a negative correlation with initial level (Wilder, 1957). The LIV posits that not only the magnitude but also the direction of response to stimulation depends upon initial level, the general notion being that there is some limited range of initial levels within which a particular direction of response will occur. To paraphrase Wilder (1957), in cases where a stimulus tends to increase organ activity (i.e., have an "excitatory" effect), the magnitude of the increase will be smaller the higher the initial level, at least within some "medium" range of initial levels. Beyond this medium range, and approaching extremely high initial levels, there will be a tendency toward "no response," or, a reversal in the usual direction of response from positive to negative. In cases where a stimulus tends to decrease organ activity (i.e., have an "inhibitory" effect) within a "medium" range of initial values, the magnitude of the decrease will be larger the higher the initial level. At extremely low initial levels, the response might be absent completely, or, reverse to an increase.

Since Wilder's work, much effort has been directed toward evaluating the LIV and examining its applicability to a number of autonomic variables. With respect to cardiac function, the LIV is reported to be applicable to HR responses in humans (e.g., Hord, Johnson, & Lubin, 1964; Lacey, 1956), dogs (e.g., Black, Carlson, & Solomon, 1962; Black, 1965), rabbits (e.g., Kazis, Milligan, & Powell, 1973), pigeons (e.g., Cohen & Pitts, 1968), and monkeys (e.g., Ramsay, 1970; Snapper, Kadden, & Schoenfeld, 1971), a significant inverse relationship having been observed between cardiac response magnitudes and pre-stimulus HR levels. (In most cases, "response" is defined as the difference between pre- and post-stimulus HR levels.) However, other investigators, using the same species as some of the above, found little or no evidence of the LIV phenomenon in the cardiac responses of their subjects (e.g., for humans, Geer, 1964; for rabbits, Manning et al., 1969; for monkeys, Downer & Thompson, 1972). These seemingly contradictory findings may stem, in part, from the numerous complexities which surround the LIV. For instance, the extent to which HR responses conform to the predictions of LIV has been reported to differ depending upon a multitude of factors, including: (a) the modality and intensity of the stimulus employed (e.g., Block & Bridger, 1962; Schmidt, Rose, & Bridger, 1974); (b) the number of stimulus presentations (e.g., Block & Bridger, 1962; Bridger & Reiser, 1959); (c) the variability of pre- and post-stimulus HR levels (e.g., Schmidt et al., 1974; Stratton, 1970); (d) whether data are compared within individual subjects or across groups of subjects (e.g., Block & Bridger, 1962; Bridger & Reiser, 1959); and, (e) the subjects' level of sleep or wakefulness when stimuli are

presented (e.g., Hutt & Hutt, 1970; Schmidt et al., 1974). Moreover, investigators have differed in their criteria for deciding whether the LIV phenomenon is present or absent in the cardiac response data of their subjects. In this regard, there has been considerable disagreement among investigators as to what constitutes the most appropriate mathematical expression of the LIV relationship. For example, based on Wilder's (1957) verbal description, the LIV is defined by some authors in terms of the Pearson product-moment correlation (r) between response magnitude and pre-stimulus levels: the LIV is said to be present when this correlation is negative and statistically significant (e.g., Benjamin, 1963; Lacey, 1956; Snapper, Kadden, & Schoenfeld, 1971). Other authors have employed regression models to describe the LIV. For example, Block and Bridger (1962) state that the size of the correlation coefficient between two variables conveys no information about the magnitude of their functional relationship: these authors suggest that the LIV phenomenon is more appropriately described by the slope (b) of the best-fit regression equation relating response magnitude to pre-stimulus levels, with the presence of LIV indicated when b is between zero and -1.0 and maximal LIV indicated when b is equal to -1.0. Hord, Johnson, and Lubin (1964) propose that LIV be described in terms of the regression of post-stimulus response level (i.e., the maximum or minimum level achieved following stimulus onset) on pre-stimulus levels. They suggest that LIV is present when the slope of this regression is between zero and +1.0, and that maximal LIV is indicated when b is zero. Similar to Hord et al. (1964), Surwillo and Arenberg (1965) define LIV in terms of the regression of post-stimulus

on pre-stimulus levels, but conclude that LIV is present only when the slope of this regression is significantly smaller than that for a "control" condition where no stimulus is presented. After examining the above diversity of measures for describing the LIV phenomenon, Steinschneider and Lipton (1965) suggested that since the correlation and regression coefficients describe different aspects of the response-initial level relationship, both be used when evaluating LIV, rather than arbitrarily selecting one or the other.

Although the LIV has been studied almost exclusively with respect to response magnitude, it may appear in the form of the response as well (Wilder, 1957). For example, Ramsay (1970) found that the cardiac CR of rhesus monkeys changed from accelerative to decelerative with increasing pre-CS rates, and a similar finding is reported by Black (1965) for dogs.

Thus, there have been many attempts to define the LIV mathematically, and to explore the conditions that affect the appearance and magnitude of the LIV relationship. However, much of the concern about LIV in psychophysiological research has centered on eliminating the dependency of response magnitude on initial level in order to make some other comparison. As Wilder (1957) stated, if the response-initial level relationship is not eliminated or otherwise taken into account, the effects of more relevant variables on response magnitudes may be confounded or even totally obscured. Investigators have directed much effort toward eliminating the response-initial level dependency by means of experimental or statistical control (see reviews by Benjamin, 1963; Lacey, 1956). While most workers agree that experimental control

is preferable, in some cases it may be impossible to achieve. In a unique experiment, Snapper et al. (1971) directly controlled pre-CS heart rates (in monkeys) by means of an electronic pacemaker to determine whether variability of maximum CS heart rates, observed during unpaced control sessions and attributed to normal fluctuations in pre-CS heart rate, would be reduced. The heart was paced at one of four constant rates during inter-trial intervals and then released from pacer control at the onset of CS. They found that fixing pre-CS HR at a constant level by pacing did not reduce variability in the maximum HR reached during CS and that maximum CS HR did not depend upon pre-CS pacing rates. Less direct forms of experimental control over pre-stimulus levels have been suggested, but not used, by several authors. For instance, Ramsay (1970) suggested that one way to control for initial levels may be to initiate stimulus deliveries only when initial values fall within a pre-specified range. Although seemingly possible, this may be extremely difficult to achieve with response systems such as the cardiac,which usually exhibits a great deal of baseline variability. Yet another solution may be to match subjects for initial levels before the experiment and then distribute them equally, on that basis, into different experimental groups. However, some of the problems involved in doing so may include the following: (1) The experimenter is forced to use an across-groups rather than a within-subjects manipulation of experimental variables. (2) Initial levels are likely to change during the course of the experiment and may do so in a way that counteracts the pre-experimental matching. (3) This type of matching aims to control for LIV between but not within subjects, and as some experimenters report

the LIV holds within but not necessarily between individuals (e.g., Block & Bridger, 1962; Bridger & Reiser, 1959; Cohen & Pitts, 1968). (4) The same absolute initial level for any two individuals may represent different initial levels relative to their individual range of response; e.g., a given initial level may lie in the upper portion of one subject's response range and in the lower portion of the other's (Block & Bridger, 1962; Heath & Oken, 1965). (5) The change-initial level relationship may itself change during the course of the experiment (e.g., Stratton, 1970).

Given the many difficulties involved in controlling pre-stimulus levels experimentally, it appears that statistical adjustment of data is perhaps the only feasible alternative. Many techniques have been proposed for statistically removing the LIV effect from response data; i.e., for freeing response data from the confounding effects of initial level (see reviews by Benjamin, 1963; Lacey, 1956). Most of these techniques involve transformation of the raw data into so-called "corrected" or "adjusted" response scores for comparing individuals or groups. Benjamin (1963) carefully evaluated several of the proposed solutions for the LIV problem and concluded in favor of techniques based on regression models, such as analysis of covariance. Benjamin found that only those scores adjusted by regression models resulted in zero correlation between the adjusted score and initial level.

In summary, then, the law of initial value has been of concern in psychophysiology, both as a direct focus of interest, and as an extraneous factor in the study of other variables. In the present experiment, the relationship between the magnitude of peak HR changes

during CS and pre-CS heart rate levels was examined within individual animals at CS-US intervals ranging from 2 to 120 sec. Regression analysis was used in order to separate the effect of pre-CS heart rate level from the effect of the CS-US interval manipulation on cardiac CR magnitudes.

Neural control of cardiac responding

There have been many attempts to assess, by means of surgical and/or pharmacologic interventions, the roles of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) in cardiac responding. Some of the earliest work in this area was performed by Cannon (1914, 1923), who examined ANS control of HR changes accompanying "strong emotions" such as fear, rage, and excitement. Based on his findings in surgically sympathectomized dogs and cats, Cannon (1923) concluded that the HR increases which accompanied these emotions were due almost exclusively to activation of the sympathetic nervous system. He further stated that the primary function of the vagus was to maintain resting heart rate level and to restore it after sudden upset. Consistent with Cannon, Bond (1943), also using sympathectomized dogs and cats, reported that cardioacceleration accompanying the "startle" reaction to a loud noise was due primarily to increased sympathetic outflow. Since these early investigators, the relative sympathetic and parasympathetic contributions to cardiac responding have been examined under a variety of experimental conditions, including: (a) operant

avoidance (e.g., Wynne & Solomon, 1955); (b) problem-solving tasks (e.g., Ulrych, 1969); (c) aversive reaction-time tasks (e.g., Obrist, Lawler, Howard, Smithson, Martin, & Manning, 1974); (d) electrical stimulation of the brain (e.g., Powell, Goldberg, Dauth, Schneiderman, & Schneiderman, 1972); (e) exercise (e.g., Cumming & Carr, 1967; Robinson, Epstein, Beiser, & Braunwald, 1966); and, (f) Pavlovian conditioning with an aversive US (e.g., Dykman & Gantt, 1959; Schoenfeld, Kadden, & Bindler, 1975). These reports generally conclude that obtained HR changes are mediated by both branches of the ANS, with the degree of sympathetic as compared with parasympathetic involvement depending upon the experimental situation and the species employed. For example, Robinson et al. (1966), in humans, reported that the tachycardiac response to exercise was mediated primarily by a decrease in vagal activity, although sympathetic outflow became increasingly important with higher work loads. Pavlovian studies, in particular, challenged the traditional notion of sympathetic activation being primarily responsible for the cardiac response to "stress," as when the heart rate CR preceding an aversive electric-shock US was sometimes found to be decelerative rather than accelerative (e.g., in humans, Hastings & Obrist, 1967; Notterman, Schoenfeld, & Bersh, 1952; in dogs, Gantt, 1960). Furthermore, in some studies which did find an accelerative CR, blockade of sympathetic activity had no effect on the response, indicating that the vagus was the major contributor (e.g., Obrist & Webb, 1967).

The literature on ANS control of Pavlovian cardiac CRs is fraught with conflicting views as to which branch of the ANS is the more important contributor to observed HR changes. That is, based on the results of

their individual experiments, some authors have attributed primary control of the cardiac CR to the sympathetic system, others to the parasympathetic system. The problem arises, in part, from the different cardiac CR patterns (e.g., accelerative, decelerative, and biphasic) displayed by the various organisms studied, and from the fact that both increases and decreases in heart rate can be mediated by either branch of the ANS. For instance, cardiac acceleration can result from either an increase in sympathetic outflow or a decrease in vagal restraint. The two innervations are thought to maintain "mutually antagonistic" or "reciprocal" influences on resting heart rate; thus, when vagal activity is blocked, resting HR increases, indicating that the vagus normally exerts a restraining influence on underlying sympathetic tone (Robinson et al., 1966; Rushmer, 1970).

Before reviewing the literature on ANS control of Pavlovian cardiac CRs in greater detail, the methodology employed in these studies will be briefly described. Usually, cardiac CRs are established in laboratory animals by pairing a visual or auditory CS with an electric-shock US. After stable CRs are obtained, one or both branches of the ANS are blocked, either through surgical ablation or administration of pharmacological agents, and the subsequent effects on the CR are assessed, most often with respect to the magnitude of response. When the CR is found to be diminished by blockade of one or the other portion of the ANS, it is usually concluded that that portion of the ANS was involved in mediating the original intact CR. In the majority of studies, pharmacological rather than surgical interventions have been employed. The pharmacological agents most commonly used are those

which selectively antagonize neurotransmitter substances at sympathetic or parasympathetic nerve endings in the heart (as well as other sites). For example, propranolol hydrochloride is a well-known beta-adrenergic blocking agent that antagonizes neurotransmitters at sympathetic nerve endings, and atropine sulfate is a well-known cholinergic blocking agent that antagonizes neurotransmitters (i.e., acetylcholine) at parasympathetic nerve endings (cf. Goodman & Gilman, 1975).

In a recent review of the literature, Cohen (1974) suggested that the relative sympathetic and parasympathetic contributions to Pavlovian cardiac CRs depend upon the particular form of the CR being studied. Accordingly, he organized his literature review by accelerative, decelerative, and biphasic cardiac CR forms, an organizational scheme that will also be followed here.

With respect to CRs of monophasic acceleration, an early study in dogs by Dykman and Gantt (1959) found that response magnitudes were markedly reduced during parasympathetic blockade by atropine. These authors concluded that the intact CR was due mainly to a decrease in vagal restraint, but, because some HR acceleration remained during vagal blockade they suggested that sympathetic outflow also contributed to the response. Evidence of primarily vagal control over CR acceleration in dogs was also reported in two other experiments (Obrist & Webb, 1967; Obrist, Howard, Lawler, Sutterer, Smithson, & Martin, 1972), after observations that sympathetic blockade by propranolol resulted in only a slight reduction in cardiac CR magnitudes. In contrast to these sources, evidence for primarily sympathetic control of accelerative CRs has also been reported. For example, after observations that

propranolol was more effective than surgical vagotomy in reducing CR acceleration in pigeons, Cohen and Pitts (1968) concluded that the CR was due primarily to increased sympathetic outflow. Similarly, Bergamaschi and Longoni (1973) found that propranolol markedly diminished the magnitude of CR acceleration in dogs, and concluded that the pre-drug response must have been due to activation of the sympathetic system.

Among studies examining decelerative CRs, the findings have been somewhat more consistent. That is, in most cases it is found that atropine or surgical vagotomy eliminates the decelerative CR, and it is concluded that the response is mediated almost exclusively by an increase in vagal restraint (e.g., for cats, Flynn, 1960; Hein, 1969; for rats, Fitzgerald, Martin, & O'Brien, 1973; for rabbits, Downs, Cardozo, Schneiderman, Yehle, Van Dercar, & Zwilling, 1972; Fredericks, Moore, Metcalf, Schwaber, & Schneiderman, 1974; Sampson, Francis, & Schneiderman, 1974; Schneiderman, Van Dercar, Yehle, Manning, Golden, & Schneiderman, 1969). Some studies also report that sympathetic blockade has no effect on the decelerative CR, and this is taken as further evidence that the sympathetic system plays almost no role in mediating the observed response (e.g., Flynn, 1960; Fredericks et al., 1974; Sampson et al., 1974). However, Kazis, Milligan, and Powell (1973) reported that both autonomic systems contributed to observed decelerative CRs. These workers found that the magnitude of CR deceleration in rabbits was reduced by either propranolol or atropine, but eliminated entirely only by combined administration of the drugs. They concluded that the normally-occurring decelerative response was the result of increased vagal discharge coupled with decreased sympathetic tone. This finding is consistent with Joseph

and Powell (1973), who reported that the magnitude of decelerative CRs in rabbits was reduced, but not eliminated, by chemical sympathectomy with 6-hydroxydopamine, a drug which causes degeneration of peripheral sympathetic nerve endings.

The relative ANS contributions to biphasic cardiac CRs have been examined in only a handful of studies. For example, Obrist, Wood, and Perez-Reyes (1965) administered atropine to human subjects who had earlier shown biphasic CRs consisting of initial acceleration followed by deceleration within a 7-sec CS-US interval, but the effects of the drug were reported only for the decelerative portion of the response. These investigators found that atropine eliminated the CR's decelerative component and "unmasked" what appeared to be a sympathetically mediated increase in HR toward the end of CS, the magnitude of which depended upon the intensity of shock US. They concluded that the decelerative portion of the original CR was vagally mediated, and that the sympathetic contribution was minimal except under conditions of severe stress (i.e., high shock intensity). An inspection of their data (their Fig. 1) additionally reveals that the initial accelerative portion of the biphasic CR was also eliminated by atropine, suggesting that the entire pattern of cardiac responding during the 7-sec CS-US interval was mediated primarily by changes in vagal tone. Evidence for primarily vagal control of biphasic CRs in humans is reported in a more recent study from Obrist's laboratory (Obrist, Lawler, Howard, Smithson, Martin, & Manning, 1974) which found that sympathetic blockade by propranolol resulted in almost no diminution in response magnitude.

Klose et al. (1975) examined ANS control of biphasic CRs in rhesus monkeys, although data were reported only for the initial accelerative portion of the response. These investigators found that CR acceleration was partially reduced by either propranolol or atropine administered separately, and totally eliminated by both drugs given together. They concluded from these observations that cardiac acceleration during CS was mediated jointly by both autonomic systems, i.e., by an increase in sympathetic outflow coupled with a decrease in vagal restraint.

A study by Schoenfeld, Kadden, and Bindler (1975), also in rhesus, is the only one which examined the independent and combined effects of sympathetic and parasympathetic blockade on both the accelerative and decelerative components of a biphasic CR. These workers found that: (a) propranolol selectively reduced or eliminated the initial accelerative portion of the response; (b) atropine selectively reduced or eliminated the subsequent decelerative portion of the response; and, (c) combined administration of propranolol and atropine eliminated both portions of the biphasic CR. It was concluded from these findings that the initial accelerative portion of the CR was due primarily to increased sympathetic activity, whereas the subsequent decelerative component was due primarily to increased parasympathetic activity.

Although the preceding literature survey deals with ANS control of the cardiac CR, some studies also report data for the shock-elicited UR. For example, Kazis et al. (1973) reported that the accelerative UR of rabbits was more drastically reduced by propranolol than by atropine, and, completely eliminated by combined administration of the drugs.

These authors concluded that although both autonomic systems contributed to shock-elicited HR increases, sympathetic activation played the major role. Other studies which report evidence of primarily sympathetic control over UR acceleration include Katcher, Solomon, Turner, LoLordo, Overmier, and Rescorla (1969), who used surgical sympathectomy in dogs, and Pappas, DiCara, and Miller (1972), who used chemical sympathectomy (i.e., 6-hydroxydopamine) in rats. In both cases, it was found that sympathectomy reduced, but did not eliminate, the accelerative UR, and the authors concluded that although the response was due primarily to sympathetic outflow, the vagal system also contributed. Klose et al. (1975) found that the accelerative UR of rhesus monkeys was reduced by either atropine or propranolol acting alone, but eliminated only when both drugs were given together. They interpreted this finding as indicating that the UR, like the CR, was jointly determined by both sympathetic and parasympathetic innervations, but offered no conclusion as to which innervation may have been the more important contributor. The ANS innervations of decelerative URs have been examined in three studies using rabbits (Fredericks et al., 1974; Sampson et al., 1974; Schneiderman et al., 1969). In each case it was concluded that the normally-occurring decelerative UR was due almost exclusively to increased vagal restraint, after observations that the response was eliminated by atropine or surgical vagotomy, but unaffected by propranolol.

In summary, then, previous investigators have offered several different, and occasionally conflicting, views of the underlying ANS contributions to HR responses in Pavlovian conditioning procedures. With respect to CR acceleration, whether it constitutes the entire

response or is part of a biphasic response, some studies suggest that the major contribution is from the sympathetic system, while others suggest that it is from the parasympathetic system. With respect to CR deceleration, there seems to be a general consensus among investigators that an increase in vagal restraint on the heart is the primary source of observed HR deceleration, although there is some evidence of substantial sympathetic input to the response (Joseph & Powell, 1973; Kazis et al., 1973). Studies examining accelerative URs suggest that increased sympathetic outflow is primarily responsible for the observed shock-elicited HR increases, while studies examining decelerative URs suggest that increased parasympathetic discharge is the major contributor to their observed HR decreases.

At least some of the differing conclusions about ANS control of the cardiac CR lie in the differing CR patterns displayed by the various organisms studied and, in addition, stem from the fact that although most studies have blocked only one branch of the ANS, inferences are made about the relative contributions of both innervations to the intact CR. For example, some workers blocked only parasympathetic innervation and, after finding that CR magnitude was significantly reduced, concluded that the response must have been mostly of vagal origin (e.g., Dykman & Gantt, 1959). However, significant reduction of the CR might have been found as well after blockade of sympathetic influences, as reported by other investigators (e.g., Cohen & Pitts, 1968; Klose et al., 1975). Cohen (1974) argues that interference with activity in one branch of the ANS might also alter activity in the other branch so as to distort the relative contributions of each to

the original CR. He suggests, therefore, that within individual experiments investigators eliminate each nerve supply to obtain as clear a picture as possible of the relative sympathetic and parasympathetic contributions to the normally-occurring CR.

It can also be noted that, for their analysis of the relative ANS contributions to the CR, most investigators have relied on comparisons among experimental groups given different drug treatments, without examining the effects of the different drugs on the cardiac CR of individual organisms. Such comparisons are liable to several errors of inference as compared with procedures in which single organisms serve as their own controls (cf. Sidman, 1960).

In the present study, a longitudinal design was employed in which each subject was exposed to all experimental conditions. At every CS-US interval, from 2 through 120 sec, selective pharmacological blocking agents were administered in order to assess the relative sympathetic and parasympathetic contributions to observed cardiac CRs. With the rhesus monkey as experimental subject, this design offered the possibility of examining the ANS inputs to different CR forms within individual animals. Since the typical cardiac CR of this organism, at long CS-US intervals, is a biphasic response consisting of initial acceleration followed by deceleration over the course of CS, the present study may obviate some of the problems of comparing data across organisms which differentially display wholly accelerative or decelerative CRs.

Method

Subjects

Six experimentally-naive male rhesus monkeys (Macaca mulatta) obtained from a commercial importer served as subjects. The animals were kept in individual cages in the laboratory vivarium for 4-6 months prior to the start of the experiment, during which time tuberculin tests were performed periodically. Their daily diet consisted of ten food biscuits (Wayne Primate Food), totalling approximately 160 gms, distributed over three feedings, plus one-quarter apple. While in cages the animals had free access to water but during the subsequent period of chair restraint their water access was restricted to mealtimes (totalling approximately 800 ml water daily). At the start of the experiment each animal weighed approximately 5 kg and was judged to be healthy.

Apparatus

Throughout the experiment, each subject was confined to a restraint chair (BRS-Foringer, No. PC-002) equipped with a thoracic plate and cummerbund for added restraint. Each chair was mounted on a mobile experimental stand so that the animals could be easily transferred

between the vivarium and testing rooms. All experimental sessions were conducted with the chaired animals in individual sound-attenuating chambers (BRS-Foringer, No. PHC-002). Each chamber was equipped with: (1) an exhaust fan for continuous ventilation; (2) a blue overhead lamp (7.5 watt) which provided ambient illumination and served also as a session indicator when lit; and (3) an audio speaker mounted on the inside rear wall that was driven by a Grason-Stadler white noise generator (No. 901B) set at 10 db below 1.5 volts to provide masking noise during sessions.

The conditional stimulus (CS) was provided by two white indicator lights (Dialco, No. 101-3850-0975-201 sockets, 24 volt, with No. 327 bulbs) mounted on a metal minibox positioned approximately 20 cm from the subject's head (at eye level).

The unconditional stimulus (US) was an AC shock of 9.0 ±.5 mA intensity and 300 msec ±4 msec duration delivered to a shaved portion of the animal's tail through two brass foil electrodes held in place with Velcro bands and coated lightly with electrode jelly to improve contact. The electrical stimulus was generated by a constant current capacitive shocker with switching circuitry designed according to the specifications of Ramsay, Knapp, and Zeiss (1970) in order to eliminate large surges of current at shock onset and offset. Switching transients were further suppressed by a synchronous switch that allowed shock onset and offset only at zero volts on the AC cycle.

Each animal's EKG was monitored through two spiral electrodes (Siemens, No. 211140) implanted subcutaneously in the chest at locations which maximized the amplitude of the R-wave relative to other components

of the EKG waveform in order to facilitate digitizing of heart beats. A typical placement consisted of one electrode inserted subcutaneously at the sternum, with the other placed laterally, approximately 15 cm to the left. To prevent tampering with the electrodes each animal wore throughout the experiment a leather jacket which covered the electrodes and connector. The EKG signal was amplified by a Beckman Type R Dynograph and R-waves were digitized by a Schmitt trigger circuit connected to the output of the polygraph amplifier. Both the EKG signal and output of the digitizer were displayed on the writing unit of the polygraph to monitor the reliability of the digitizer circuit.

All data recording, timing functions, and stimulus presentations were controlled by a PDP-8 computer using a program system and interface designed by Snapper and Kadden (1973). The computer recorded intervals between successive cardiac systoles (R-waves) to the nearest .01 sec and stored these data on paper tape for later treatment offline.

Procedure

Two weeks before the start of the experiment all animals were implanted with EKG electrodes and placed in restraint chairs while tranquilized with approximately 100 mg Vetalar (ketamine hydrochloride, Parke-Davis). On each of five successive days preceding the first experimental session, each animal's tail was taped to the frame of the experimental stand, shock electrodes were put on, and approximately 15 min later he was placed in the experimental chamber for 2 hrs with

the overhead lamp and white noise on. Neither CS nor US were presented.

Experimental sessions were conducted daily except on the following occasions: (1) after a session in which drugs were administered a 48-hr waiting period intervened before the next scheduled session; and, (2) since implanting a pair of EKG electrodes required tranquilizing the subject with 100 mg Vetalar, a session was not held for 24 hrs thereafter.

All sessions began with a 10-min waiting period in the chamber with overhead lamp and masking noise on, followed by 20 CS-US pairings ("trials") at an average inter-trial interval of 5 min (range of 3.5 to 6.5 min). The experimental design involved eight different CS-US interval durations, measured from the onset of CS to the subsequent onset of US, of 2, 4, 6, 10, 20, 40, 60, and 120 sec. Each CS-US interval value was in effect for eight consecutive sessions: all animals began with the 2-sec CS-US value and progressed through longer interval values to 120 sec. A delay conditioning procedure was used throughout the experiment: CS remained on throughout the entire CS-US interval, and CS offset always coincided with US onset.

Autonomic blocking agents were administered to each animal during the 6th, 7th, and 8th sessions at each CS-US value. The substances used were: propranolol hydrochloride (Inderal, Ayerst) and atropine sulfate (Atropine, Lilly). The drugs were always injected intravenously in the animal's leg. The dosage of each drug was .16 mg/kg, an amount found adequate to achieve autonomic blockade in an earlier study from this laboratory (Schoenfeld et al., 1975). Propranolol was administered in the 6th session at each CS-US value, atropine was administered in

the 7th, and both drugs were administered in combination (from separate syringes) in the 8th session. During each drug session, 10 trials were given prior to drug administration (hereafter called pre-drug trials); the subject was then removed from the chamber, injected with the drug(s), and returned to the chamber for 10 more trials (hereafter called post-drug trials). A 10-min waiting period intervened between drug injection and the first post-drug trial to allow the drug to take effect, and to allow the disruptive effects of handling to subside before data collection.

Following exposure to CS-US intervals from 2 through 120 sec, all animals were re-exposed to the 20-sec interval for five consecutive sessions of 20 trials each. During a number of subsequent sessions, with the 20-sec interval still in effect, each animal was tested under several differing dosages of propranolol and of atropine. The ganglionic blocking agent, chlorisondamine (Ecolid, Ciba-Geigy), was also used. These additional drug manipulations were performed in an attempt to clear up some ambiguities in results obtained with the .16 mg/kg dosages. The details of these manipulations will be described with the results.

As the final stage of the experiment, all subjects were re-exposed for eight sessions (of 20 trials each) to the 2-sec CS-US interval, where the experiment had begun.

Data recording and analysis

On each trial, cardiac interbeat time (IBT) values were recorded in successive 2-sec periods beginning 2 sec before CS onset, continuing throughout the entire duration of CS, and for 12 sec following the onset of US. Recording was suspended during the .30-sec shock delivery and for 1.7 sec thereafter, due to movement artifacts induced by the shock.

Unfortunately, much of the post-shock UR data were lost due to an error in the computer data acquisition program. This error was detected (and subsequently corrected) after subjects had already been exposed to CS-US intervals from 2-120 sec. Therefore, UR data will be presented from re-exposure to the 20-sec CS-US interval only.

Most quantitative analyses of data were accomplished by reading the paper-tape output of sessions into a PDP 8/L computer under the control of a special-purpose program written in FOCAL language. From the individual IBT values a mean was computed for each 2-sec period of each trial by averaging all IBTs which began within the same 2-sec period. Thus, a trial of raw data was transformed into: (a) a mean for the 2-sec period just prior to CS onset; (b) a mean for each 2-sec segment of the CS-US interval; and, (c) a mean for each 2-sec segment of the 12-sec post-US recording period (when post-US data were available). Any IBT value that appeared to be distorted by movement artifact or otherwise "noisy" EKG signal, as indicated by the polygraph tracing, was eliminated from the data by setting upper and lower limits for IBT values which would be accepted by the computer program as data. Sometimes

an entire trial of data had to be eliminated because of recording difficulties.

Interbeat time values were not converted into heart rate values because the nonlinearity of this transformation can result in errors of interpretation (Khachturian et al., 1972). Nevertheless, in keeping with conventional practice, all data described verbally in the text are stated in terms of heart rate (larger interbeat times indicate lower heart rates, and vice versa). To facilitate conceptualization of IBT data in terms of heart rate, the ordinates of figures have been inverted so that increasing distances from the origin of the ordinate represent a decrease in IBT (increase in heart rate).

Results

CR form

Figures 1-6 present cardiac CR functions, composed of mean interbeat time values in successive 2-sec segments of the CS-US interval, for each of the six subjects. Within a figure, separate functions for CS-US intervals from 2 to 120 sec are shown. Each function begins with the 2 sec immediately prior to CS onset and continues until US onset. Each datum point is the mean of all pre-drug trials of the last three sessions at the designated CS-US interval. The ordinate is in units of interbeat time, but the scale of the ordinate is inverted so that a rising function represents an increase in heart rate, and a falling function represents a decrease in heart rate. Figures 1-6 show the following with respect to the form of the cardiac rate CR.

At the first three CS-US intervals from 2-6 sec, there is marked variability of CR form both within and between subjects. Among the 18 functions plotted for these intervals (3 intervals for each of six subjects), there is at least one instance of each of the following different CR forms: (a) a monophasic heart rate acceleration across the entire CS-US interval; (b) a monophasic heart rate deceleration across the CS-US interval; (c) a biphasic heart rate pattern of initial acceleration followed by deceleration within the CS-US interval; (d) a biphasic heart rate pattern of deceleration followed by acceleration;

Figures 1-6. Mean cardiac CR functions, for individual subjects, at CS-US intervals from 2 through 120 sec. Re-exposure functions (square data points) for the 2-sec and 20-sec CS-US intervals are shown within the same panels as their corresponding original exposure functions (round data points). The interbeat time axis is inverted so that the cardiac response functions can be conceptualized more easily as changes in heart rate.

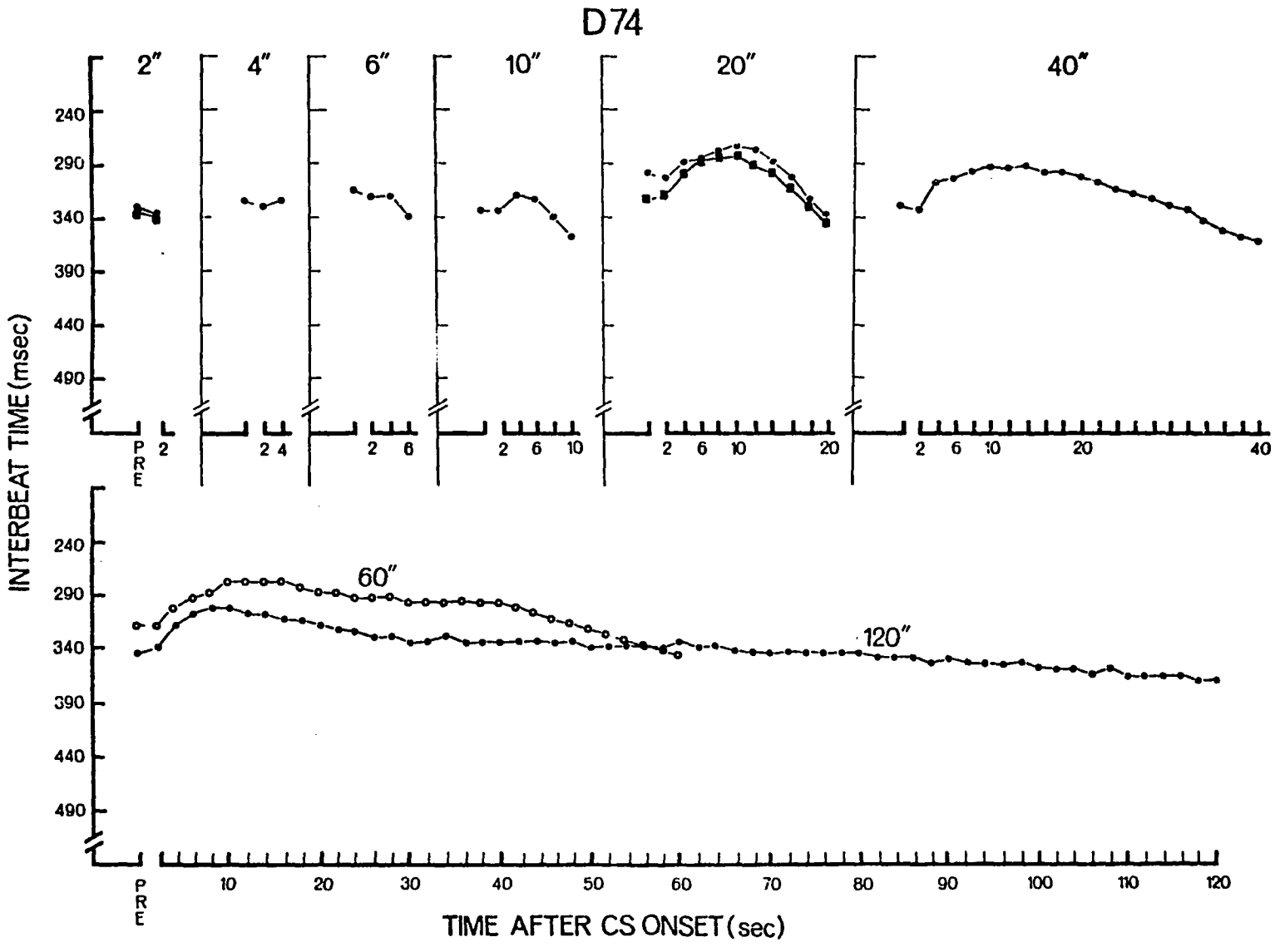
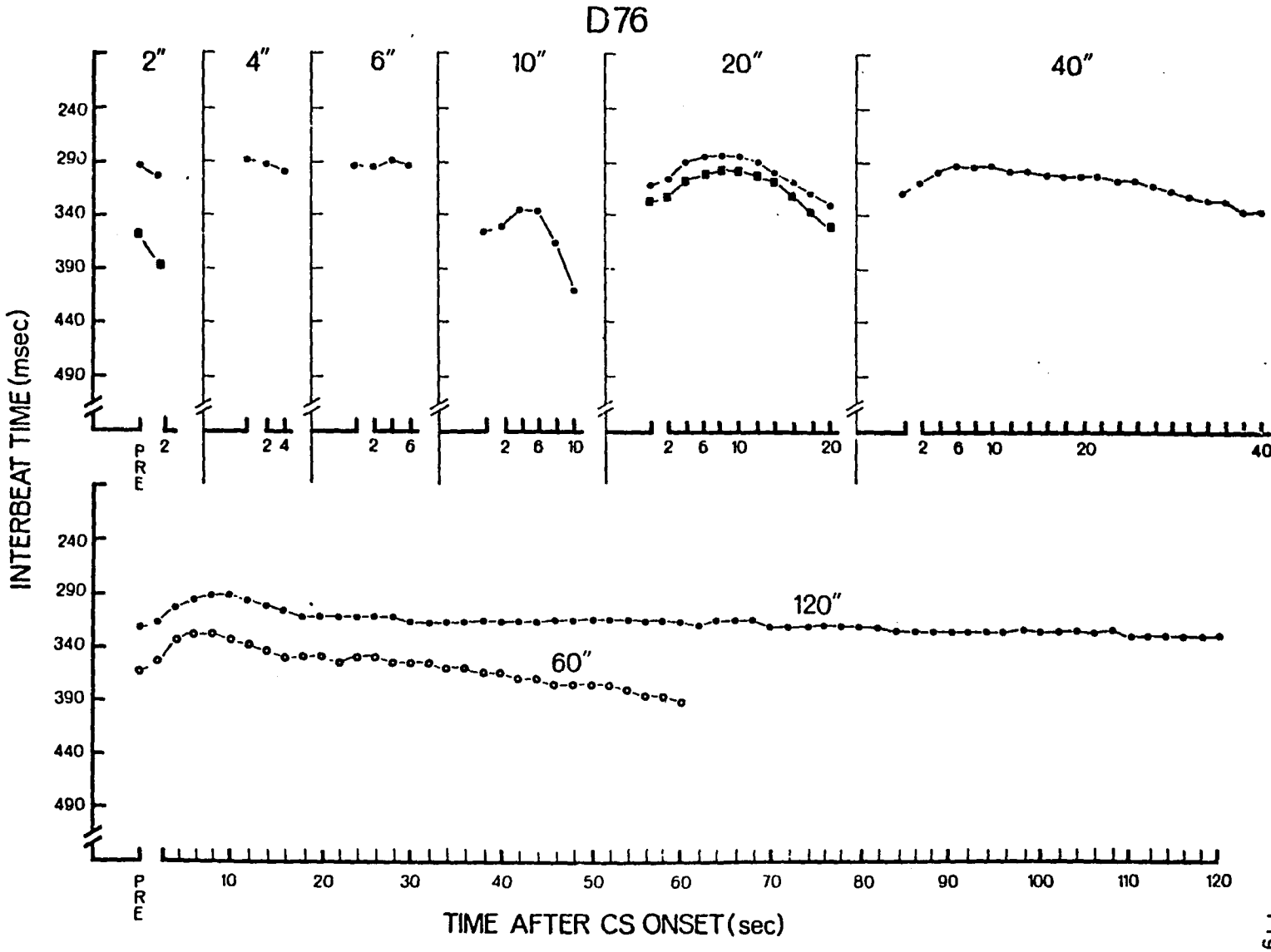

D74
2"
4"
6"
10"
20"
40"
60"
120"
INTERBEAT TIME (msec)
240
290
340
390
440
490
PRE
2
4
6
10
20
40
60
80
90
100
110
120
TIME AFTER CS ONSET (sec)

Fig.1


D76
2"
4"
6"
10"
20"
40"
240
290
340
390
440
490
INTERBEAT TIME (msec)
PRE
2
2 4
2 6
2 6 10
2 6 10 20
2 6 10 20 40
120"
60"
10 20 30 40 50 60 70 80 90 100 110 120
TIME AFTER CS ONSET (sec)

51
Fig. 2

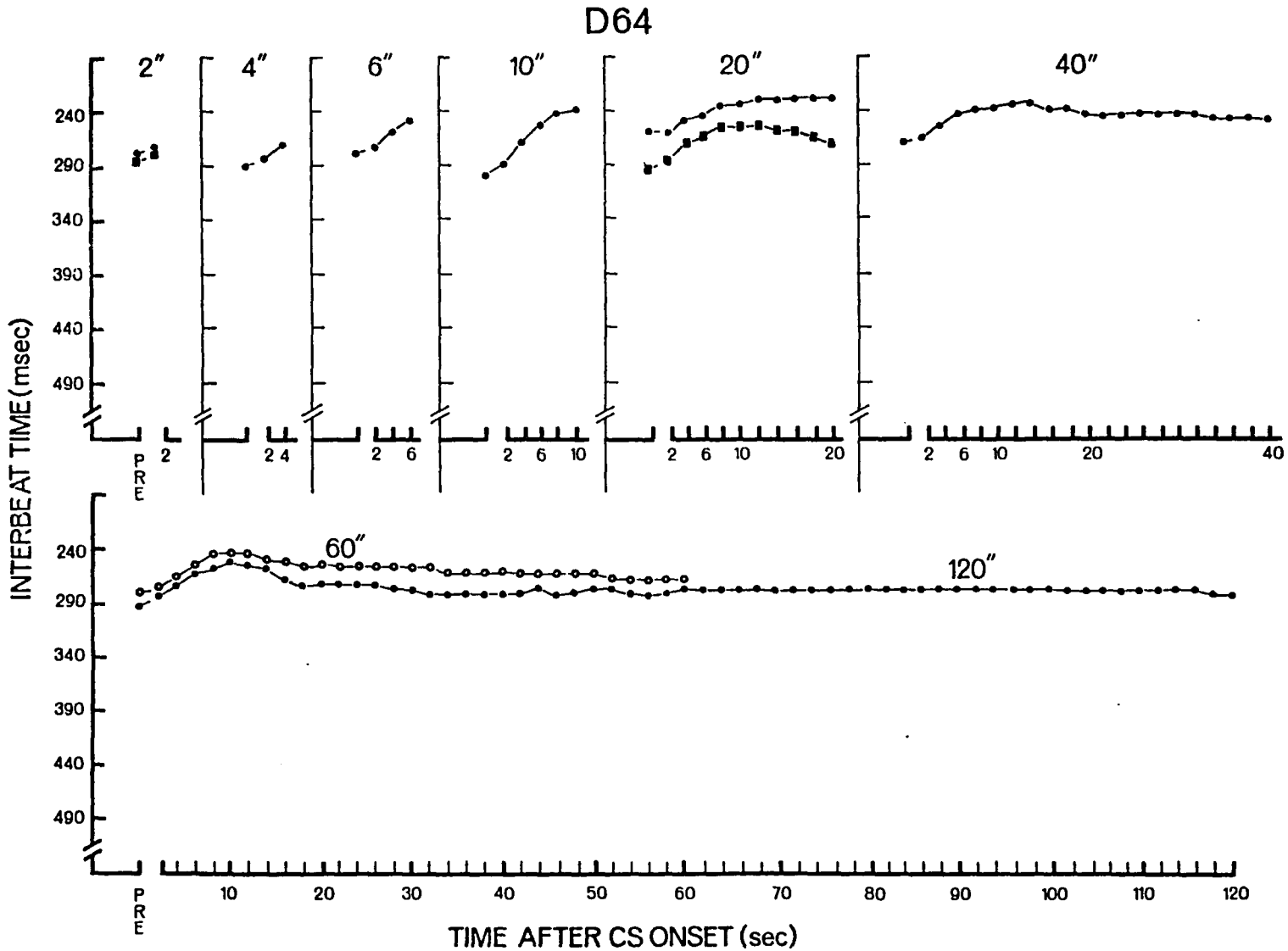
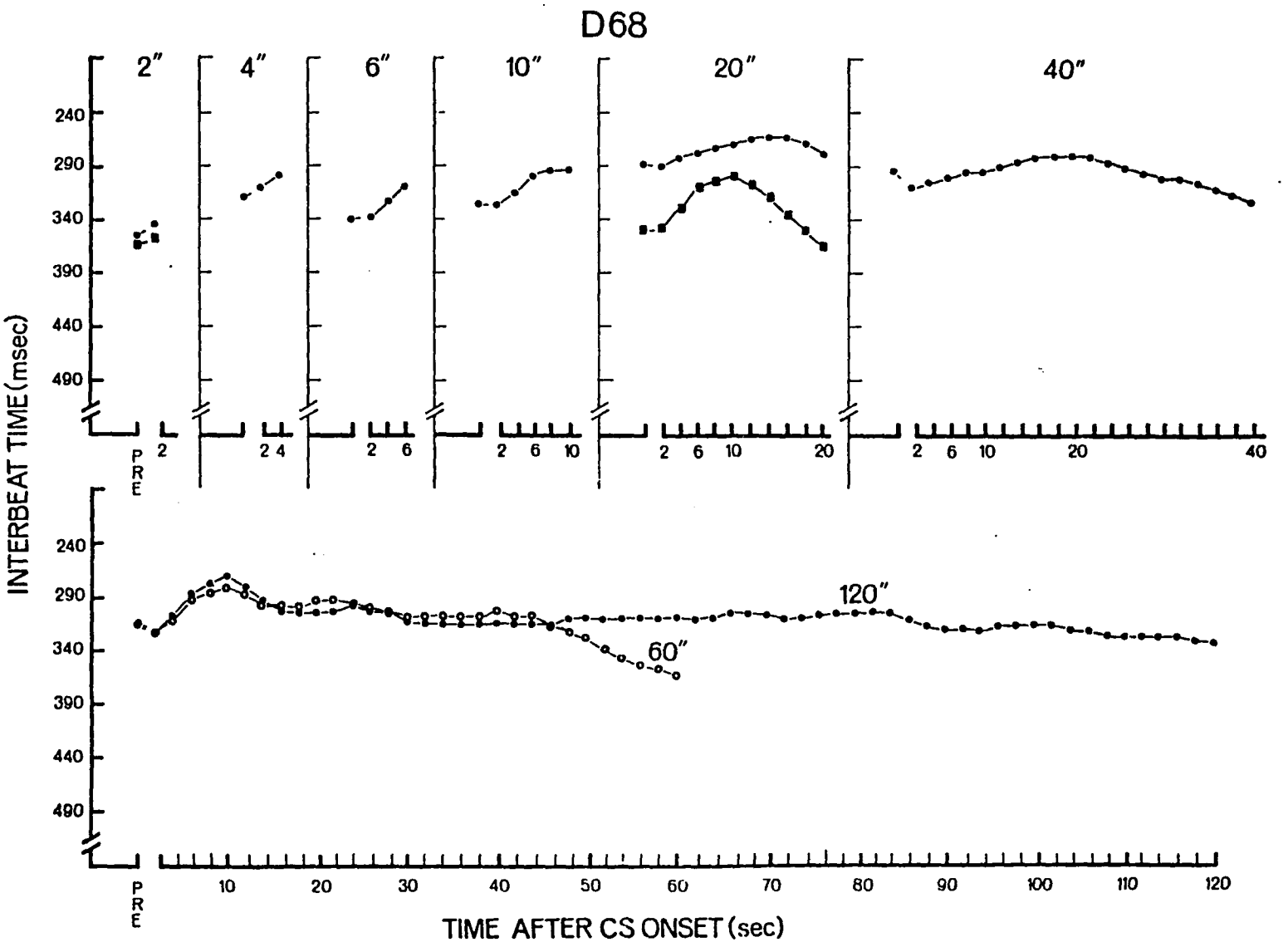

D64
2″
4″
6″
10″
20″
40″
60″
120″
INTERBEAT TIME (msec)
240
290
340
390
440
490
PRE
2
2 4
2 6
2 6 10
2 6 10 20
2 6 10 20 40
10 20 30 40 50 60 70 80 90 100 110 120
TIME AFTER CS ONSET (sec)

Fig. 3


D68
2"
4"
6"
10"
20"
40"
60"
120"
INTERBEAT TIME (msec)
240
290
340
390
440
490
PRE
2
2 4
2 6
2 6 10
2 6 10 20
2 6 10 20 40
10
20
30
40
50
60
70
80
90
100
110
120
TIME AFTER CS ONSET (sec)

53
Fig. 4

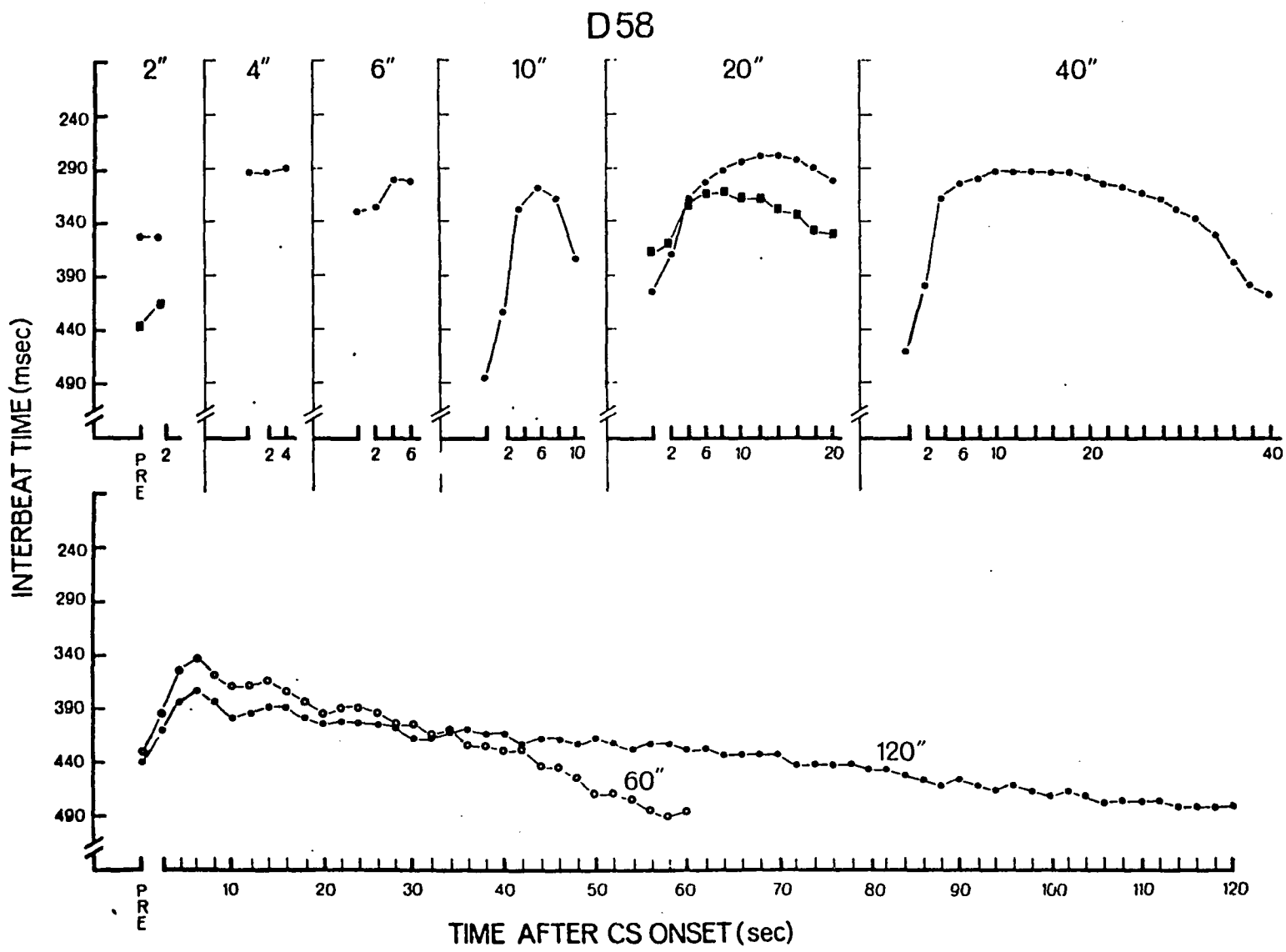

D58
2"
4"
6"
10"
20"
40"
240
290
340
390
440
490
PRE
2
2 4
2 6
2 6 10
2 6 10 20
2 6 10 20 40
INTERBEAT TIME (msec)
120"
60"
10
20
30
40
50
60
70
80
90
100
110
120
TIME AFTER CS ONSET (sec)

Fig.5

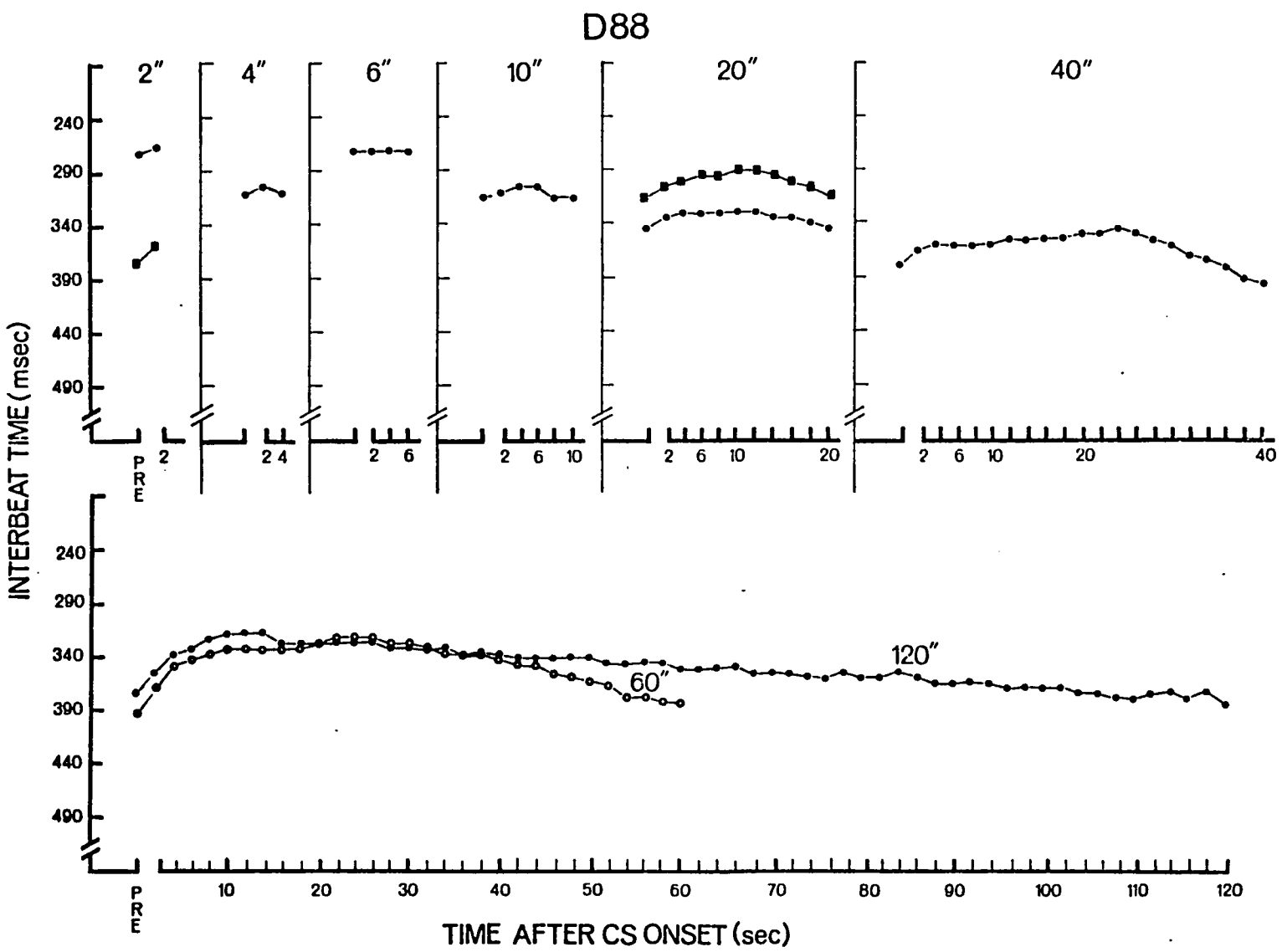

D88
2″
4″
6″
10″
20″
40″
240
290
340
390
440
490
INTERBEAT TIME (msec)
PRE
2
2 4
2 6
2 6 10
2 6 10 20
2 6 10 20 40
60″
120″
10 20 30 40 50 60 70 80 90 100 110 120
TIME AFTER CS ONSET (sec)

Fig. 6

and even, (e) no conditional heart rate response. Subjects D64 and D68, however, show monophasic acceleration until US onset at all three CS-US intervals.

At the 10-sec CS-US interval, there is much greater consistency of CR form, with all subjects showing HR acceleration for at least the first 4 sec of CS. Four subjects reach a peak of acceleration at 4-6 sec after CS onset and then decelerate until US, while D64 and D68 again show monophasic HR acceleration across the entire CS-US interval.

At the 20-sec interval, five of the six subjects show a biphasic HR pattern of acceleration followed by deceleration during CS. Only subject D64 fails to clearly display HR deceleration toward the end of CS. The initial accelerative component lasts for at least 10 sec and generally peaks near the middle of the interval before reversing to deceleration. This duration of initial acceleration differs from that of the preceding 10-sec interval, where most subjects reversed to deceleration within 6 sec after CS onset. Lowest HR after the peak occurs during the final 2 sec before US: at that point heart rates are below the level of pre-CS in three animals (D74, D76, and D88). Subjects D76 and D58 show less rapid deceleration from the peak during the 20-sec interval as compared with that of the previous 10-sec interval.

At the 40-sec interval, CS onset results in HR acceleration for at least 14 sec followed by a longer-lasting deceleration of at least 20 sec. All subjects display a later peak of acceleration than at the two previous intervals. Subjects D68 and D88, for example, show peak acceleration near the middle of the CS-US interval (20-24 sec into CS). Similarly, D58 reaches a peak at 10 sec into CS and then

sustains that peak rate until 20 sec, before reversing to deceleration. For all subjects, the lowest HR after the peak again occurs during the final 2 sec before US. Terminal CS rates drop below pre-CS levels for all animals except D64 and D58.

At the 60-sec interval, a long-duration biphasic CR function is again evident during CS, with the decelerative component occupying the major portion of the CS-US interval. Although in four subjects the duration of the initial accelerative component, and thus the location of peak HR in CS, is the same as that of the previous 40-sec interval, two subjects (D58 and D68) show an earlier peak of acceleration than at the 40-sec interval. Both of these animals also display a fractionation of the subsequent decelerative component into smaller phasic cycles of acceleration followed by deceleration. As at the 20- and 40-sec intervals, lowest HR after the peak again occurs close to US (2-4 sec before) although now terminal CS heart rates reach or drop below pre-CS levels for all animals except D64. Subject D64 is consistently unlike the other animals in that his cardiac CR pattern, at each CS-US interval from 10-120 sec, shows little (if any) HR deceleration from the peak, with maximal or near maximal heart rates sustained until the onset of US.

At the 120-sec interval, the biphasic CR form is maintained although the decelerative component now occupies almost the entire duration of CS. As can be seen, CS onset results in HR acceleration for 10 sec or less, followed by a gradual deceleration which stretches across the remaining 110 sec of the interval. The point of lowest HR in the biphasic function occurs for most subjects during the final 2-4 sec before US, although two subjects (D76 and D58) show their

lowest HRs 8-12 sec before US. Terminal CS rates drop below pre-CS levels in all subjects except D64, who maintains a constant elevated HR level across the latter 100 sec of CS. A comparison of cardiac rate patterns at CS-US intervals of 60- and 120-sec, within individual animals, shows that the two functions closely parallel one another for approximately the first 40 sec after CS onset; during the next 20 sec, however, heart rates decrease more rapidly within the 60-sec interval as the delivery of US draws near. At 60 sec into the 120-sec interval heart rates are still higher than pre-CS levels while at that same point within the 60-sec interval heart rates are already lower than pre-CS levels. The location of peak acceleration within the 120-sec interval is nearly identical to that of the 60-sec interval for all subjects except D88 who shows a much earlier peak of acceleration within the 120-sec interval. All subjects show an earlier peak of acceleration at the 120-sec CS-US interval as compared with the 40-sec interval.

Following exposure to CS-US intervals from 2-120 sec, all subjects were re-exposed to the 20-sec and 2-sec intervals, in that order. (Re-exposure intervals will be designated by the Roman numeral II.) To facilitate comparisons, re-exposure CR functions (square data points) are presented within the same panels of Fig. 1-6 as their corresponding original exposure functions.

Figures 1-6 reveal that at 20-sec II all subjects retain the biphasic CR form but only three of them (D74, D76, and D88) fully recover their original rates of acceleration and deceleration within CS. The other three display earlier peaks of acceleration and faster rates of

deceleration during re-exposure as compared with original exposure. Comparisons can also be made between HR patterns at 20-sec II and those of the immediately preceding 120-sec interval. In this regard, subjects D64 and D58 show HR patterns at 20-sec II which are identical to those of the first 20 sec of the 120-sec interval. Such a finding would suggest that US onset at 20-sec II merely truncated the CR pattern established at the previous longer CS-US interval of 120 sec. The four other subjects, however, show more rapid deceleration from the preceding peak of acceleration at 20-sec II than during the identical time periods, measured from CS onset, of the 120-sec interval. At 20 sec into the 120-sec interval heart rates are still higher than pre-CS levels whereas at the same point in the 20-sec interval heart rates are already below pre-CS levels. Apparently, if these animals had not adjusted their rates of deceleration to the shorter CS-US interval of 20 sec, they would not have reached baseline heart rate level before the onset of US.

Figures 1-6 also reveal that during re-exposure to the 2-sec CS-US interval, original performance was systematically recovered in all subjects. A decelerative CR is again evident in subjects D74 and D76 while an accelerative CR is again evident in each of the four other animals.

It appears, then, that from a variety of cardiac CR forms at the initial 2-6 sec CS-US intervals there emerged a consistent biphasic CR pattern of initial acceleration followed by deceleration at CS-US intervals from 10-120 sec. Locations of peak acceleration and deceleration changed as a function of CS-US length: peaks of acceleration occurred progressively further from CS onset as the CS-US interval

increased from 10-40 sec, but then moved closer to CS onset at longer intervals of 60 and 120 sec. The peak of deceleration (lowest HR) in the biphasic function moved increasingly further from CS onset as the CS-US interval increased from 10-120 sec and almost always occurred within the final 2-4 sec before US. Another aspect of the biphasic CR which changed with the length of the CS-US interval was the rate of HR deceleration from the preceding peak of HR acceleration in CS: more rapid decelerations were noted at shorter CS-US intervals when compared with longer intervals. During re-exposure to the 20-sec CS-US interval, the biphasic CR pattern was retained but only three subjects closely matched their original rates of acceleration and deceleration within CS. Re-exposure to the 2-sec interval, where the experiment had begun, systematically recovered the original accelerative or decelerative CR form in all subjects.

For all CS-US intervals 10 sec and longer, the following computations were made: (a) latency from CS onset to the peak of acceleration, and (b) rate of HR deceleration from the peak. Table 1 lists for each subject at each CS-US interval: (1) the mean latency from CS onset to peak HR in CS; (2) the standard deviation of latency values; (3) the ratio of standard deviation to CS-US interval length; and (4) the mean time between peak HR in CS and the onset of US. Latency values were obtained as follows: for each trial, peak HR was located by counting the number of 2-sec periods from CS onset to the smallest mean IBT (highest HR) within CS. (In the case of ties only the first 2-sec period in which the highest HR occurred was counted.) These values were then averaged across all pre-drug trials of the last three sessions

Table 1

Mean latency of peak HR in CS, standard deviation (SD) of latency values, ratio of standard deviation to CS-US interval length (SD/CS-US), and mean time between peak HR in CS and US onset (peak to US interval) as a function of CS-US interval length

		CS-US Interval (sec)					
S#		10	20	40	60	120	20 II
D74	Mean latency(sec)	4.54	10.26	14.34	17.14	15.41	8.46
	SD	1.02	2.26	5.12	7.42	20.50	2.22
	SD/CS-US	0.10	0.11	0.13	0.12	0.17	0.11
	peak to US(sec)	5.46	9.74	25.66	42.86	104.59	11.54
D76		5.12	8.26	11.06	7.20	12.80	8.90
		5.76	2.48	5.76	1.90	14.76	1.62
		0.58	0.12	0.14	0.03	0.12	0.08
		4.88	11.74	28.94	52.80	107.20	11.10
D64		10.00	15.58	17.20	17.20	16.12	10.42
		0.00	2.02	9.70	9.70	13.00	2.16
		0.00	0.10	0.24	0.16	0.11	0.11
		0.00	4.42	22.80	42.80	103.88	9.58
D68		8.62	14.22	18.28	19.94	24.16	9.50
		1.50	3.26	5.20	10.89	20.34	1.86
		0.15	0.16	0.13	0.18	0.17	0.09
		1.38	5.78	21.72	40.06	95.84	10.50
D58		6.52	12.78	15.58	10.86	16.73	11.46
		0.88	2.50	6.38	8.04	21.78	4.44
		0.09	0.13	0.16	0.13	0.18	0.22
		3.48	7.22	24.42	49.14	103.27	8.54
D88		5.14	8.66	19.94	24.06	20.34	9.76
		2.04	4.30	8.50	10.42	12.51	3.64
		0.20	0.21	0.21	0.17	0.10	0.18
		4.86	11.34	20.06	35.94	99.66	10.24

for each CS-US interval and converted into seconds post-CS onset. The mean time between peak HR and the onset of US was obtained by subtracting the mean latency to peak (in sec) from the duration of the CS-US interval.

Table 1 indicates that the latency to peak HR in CS increased with the length of the CS-US interval, although there was a reversal of this trend at the 60- or 120-sec interval in all subjects except D68. These reversals are obscured in the group function (Fig. 7), due to averaging. Most subjects showed a shorter latency to peak CS heart rate at 20-sec II, as compared with original exposure.

Table 1 also indicates that variability of CR peak location increased in roughly constant proportion with the length of the CS-US interval: for any one subject (except D76), the ratio of standard deviation to CS-US interval length remains fairly constant across intervals. Table 1 also shows that the peak-to-US interval increased much more rapidly than the latency from CS onset to the peak, with longer CS-US intervals. This reflects the fact that the latency to peak did not lengthen as rapidly as the CS-US interval.

A further analysis of the latency data was made by constructing relative frequency distributions of the temporal locations of peak CS HR within CS-US intervals of 10, 40, and 120 sec, as shown in Figs. 8-13. These distributions were constructed by making frequency counts, across trials, of the 2-sec CS periods in which the maximum mean HR (minimum mean IBT) occurred. These figures show how changes in the CS-US interval affected the distribution of maxima within CS: At the 10-sec CS-US interval, maximum HR almost always occurred within the first 6 sec of

Figure 7. Group function for mean latency to peak acceleration at CS-US intervals of 10-120 sec original exposure (closed data points) and 20-sec re-exposure (open datum point). Each point represents mean time (sec) from CS onset to the peak, for all pre-drug trials at each condition, averaged over six subjects.

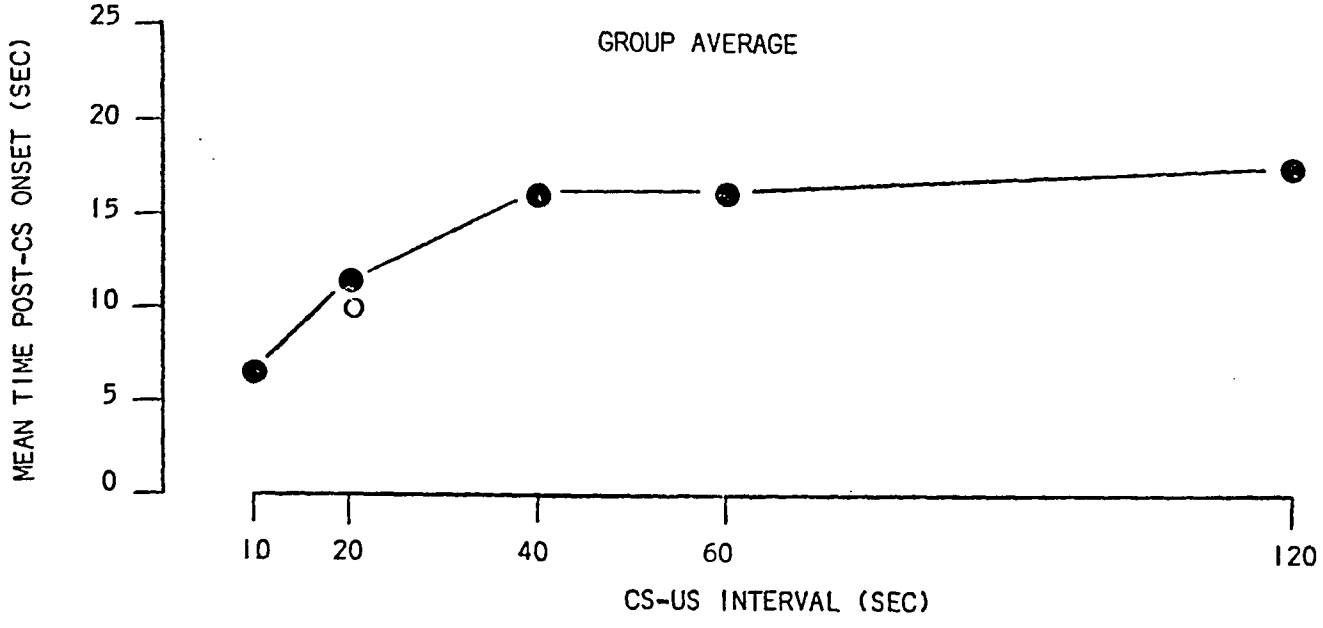
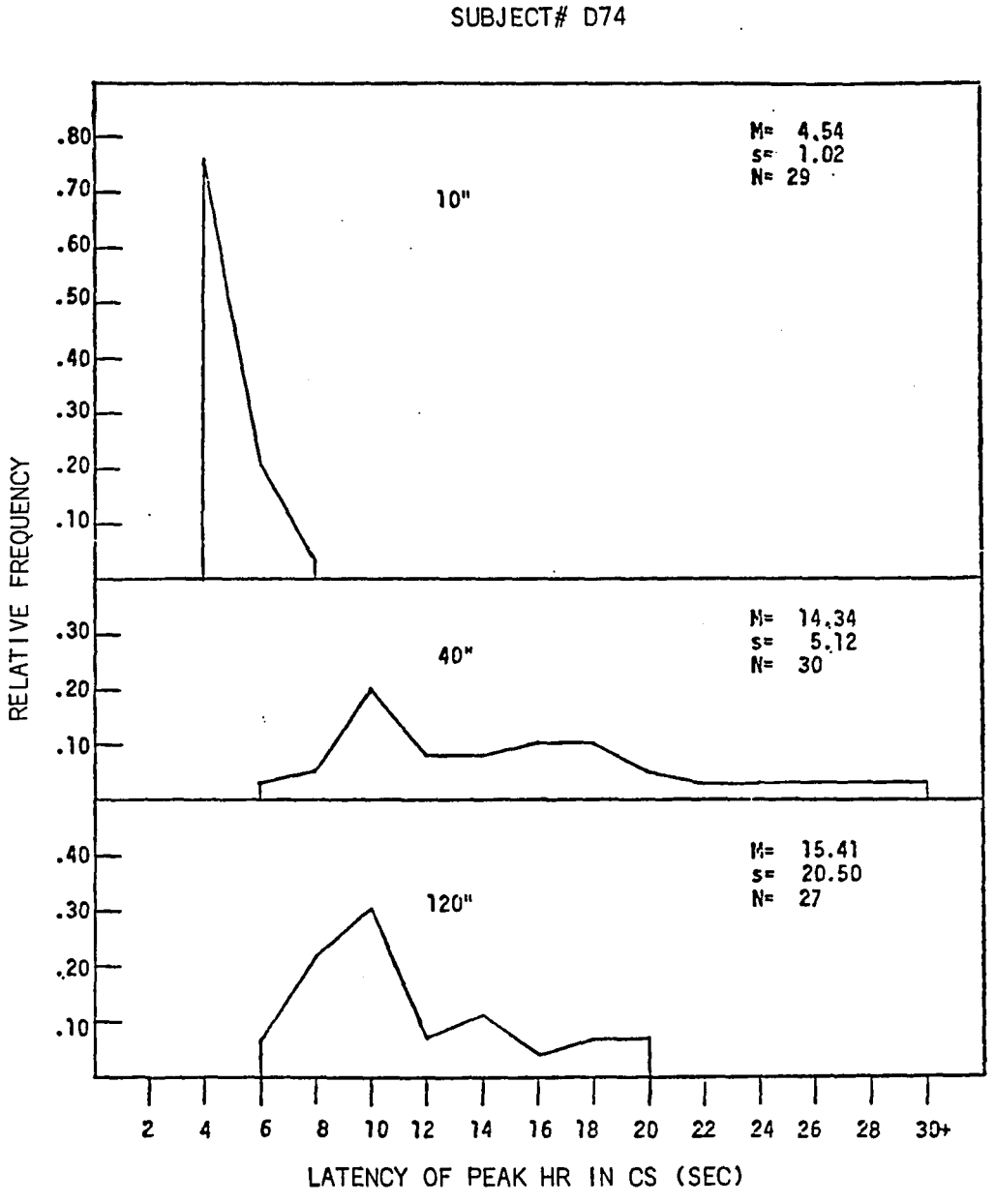

GROUP AVERAGE
MEAN TIME POST-CS ONSET (SEC)
25
20
15
10
5
0
10
20
40
60
120
CS-US INTERVAL (SEC)

Fig.7

Figures 8-13. Relative frequency distributions of the location of peak heart rate within successive 2-sec CS periods, for each subject, at CS-US intervals of 10, 40, and 120 sec. No distribution is shown for subject D64 at the 10-sec CS-US interval, because his peak heart rate invariably occurred during the final 2 sec of CS. Latencies of 30 sec and longer are grouped into a single class interval designated "30+." Each distribution is based on all pre-drug trials of the last three sessions at the designated CS-US interval. Means (M) and standard deviations (s) of the distributions are shown at the upper right of each figure panel, as are the number of trials (N) upon which each distribution is based.

Fig.8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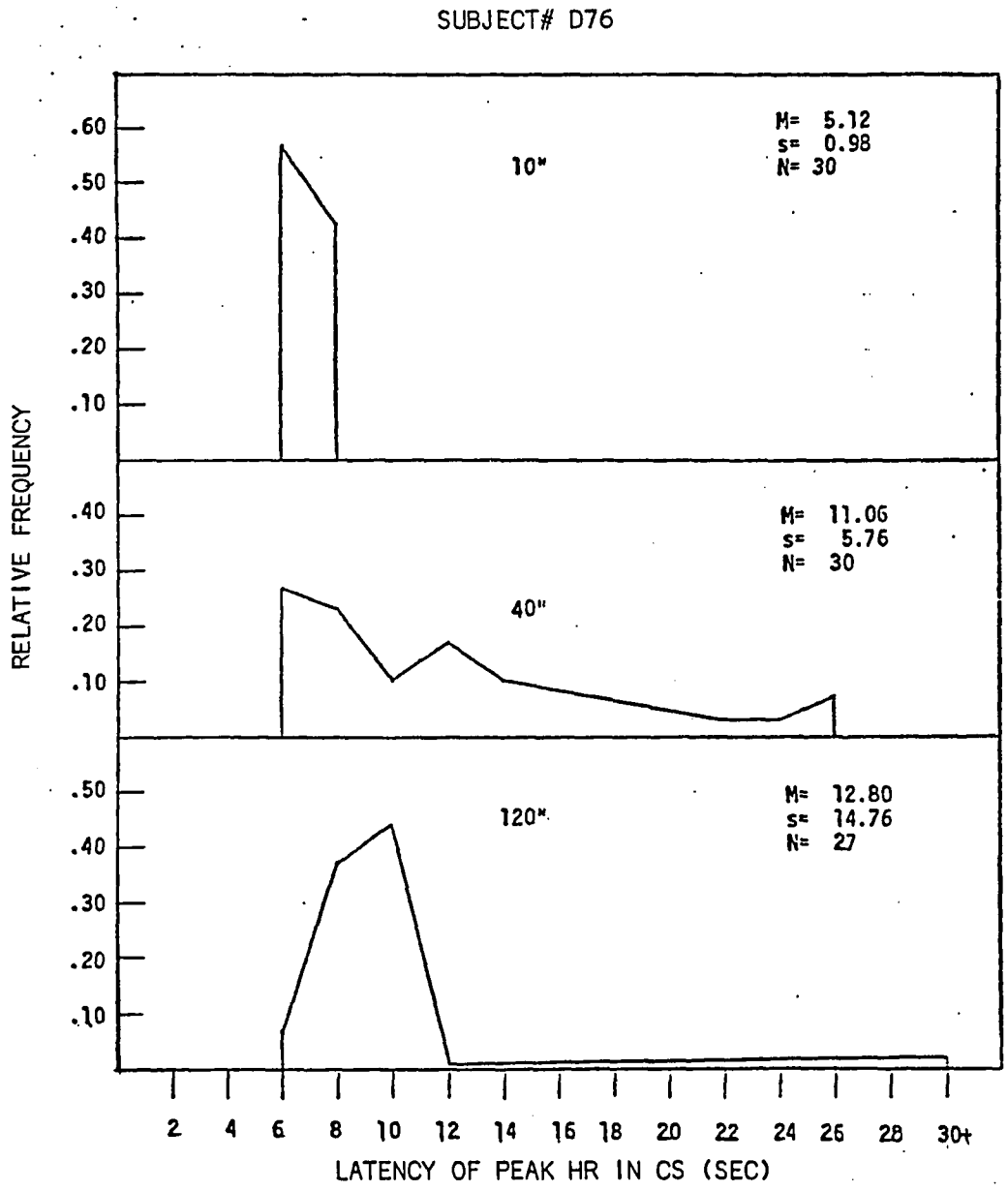
10"
M= 14.34
s= 5.12
N= 30
40"
M= 15.41
s= 20.50
N= 27
120"
.80
.70
.60
.50
.40
.30
.20
.10
.30
.20
.10
.40
.30
.20
.10
RELATIVE FREQUENCY
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30+
LATENCY OF PEAK HR IN CS (SEC)

Fig.9


SUBJECT# D76
RELATIVE FREQUENCY
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.50
.40
.30
.20
.10
10"
M= 5.12
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N= 30
.40
.30
.20
.10
40"
M= 11.06
s= 5.76
N= 30
.50
.40
.30
.20
.10
120"
M= 12.80
s= 14.76
N= 27
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30+
LATENCY OF PEAK HR IN CS (SEC)

Fig.10

SUBJECT# D64

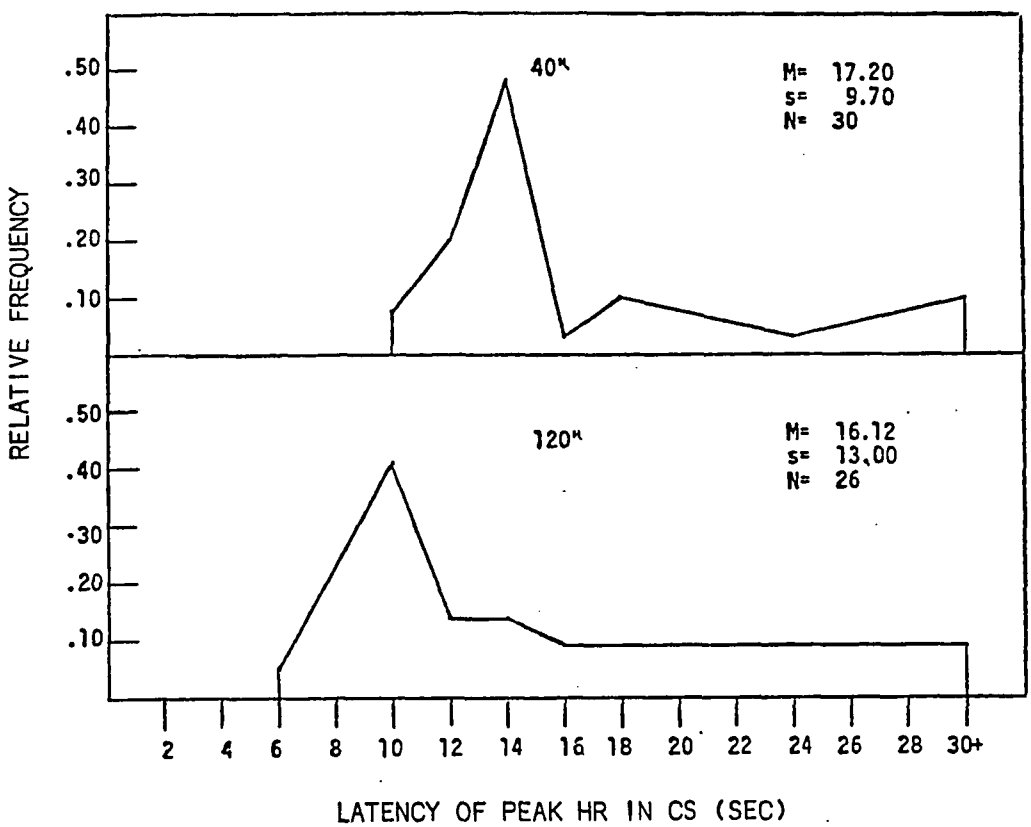


Fig.11

SUBJECT# D68

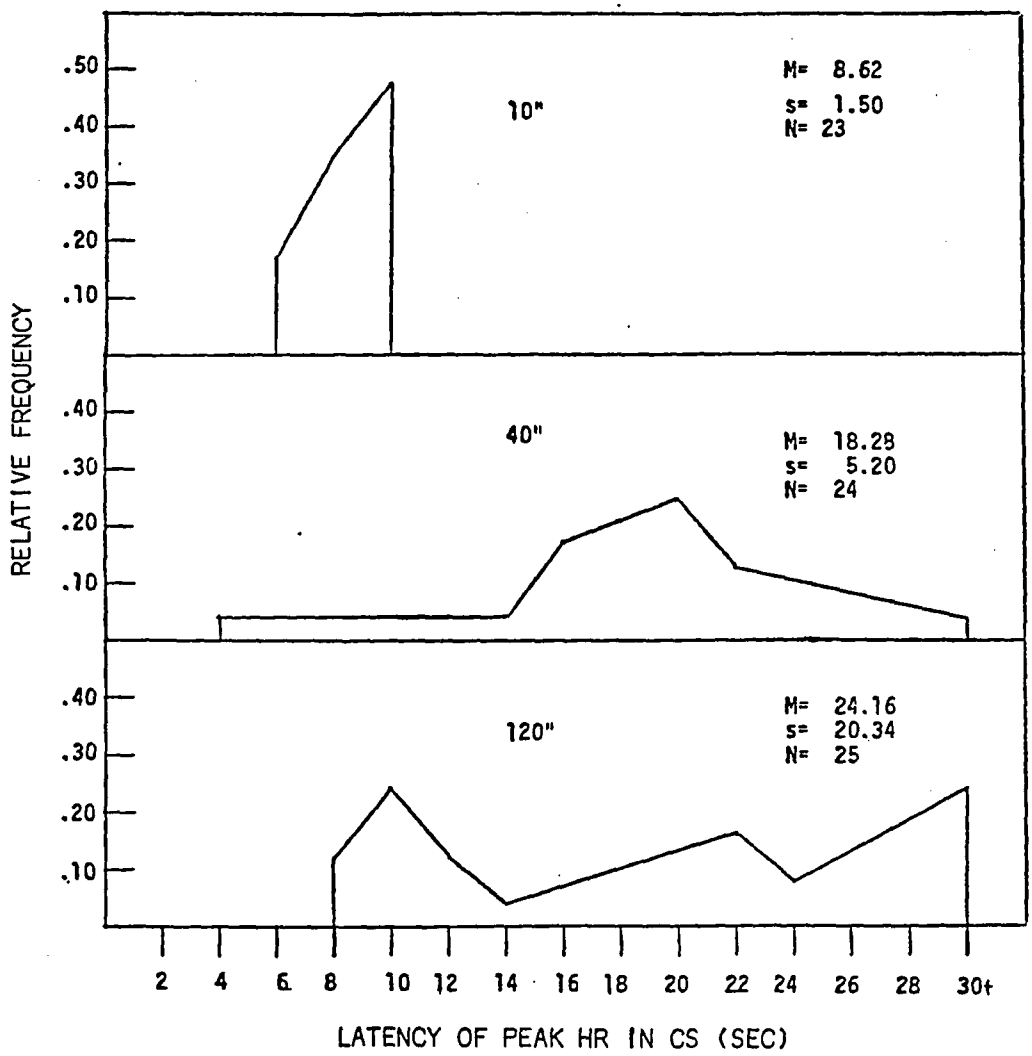
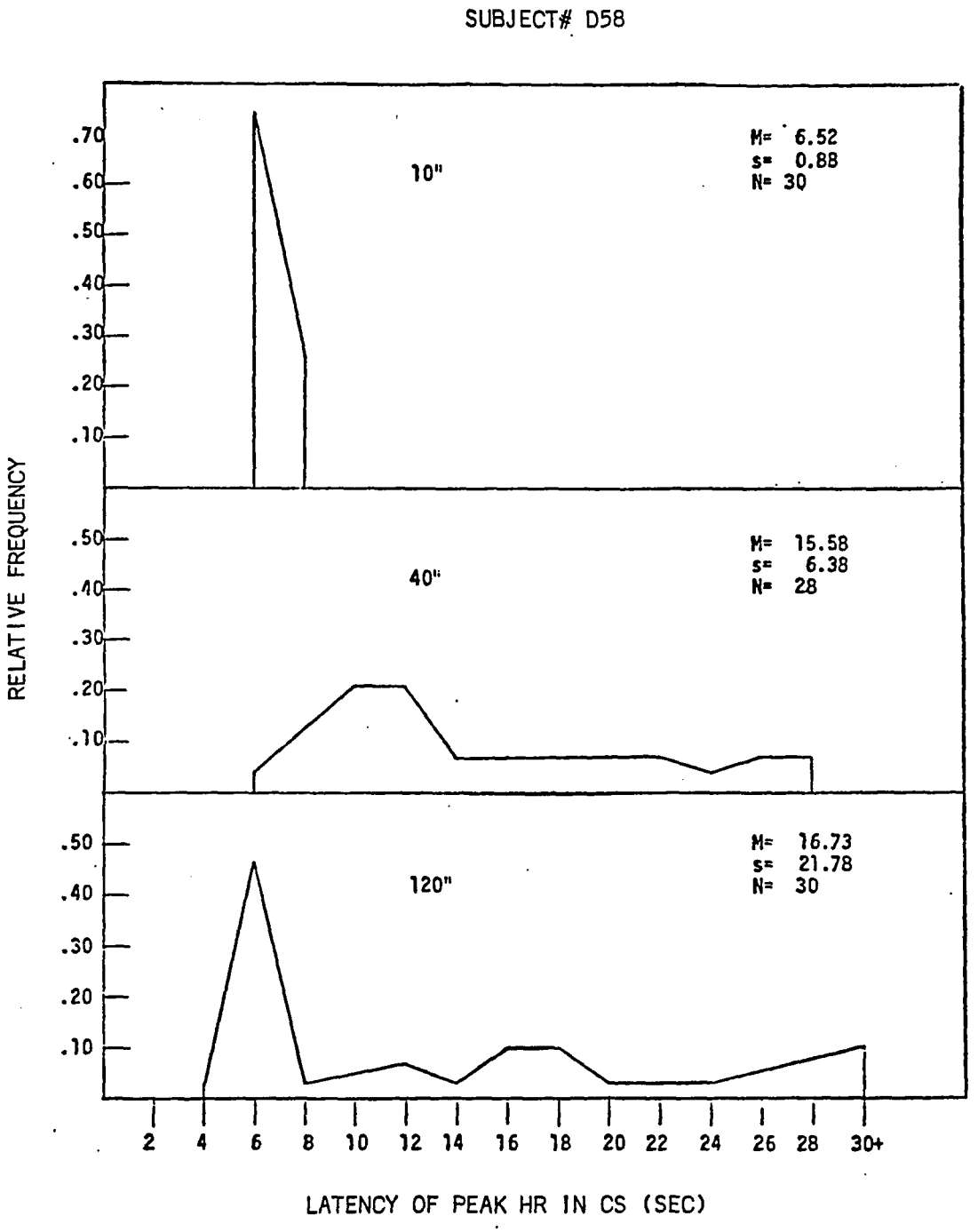


Fig.12


SUBJECT# D58
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.60
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.40
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.20
.10
10"
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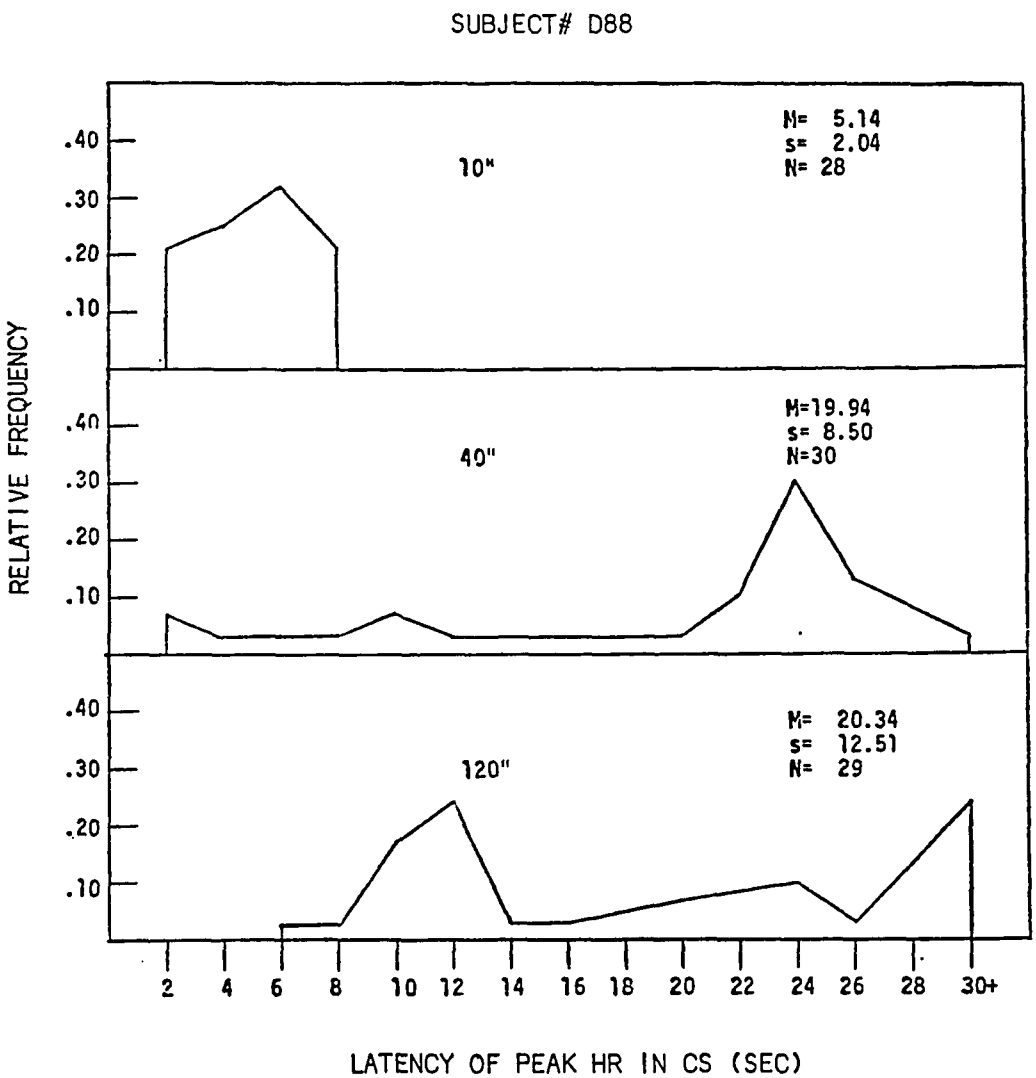
N= 30
.50
.40
.30
.20
.10
40"
M= 15.58
s= 6.38
N= 28
.50
.40
.30
.20
.10
120"
M= 16.73
s= 21.78
N= 30
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30+
LATENCY OF PEAK HR IN CS (SEC)

Fig.13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N= 28
40"
M=19.94
s= 8.50
N=30
120"
M= 20.34
s= 12.51
N= 29
RELATIVE FREQUENCY
.40
.30
.20
.10
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30+
LATENCY OF PEAK HR IN CS (SEC)

CS, except for D64 who invariably accelerated until the end of CS. At the 40-sec interval, however, there is both a decrease in the number of maxima early in CS (i.e., within the first 20 sec after CS onset) and an increase in the number later in CS. For all subjects except D76 the mode of the distribution is shifted to the right (i.e., toward longer latency values), relative to the 10-sec interval. This is seen most dramatically in the case of D88. At the 120-sec interval, as compared with the 40-sec, there are a greater number of maxima early in CS. For example, three subjects (D76, D64, and D58) display peak heart rates within 6-10 sec of CS onset on nearly half of all trials at the 120-sec interval, and two other animals (D68 and D88) display bimodal frequency distributions indicating that peak HR occurs either during the first 12 sec of CS or at least 30 sec after the onset of CS.

Table 2 lists, for each subject, mean rate of cardiac deceleration between the peak of acceleration and the subsequent peak of deceleration at CS-US intervals of 10-120 sec. Rate of deceleration was computed as follows. For each trial, the magnitude of HR deceleration was obtained by subtracting the mean minimum IBT (highest HR) in CS from the subsequently observed mean maximum IBT (lowest HR) toward the end of CS. This difference (in msec) was then divided by the number of 2-sec time periods between the locations of peak acceleration and deceleration, thereby yielding the average rate of deceleration per 2 sec. These rate values were then averaged over all pre-drug trials for each subject at each CS-US interval, and listed in Table 2.

The data in Table 2 indicate that the rate of cardiac deceleration in the biphasic CR function decreased with CS-US intervals from 10-120 sec.

Table 2

Mean rate of cardiac deceleration (msec increase in IBT per 2 sec), after peak acceleration, as a function of CS-US interval

		CS-US Interval (sec)					
		10	20	40	60	120	20 II
Subject#	D74	17.55	14.91	6.41	3.32	1.45	12.41
	D76	37.74	9.58	4.72	2.06	0.66	10.87
	D64[a]		1.40	2.20	1.92	2.82	3.42
	D68	4.22	8.68	5.89	4.32	3.97	13.58
	D58	42.55	8.07	11.30	5.86	2.43	15.93
	D88	5.70	5.23	6.30	5.01	1.64	5.95
	MEAN	21.55	7.98	6.14	3.75	2.16	10.36

[a] No deceleration at 10-sec CS-US

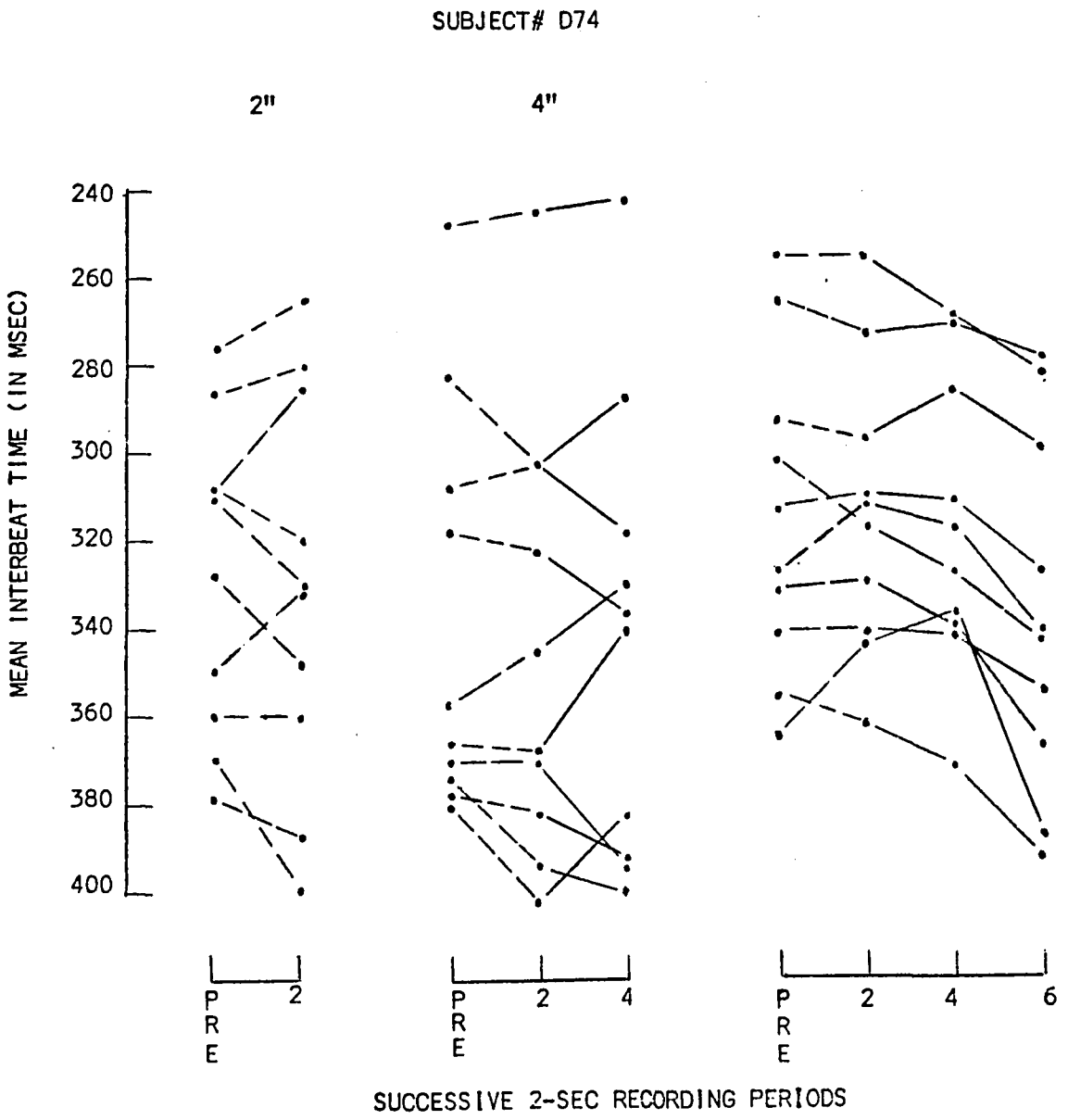
This effect is most pronounced in subject D76 and absent in D64. The data also show that the rate of deceleration increased several-fold when the CS-US interval was reduced from 120 sec back to 20 sec; for most subjects, heart rates decelerated more rapidly during 20-sec II as compared with original exposure. Unlike the peak-acceleration data, a visual inspection of the deceleration data showed that at each CS-US interval from 10-120 sec, there was almost no variability in the location of peak deceleration. Figs. 1-6 thus accurately reflected that the point of lowest HR in the biphasic CR function almost always occurred within the final 2-4 sec before US.

Thus, the data appear to indicate that there were changes not only in the form of the cardiac CR but also in the temporal distribution of heart rates within the CS-US interval, as a function of CS-US interval length. Over CS-US intervals of 10-120 sec, latency to peak acceleration and also the interval between peak acceleration and US onset increased, although shorter latencies to peak acceleration were noted at the two longest CS-US intervals of 60- and 120-sec when compared with the 40-sec interval. Also, variability in location of peak HR in CS increased, but in roughly constant proportion to the length of the CS-US interval. Location of maximum deceleration in the biphasic CR function shifted progressively further from CS onset with longer CS-US intervals, and almost always occurred just prior to the onset of US. The rate of HR deceleration from the preceding peak of acceleration was inversely related to the length of the CS-US interval: the longer the interval the slower the decline in HR from peak acceleration to peak deceleration.

The form of the cardiac rate CR changed not only with the length of the CS-US interval, but also with changes in pre-CS heart rate level. The data are presented in Figs. 14-19, which show ten cardiac CRs for each subject at CS-US intervals of 2, 4, and 6 sec. Each group of ten CRs was selected from the intact pre-drug trials at each CS-US interval so as to include: (a) the CR following the highest pre-CS HR level; (b) the CR following the lowest pre-CS HR level; and, (c) eight additional CRs, selected at random, with the restriction that no more than one CR would be shown for any given pre-CS level. Each datum point in these figures represents the mean IBT (in msec) in a 2-sec recording period for a single trial.

Figures 14-19 indicate that CR form can change markedly with changes in pre-CS heart rate. Moreover, the CRs of four subjects (D64, D68, D58, and D88) conform closely to the predictions of the law of initial value in that low pre-CS heart rates tend to be followed by large increases in HR during CS, whereas high pre-CS rates tend to be followed by smaller increases or even decreases in HR during CS. Note that at the highest pre-CS rates the CR function is often entirely flat (i.e., HR changes within the CS-US interval are absent), suggesting a "ceiling" effect. Particularly noticeable for three of these animals (D64, D68, and D58) is a narrowing in the range of observed rates from pre-CS into CS, indicating that CS onset produced a decrease in HR variability. Similar observations have been reported by Lynch (1968) and by Ramsay (1970). In contrast to the above, the responses of subjects D74 and D76 do not conform to LIV: D76 shows a reverse LIV effect as indicated by larger decelerations with lower pre-CS heart

Figures 14-19. Ten cardiac CRs at differing pre-CS heart rates for each subject at CS-US intervals of 2, 4, and 6 sec. Each figure is divided into three panels showing, from left to right, data for the 2-sec, 4-sec, and 6-sec CS-US intervals. Each datum point represents the mean IBT (in msec) in a 2-sec recording period for a single trial.


SUBJECT# D74
2"
4"
MEAN INTERBEAT TIME (IN MSEC)
240
260
280
300
320
340
360
380
400
PRE
2
PRE
2
4
PRE
2
4
6
SUCCESSIVE 2-SEC RECORDING PERIODS

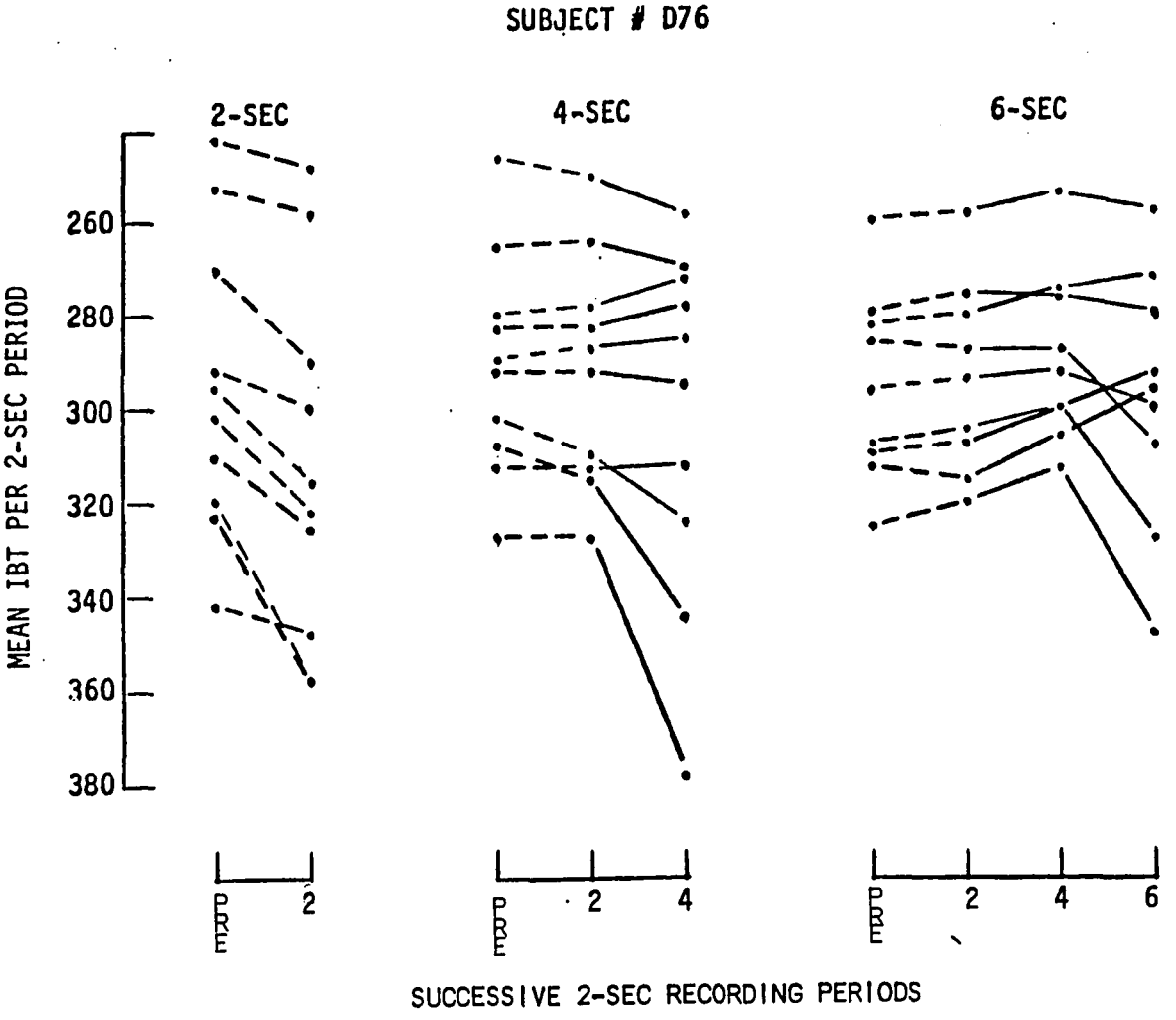

SUBJECT # D76
2-SEC
4-SEC
6-SEC
MEAN IBT PER 2-SEC PERIOD
260
280
300
320
340
360
380
PRE
2
4
6
SUCCESSIVE 2-SEC RECORDING PERIODS

Fig.16

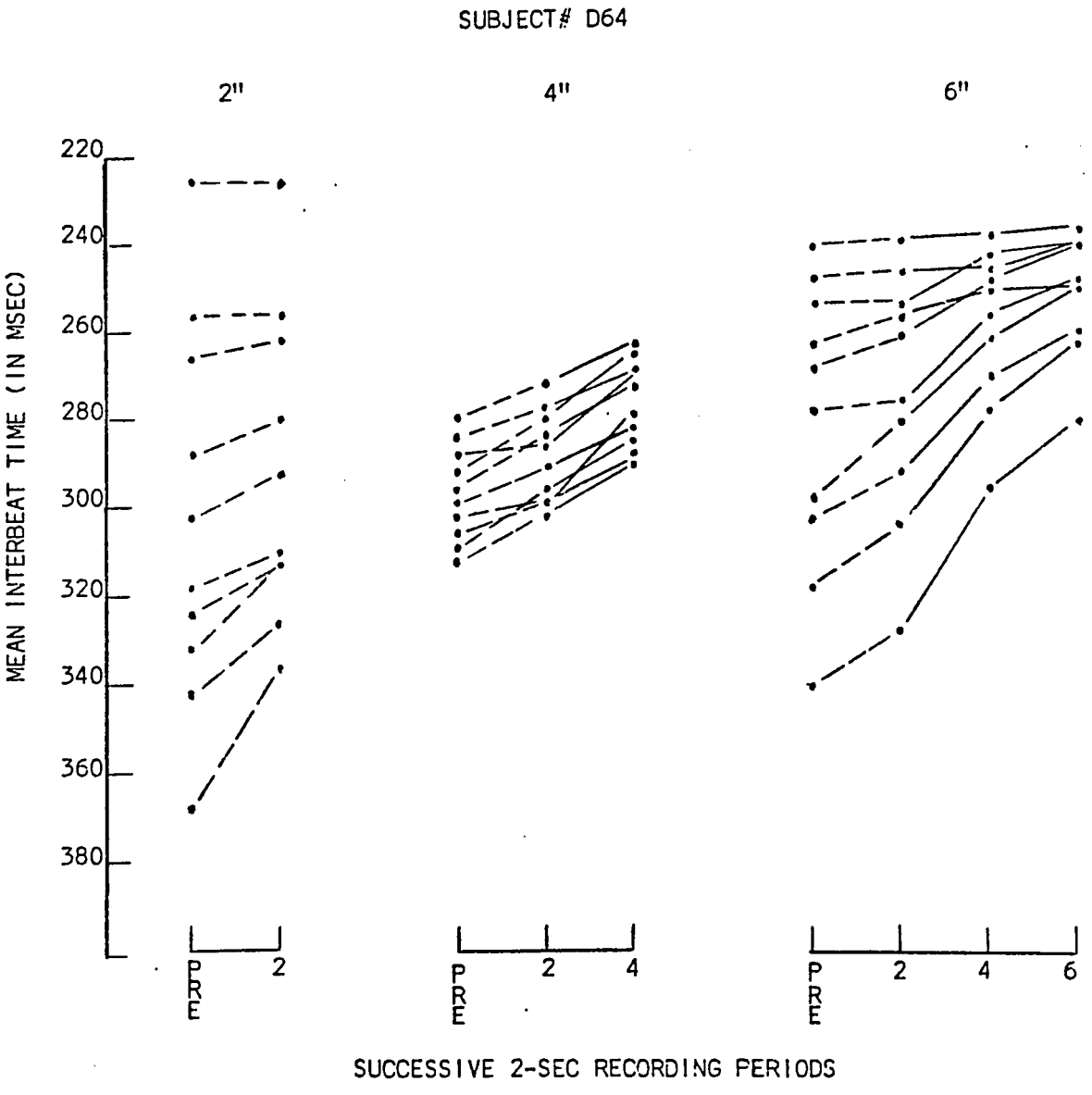

SUBJECT# D64
2"
4"
6"
MEAN INTERBEAT TIME (IN MSEC)
220
240
260
280
300
320
340
360
380
PRE
2
4
6
SUCCESSIVE 2-SEC RECORDING PERIODS

Fig.17

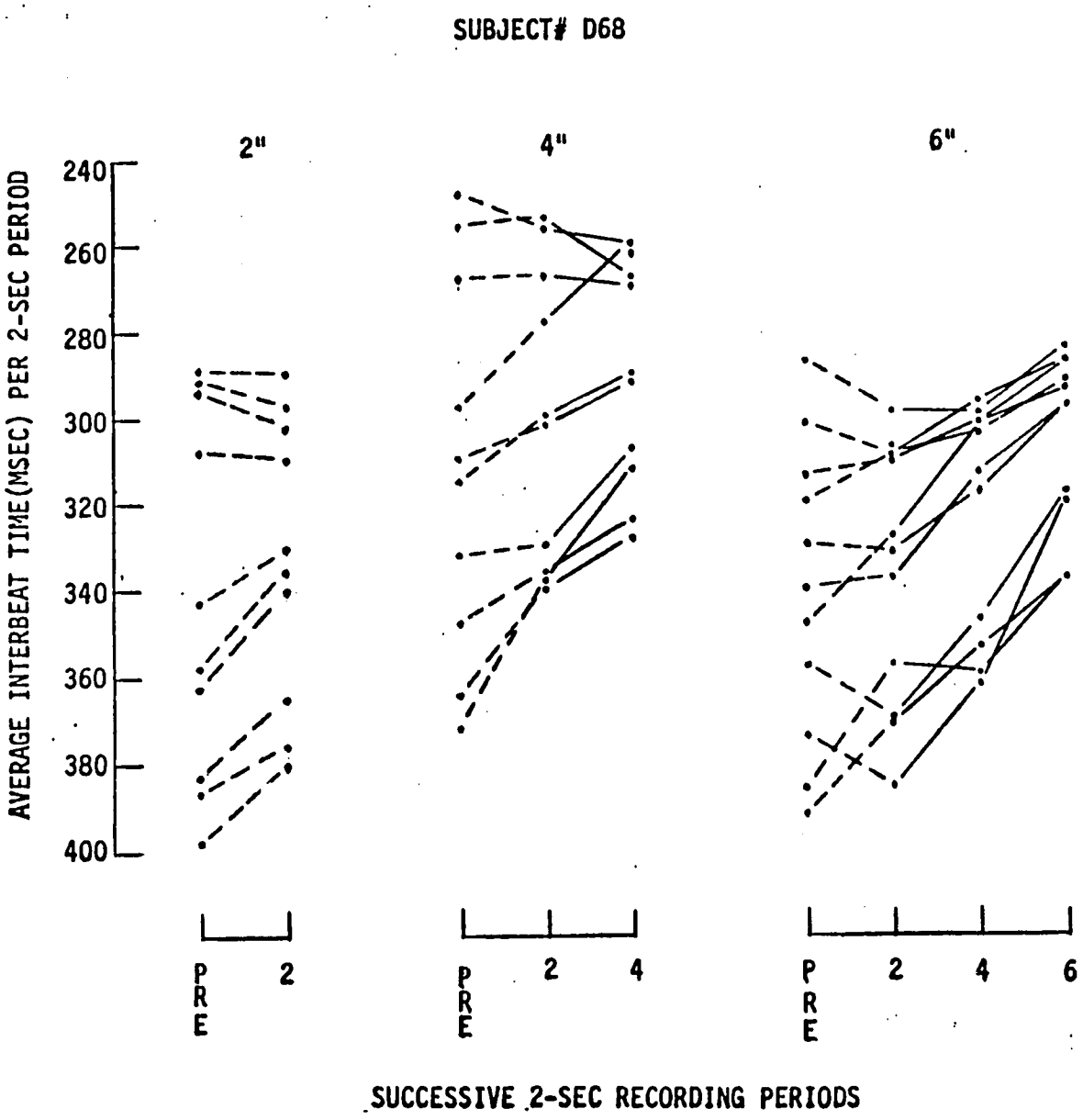

SUBJECT# D68
2"
4"
6"
AVERAGE INTERBEAT TIME(MSEC) PER 2-SEC PERIOD
240
260
280
300
320
340
360
380
400
PRE
2
4
6
SUCCESSIVE 2-SEC RECORDING PERIODS

Fig.18

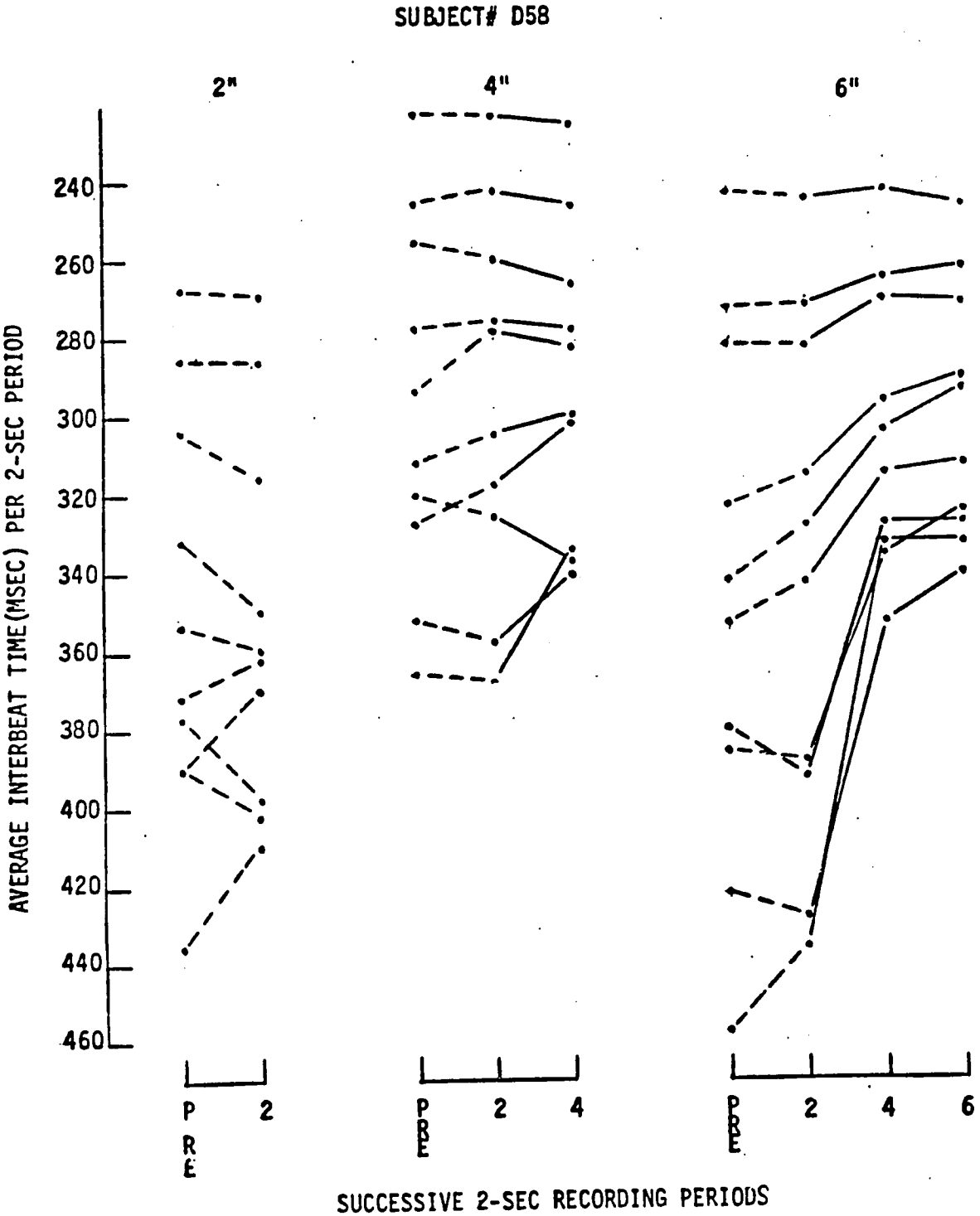
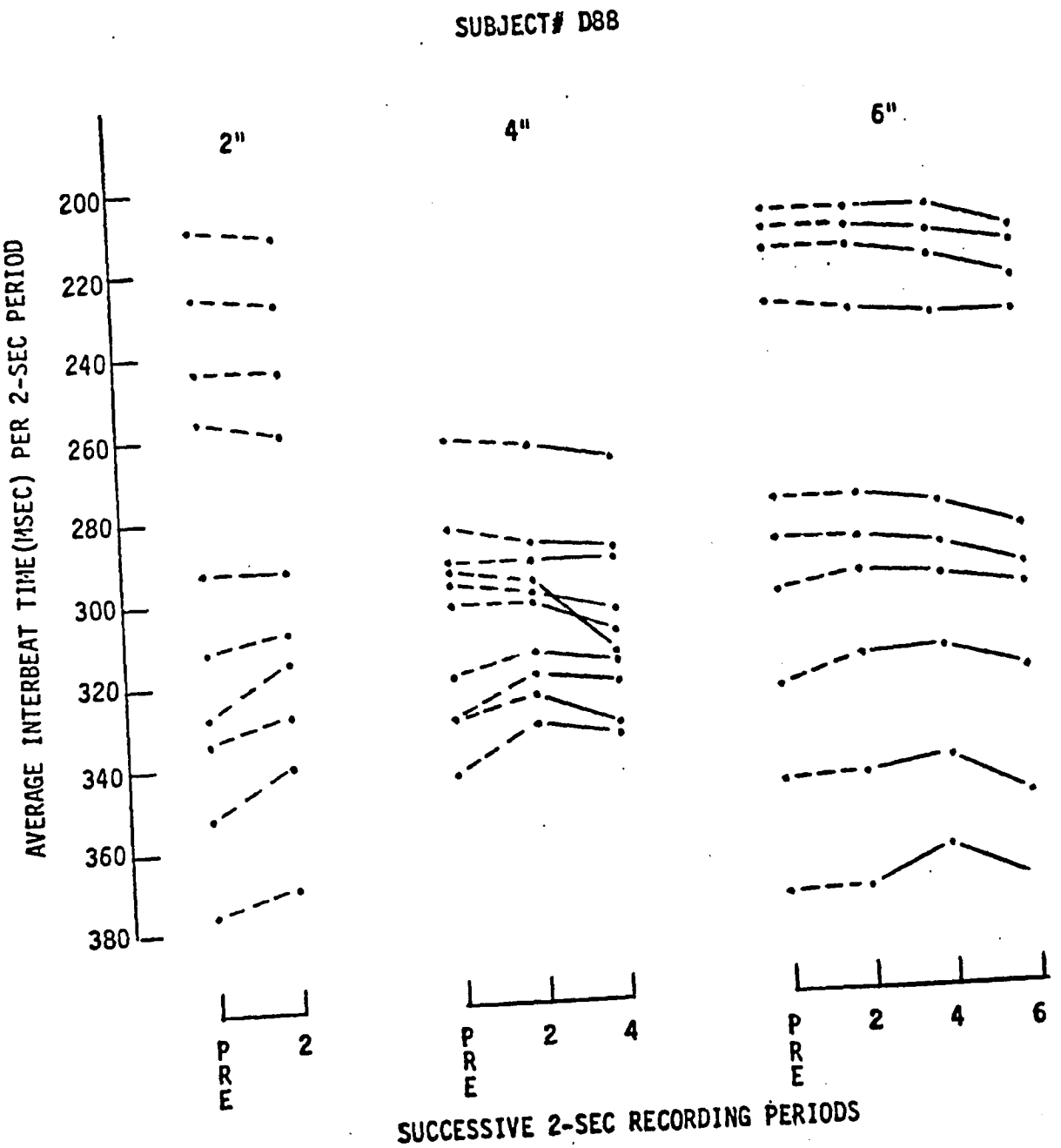

SUBJECT# D58
2"
4"
6"
240
260
280
300
320
340
360
380
400
420
440
460
AVERAGE INTERBEAT TIME(MSEC) PER 2-SEC PERIOD
PRE
2
4
6
SUCCESSIVE 2-SEC RECORDING PERIODS

Fig.19

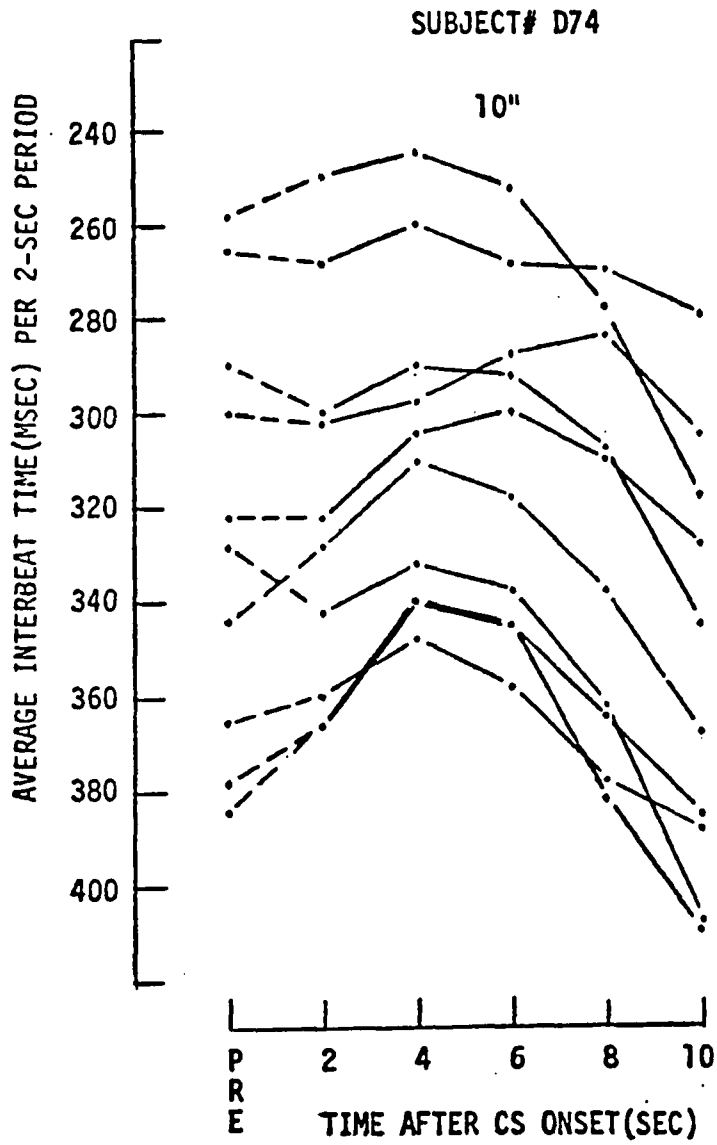

SUBJECT# D88
2"
4"
6"
AVERAGE INTERBEAT TIME(MSEC) PER 2-SEC PERIOD
200
220
240
260
280
300
320
340
360
380
PRE
2
4
6
SUCCESSIVE 2-SEC RECORDING PERIODS

rates, while D74 shows no systematic relationship between pre-CS rates and response to CS.

An additional finding from these single-trial data is that the biphasic CR pattern of initial acceleration followed by deceleration occurred within CS-US intervals as short as 4 or 6 sec. Three animals (D74, D76, and D88) display the biphasic waveform on at least several trials at the 6-sec CS-US interval, and D88 displays it as well at the 4-sec interval. In most of these cases, the biphasic CR form appeared only on trials where the pre-CS HR level was low.

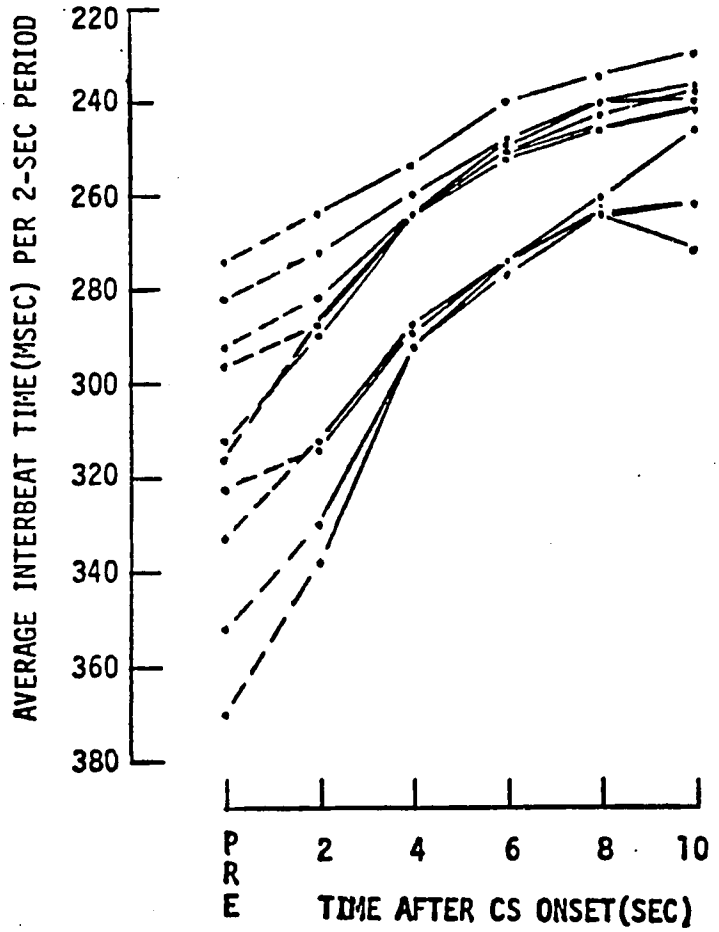
It appears, then, that at CS-US intervals of 2-6 sec, cardiac CR forms varied not only among subjects but within subjects as well; and, that some of this within-subjects variability could be attributed to fluctuations in pre-CS heart rates (i.e., an LIV effect). This variability of CR form did not, however, extend to the case of longer CS-US intervals (10-120 sec) where much greater stability of response patterning was found. For example, Figs. 20-22 present ten cardiac CRs (chosen in the same manner as described earlier) for each of three randomly selected subjects (D74, D64, and D58) for the 10-sec CS-US interval. These data demonstrate that the form of the cardiac CR remained consistent within subjects (across trials) despite continued wide fluctuations in pre-CS heart rates. The data for subject D58 are striking: on each trial he exhibits the same HR pattern during CS, irrespective of pre-CS rates; note also the sharp narrowing of heart rates from pre-CS into CS. Of these three animals, D74 shows the least consistency of CR form although an overall acceleration-deceleration pattern is maintained. As was the case for this animal at shorter CS-US intervals (2-6 sec), his HR either

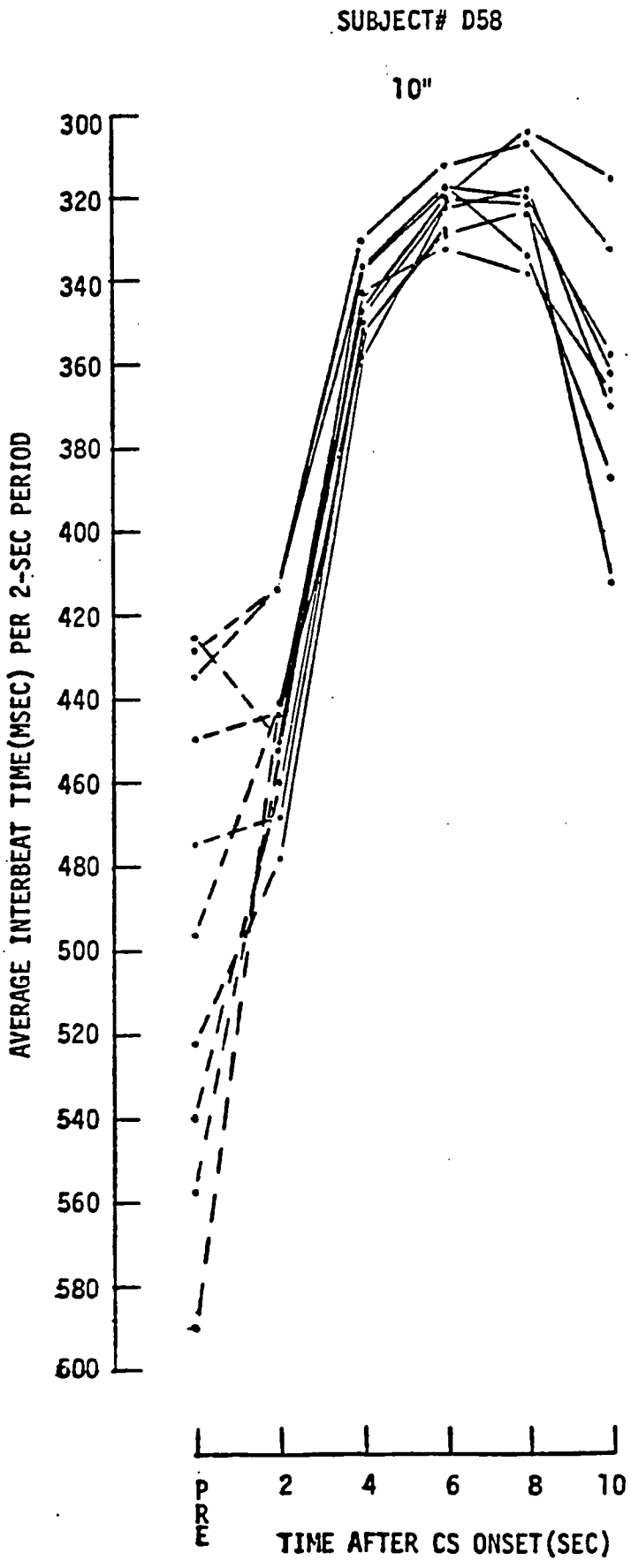
Figures 20-22. Ten cardiac CRs at differing pre-CS HR levels, for subjects D74, D64, and D58 (10-sec CS-US interval).


SUBJECT# D74
10"
AVERAGE INTERBEAT TIME(MSEC) PER 2-SEC PERIOD
240
260
280
300
320
340
360
380
400
PRE
2
4
6
8
10
TIME AFTER CS ONSET(SEC)

SUBJECT# D64

10"




SUBJECT# D58
10"
AVERAGE INTERBEAT TIME(MSEC) PER 2-SEC PERIOD
300
320
340
360
380
400
420
440
460
480
500
520
540
560
580
600
PRE
2
4
6
8
10
TIME AFTER CS ONSET(SEC)

increases or decreases at CS onset (i.e., within the first 2 sec of CS), independent of pre-CS HR level. Note for all three subjects that although overall CR form is relatively unaffected by changes in pre-CS rate, magnitudes of peak HR acceleration adhere to LIV; i.e., the change from pre-CS level to maximum CS level decreases as pre-CS level increases. The progressive flattening of D64's response curves with higher pre-CS rates demonstrates the "ceiling" effect of the LIV, whereas D58's data show that the inverse relationship between pre-CS level and magnitude of change is due to an invariant maximum CS HR level imposed upon differing pre-CS rates (cf. Block & Bridger, 1962).

CR magnitude

Correlation and regression coefficients relating cardiac CR magnitudes to pre-CS HR levels were computed for each subject at each CS-US interval value (2-120 sec). CR magnitude is defined here as the change in IBT (in msec) from pre-CS level to maximum or minimum level within CS (i.e., maximum or minimum CS level minus pre-CS level), based upon 2-sec averaging periods, and expressed in the form of a "change" or "difference" score. CR magnitude was computed for each trial, in one of two ways depending upon the form of the conditioned response: (1) At CS-US intervals of 2, 4, and 6 sec, where the CR was either accelerative or decelerative, CR magnitude was obtained by subtracting the mean IBT of the 2-sec pre-CS period from the mean of the 2-sec period within CS which differed maximally from mean pre-CS. (2) At

CS-US intervals from 10-120 sec, where the CR was biphasic (acceleration followed by deceleration), an attempt was made to differentiate the two components of the response. The magnitude of the initial accelerative component was computed by subtracting the mean pre-CS level from the smallest mean IBT (highest HR) within CS. The magnitude of the decelerative component was computed by subtracting that same smallest mean IBT within CS from the subsequently observed largest mean IBT (lowest HR toward the end of CS).

Table 3 lists, for each subject, the product-moment correlation and regression coefficient between: (1) pre-CS level and the maximum change from pre-CS level at CS-US intervals of 2, 4, and 6 sec; (2) pre-CS level and the magnitude of the initial accelerative component of the CR at CS-US intervals from 10-120 sec; and, (3) maximum CS level (peak of acceleration) and the magnitude of the subsequent decelerative component of the CR at CS-US intervals from 10-120 sec. Each coefficient is based on all pre-drug trials for the last three sessions at the designated CS-US interval.

The LIV can be said to be operating in the present cardiac CR data when the regression coefficient relating CR magnitude to pre-CS (or maximum CS) levels is negative and the correlation coefficient is statistically significant at $p < .05$. With respect to cardiac acceleration to CS, a negative slope value would mean that the magnitude of CR acceleration is smaller the higher the initial HR level. With respect to cardiac deceleration it would mean that the magnitude of CR deceleration is larger the higher the initial heart rate.

Table 3

Correlation (r) and regression (b) coefficients of: (1) pre-CS levels with maximum change scores at the 2, 4, and 6 sec CS-US intervals; (2) pre-CS levels with the magnitude of initial accelerative phase of the CR at the 10-120 sec CS-US intervals= A; (3) maximum CS levels with the magnitude of the subsequent decelerative phase of the CR at the 10-120 sec intervals= D.

		CS-US Interval (sec)													
		2	4	6	10		20		40		60		120	
S#					A	D	A	D	A	D	A	D	A	D
D74	r	+.26	-.01	-.17	-.55*	+.08	-.12	-.51*	-.26	-.13	-.41*	-.24	-.45*	-.48*
	b	+.15	.00	-.14	-.23	+.04	-.08	-.40	-.13	-.09	-.28	-.25	-.28	-.74*
	N[a]	(22)	(28)	(30)	(30)		(24)		(30)		(28)		(27)	
D76	r	+.69*	+.46*	+.15	-.63*	+.42	-.81*	+.59*	-.94*	+.74*	-.66*	+.19	-.65*	+.37*
	b	+.31	+.37	+.11	-.24	+1.28	-.37	+1.07	-.41	+.98	-.44	+.22	-.28	+.24
	N	(27)	(29)	(30)	(30)		(24)		(30)		(30)		(27)	
D64[b]	r	-.82*	-.89*	-.95*	-.98*		-.90*	-.42*	-.86*	-.27	-.92*	+.06	-.45*	+.24
	b	-.15	-.38	-.60	-.71		-.95	-.20	-.63	-.21	-.64	+.05	-.24	+.28
	N	(27)	(29)	(30)	(26)		(19)		(30)		(30)		(22)	
D68	r	-.55*	-.71*	-.80*	-.57*	+.37	-.91*	-.10	-.88*	-.11	-.86*	-.26	-.84*	+.20
	b	-.16	-.35	-.54	-.29	+.11	-1.17	-.13	-.79	-.30	-.93	-.45	-.69	+.47
	N	(25)	(27)	(29)	(23)		(28)		(29)		(30)		(25)	
D58	r	-.28	-.75*	-.96*	-.98*	+.18	-.95*	-.30	-.94*	+.26	-.85*	+.82*	-.75*	-.19
	b	-.07	-.31	-.60	-.96	+.91	-1.16	-.23	-.77	+.78	-.24	+.47	-.54	-.39
	N	(29)	(23)	(29)	(27)		(18)		(28)		(30)		(30)	
D88	r	-.68*	-.55*	+.35	-.70*	+.38*	-.76*	+.06	-.90*	+.16	-.94*	-.22	-.94*	+.53*
	b	-.07	-.25	+.07	-.23	+.12	-.31	+.04	-.64	+1.16	-.97	-.39	-.74	+1.76
	N	(29)	(23)	(29)	(27)		(18)		(28)		(30)		(29)	

[a] N represents the number of intact pre-drug trials upon which each coefficient is based.

[b] No CR deceleration at the 10-sec CS-US interval.

* $p < .05$.

The data in Table 3 indicate that at CS-US intervals from 10-120 sec, the LIV was consistently evident in the accelerative but not the decelerative component of the biphasic HR CR. For the accelerative component, all slope values are negative (-.08 to -1.17) and 28 of 30 correlation coefficients differ significantly from zero. For the decelerative component, however, slope values are both positive and negative (+1.76 to -1.16) and most correlation coefficients do not differ significantly from zero. Consistent with earlier observations from the single-trial data in Figs. 14-19, Table 3 also indicates that at CS-US intervals from 2-6 sec: (a) the LIV was operating in the cardiac CR data of subjects D64, D68, D58, and D88, as evidenced by negative slope values and significant correlations between CR magnitude (maximum change from pre-CS) and pre-CS HR level; (b) a reverse LIV effect was operating in the CR data of subject D76, as evidenced by positive slope values associated with significant correlations (it will be recalled that this animal showed larger CR decelerations with lower pre-CS rates --exactly the opposite of what LIV would predict); and, (c) no LIV effect was operating in the CR data of D74 as evidenced by the absence of significant r values.

Mean correlation and regression coefficients for the six subjects at CS-US intervals from 2-120 sec are plotted in Fig. 23. Data points for the 10-120 sec intervals are based on the CR's initial accelerative component only: data for the CR's decelerative component were excluded from this analysis. Figure 23 indicates that the degree of linear dependency of CR magnitude upon pre-CS level changed as a function of CS-US interval length: both the regression and correlation coefficients

Figure 23. Mean correlation (squares) and regression (circles) coefficients relating cardiac CR magnitudes to pre-CS HR levels, at CS-US intervals from 2-120 sec. Each datum point represents the mean of six subjects for the designated CS-US interval value. The break in the abscissa after the 6-sec CS-US interval denotes a change in scale.

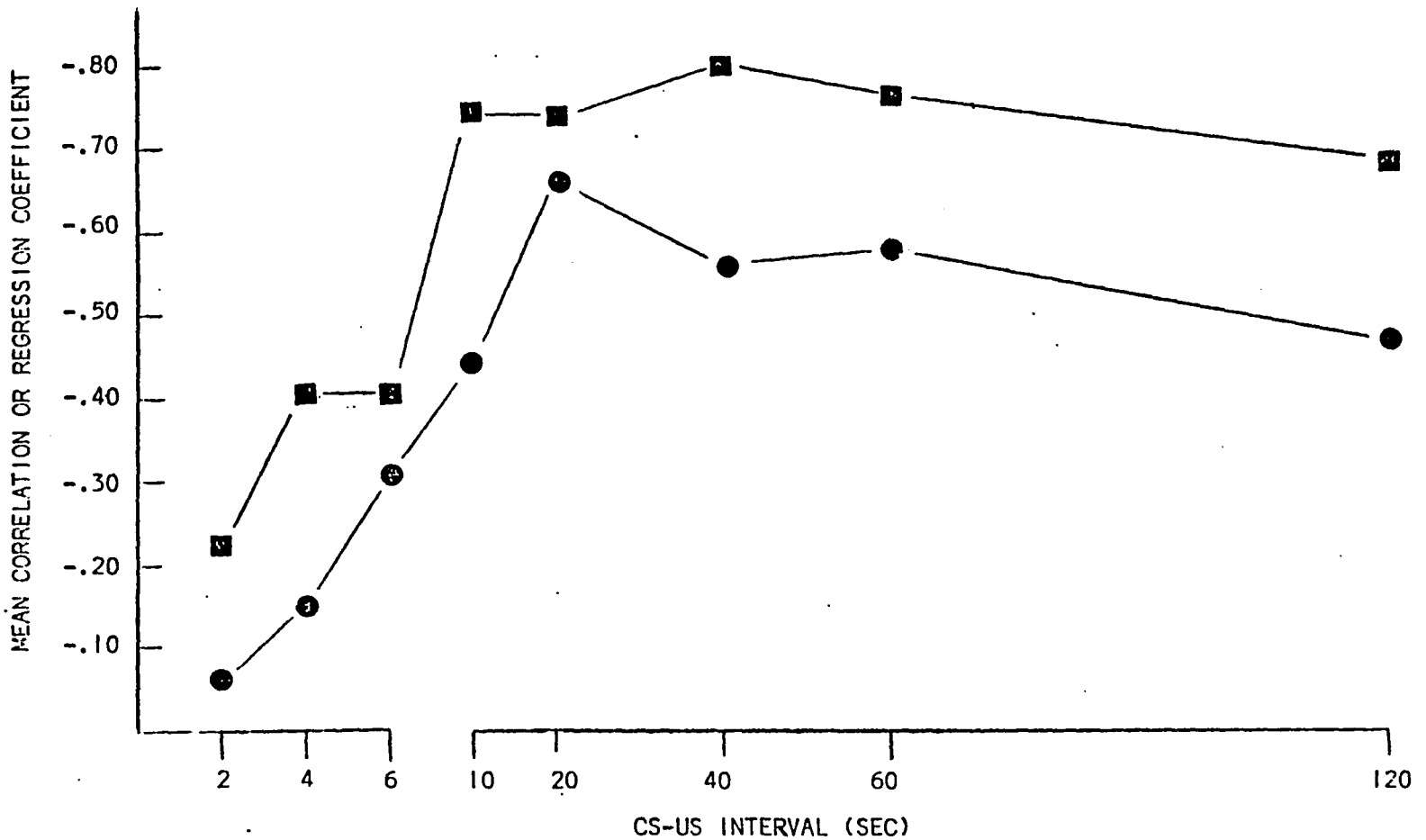

MEAN CORRELATION OR REGRESSION COEFFICIENT
-.80
-.70
-.60
-.50
-.40
-.30
-.20
-.10
2
4
6
10
20
40
60
120
CS-US INTERVAL (SEC)

Fig.23

assume increasingly negative values (i.e., approach values of -1.0) over the first five CS-US intervals from 2-20 sec. Slope values peak at the 20-sec interval and then decrease slightly over the next three CS-US intervals (from 40-120 sec), while *r* values peak at the 40-sec interval and then decrease.

Statistical adjustment of CR magnitude data

As mentioned earlier, there is concern in the literature that the effects of experimental variables on response magnitudes might be distorted or even totally obscured by the dependency of response magnitude on pre-stimulus level (Lacey, 1956; Wilder, 1957). Usually, when a dependency of this sort is found, experimenters have resorted to statistical adjustment of data in order to counteract the confounding of response magnitude with initial level. Based on Benjamin's (1963) demonstration that only regression models result in adjusted scores having a zero correlation with initial level, a regression technique was used in the present case to separate the effects of the CS-US interval variable on cardiac CR magnitude as distinct from any indirect effects on the CR arising from changes in pre-CS heart rate level. Analysis of covariance was not used in favor of a simpler regression technique because an important pre-requisite assumption of the covariance model was violated; namely, homogeneity of regression coefficients (equalty of slopes) between and within treatment conditions (Winer, 1971). This could be seen by the fact that: (a) slope values differed

widely both between and within subjects, at CS-US intervals from 2-120 sec, as shown in Table 3; and, (b) slope values changed systematically with the duration of the CS-US interval, as shown in Fig. 23. Analysis of covariance is especially inappropriate when regression coefficients are themselves systematically affected by the treatment conditions being compared (Stratton, 1970; Winer, 1971).

The present regression technique differs from analysis of covariance in that regression coefficients were not pooled across subjects or treatment conditions, and individual-subject rather than group data were adjusted. The formula used to adjust difference scores (D) for initial level (X) is:

$$D' = D - b(X - \overline{X}) \qquad (1)$$

where D' is the adjusted score, $\underline{b}$ is the linear regression coefficient, and $\overline{X}$ is the mean initial level for all treatment conditions being compared (Benjamin, 1963, 1967). The adjusted score, D', represents the difference between a subject's actual score (D) and the score predicted for that subject on the basis of the regression of D on X. Subtracting the quantity $\underline{b}(X - \overline{X})$ from the difference score actually obtained under each treatment condition in effect removes the regression of D on X, leaving adjusted scores that are uncorrelated with initial level.

The question posed was: what changes in cardiac CR magnitude occurred over CS-US intervals from 2-120 sec, assuming that pre-CS HR level was the same across all CS-US intervals? The data which formed the basis of the regression analysis are presented in Table 4. For each subject at each CS-US interval, mean pre-CS HR level is designated

Table 4

Mean pre-CS level scores (X)[a], mean difference scores (D)[b], and adjusted mean difference scores (D') at CS-US intervals of 2-120 sec. Both X and D are means of all pre-drug trials at the designated interval. All values are rounded to the nearest msec.

		CS-US Interval (sec)							
S#		2	4	6	10	20	40	60	120
D74 [c] ($\bar{X}$=326)	X	329	325	317	340	301	335	320	346
	D	+8	+8	+21	-19	-27	-43	-45	-50
	D'	+7	+8	+20	-16	-29	-42	-47	-44
D76 ($\bar{X}$=327)	X	290	291	291	354	310	327	365	322
	D	+16	+6	+4	-23	-29	-36	-39	-30
	D'	+28	+20	+7	-17	-36	-36	-23	-31
D64 ($\bar{X}$=282)	X	285	291	278	300	260	269	284	293
	D	-6	-23	-28	-60	-35	-37	-40	-41
	D'	-6	-16	-25	-48	-57	-46	-39	-39
D68 ($\bar{X}$=319)	X	355	321	342	326	289	295	316	317
	D	-6	-19	-33	-37	-31	-28	-44	-51
	D'	-1	-19	-21	-36	-68	-48	-47	-53
D58 ($\bar{X}$=403)	X	358	300	345	489	415	464	417	438
	D	+2	-8	-46	-185	-135	-178	-89	-72
	D'	-2	-40	-81	-102	-121	-131	-85	-53
D88 ($\bar{X}$=336)	X	279	308	278	319	348	380	398	376
	D	-3	+1	+7	-12	-25	-41	-86	-65
	D'	-7	-6	+12	-16	-21	-13	-25	-35
MEAN	X	316	306	309	355	320	345	350	350
	D	+3	-6	-13	-56	-47	-60	-57	-51
	D'	+3	-9	-21	-39	-54	-52	-44	-43

[a] smaller IBTs indicate higher heart rates, and vice versa

[b] positive difference scores represent deceleration from pre-CS level; negative scores represent acceleration

[c] mean pre-CS level for all eight CS-US interval conditions

"X" and mean CR magnitude is designated "D". For CS-US intervals from 2-6 sec, D represents the difference (in msec) between the mean IBT of the 2-sec pre-CS period and the mean of the 2-sec period within CS which differed maximally from mean pre-CS. For CS-US intervals from 10-120 sec, D represents the difference between the mean IBT of the 2-sec pre-CS period and the smallest mean IBT (highest HR) within CS; i.e., the magnitude of the initial accelerative component of the CR Each X and D value in Table 4 is the average of all intact pre-drug trials for the designated CS-US interval value. For all animals, pre-CS levels (X values) differ substantially among the eight different CS-US interval conditions. In most cases, pre-CS HR levels tended to decrease (as indicated by larger IBTs) over the course of the experiment.

The adjustment of difference scores (D) for pre-stimulus levels (X) was performed for each individual subject as follows. First, X values were averaged across all eight CS-US durations (2-120 sec) to give a grand mean, designated $\overline{X}$. (Values of $\overline{X}$ are listed in parentheses directly below the subject numbers in Table 4.) The statistical question took the following form: based upon the regression of CR magnitude (D) on pre-CS levels (X), what magnitude of response would have been expected at each CS-US interval if the mean pre-CS level at that interval were $\overline{X}$? The answer was obtained by generating an adjusted score (D') for each of the eight different CS-US intervals through the use of formula (1) above. Specifically, the numerical values of X, D, and $\underline{b}$ obtained at that particular CS-US interval were substituted in formula (1), together with the numerical value of $\overline{X}$ for that subject, to give an adjusted score, D'. The adjusted score (D') for each subject at each

CS-US interval is listed in Table 4. The mean adjusted score (square data points) and the mean unadjusted score (round data points) for all six subjects at each CS-US interval are plotted in Fig. 24.

The adjusted scores in Table 4 show that with CS-US intervals increasing from 2 to 120 sec, cardiac CR magnitude increased to a maximum value at the 20-, 40-, or 60-sec CS-US interval, and then decreased at longer interval values. One subject (D88) displayed his largest cardiac CRs at the 120-sec interval. Differences between animals in the CS-US interval of largest cardiac CRs are obscured by the averaged function (for adjusted scores) in Fig. 24 which peaks at the 20-sec interval. The unadjusted function is similar, but less orderly, and peaks at the 40-sec interval. Statistical comparisons (t-tests) of the mean adjusted scores at CS-US intervals of 2, 20, and 120 sec, revealed that cardiac CR magnitudes increased significantly over CS-US intervals from 2 to 20 sec ($t = 4.0351$, $df = 5$, $p < .001$); there was no significant difference in CR magnitude at CS-US intervals of 20 and 120 sec ($t = 1.0329$, $df = 5$, $p > .10$).

Drug effects

Effects on baseline (pre-CS) HR levels and on cardiac CR magnitudes of sympathetic blockade by propranolol, of parasympathetic blockade by atropine, and of double blockade by a combination of propranolol and atropine, were evaluated for each subject at each CS-US interval condition.

Figure 24. Mean adjusted cardiac CR magnitude scores (square data points) and mean unadjusted magnitude scores (round data points) for all subjects, at CS-US intervals from 2 to 120 sec.

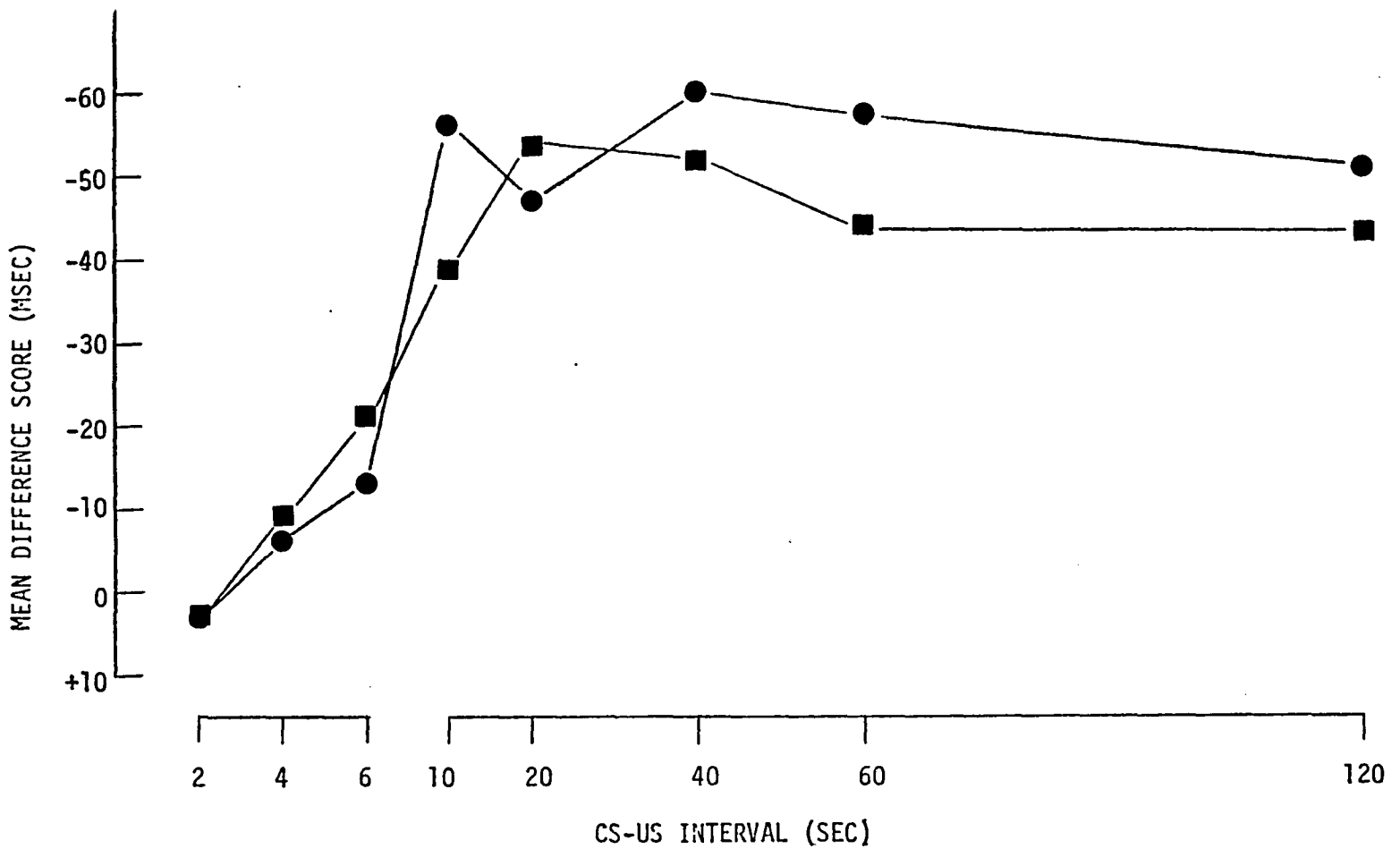

MEAN DIFFERENCE SCORE (MSEC)
-60
-50
-40
-30
-20
-10
0
+10
2
4
6
10
20
40
60
120
CS-US INTERVAL (SEC)

Fig.24

Pre-CS heart rate

The drug effects on baseline HR levels were similar across CS-US interval conditions and, therefore, the data for each subject were averaged over all eight CS-US values (2-120 sec). Table 5 lists, for each subject, the mean IBT (in msec) of the 2-sec pre-CS period under pre- and post-drug conditions, averaged over the eight CS-US intervals from 2-120 sec. Again, larger IBTs indicate lower HRs and vice versa.

Table 5 shows that propranolol markedly lowered baseline HR levels, in all subjects, relative to pre-drug rates, whereas atropine markedly raised baseline rates relative to pre-drug rates. The combination of propranolol and atropine lowered HRs in four subjects and raised baseline rates in two subjects, but not to the HR levels seen under propranolol or atropine administered separately. Statistical comparisons (t-tests) of the pre- and post-drug means of all six subjects revealed that significant effects on baseline HR levels were exerted by propranolol (t = +7.347, df = 47, $p < .05$) and by atropine (t = -7.228, df = 47, $p < .05$), but not by the combination propranolol and atropine (t = +2.001, df = 47, $p > .05$).

Unmodified CR magnitude data

Effects of the drugs on cardiac CR magnitudes at CS-US intervals from 2-6 sec, not taking into account any effects of the drugs on baseline heart rate, are presented in Table 6 which lists, for each subject, mean CR magnitude scores (in msec) under pre- and post-drug conditions. Each magnitude score in the table represents the difference (in msec)

Table 5

Mean pre-CS IBT (in msec) under pre-drug (PRE), propranolol (PR), atropine (AT), and the combination of propranolol plus atropine (PR+AT), averaged over CS-US intervals from 2 to 120 sec

		PRE	PR	AT	PR+AT
Subject#	D74	327	397	254	347
	D76	313	396	257	393
	D64	283	367	229	322
	D68	320	400	258	357
	D58	403	483	275	358
	D88	336	405	254	313
	MEAN	330	408*	255*	348

* Significant difference ($p < .05$) between pre and post-drug group mean, based on t-test.

Table 6

Mean cardiac CR magnitude scores[a] (in msec) under pre-drug (Pre), propranolol (Pr), atropine (At), and the combination of propranolol and atropine (Com), for CS-US intervals of 2, 4, and 6 sec.

S#	CS-US	Pre	Pr	At	Com
D74	2	+ 8	+15	- 1*	- 1*
	4	+ 8	+14	0*	- 6*
	6	+21	+29	- 4*	- 3*
D76	2	+16	+62*	+ 1*	+ 1*
	4	+ 6	+20*	0*	- 1*
	6	+ 4	+ 9	- 1*	- 5*
D64	2	- 6	- 4	0*	+ 1*
	4	-23	-22	- 2*	- 2*
	6	-28	-25	- 3*	- 7*
D68	2	- 6	+16*	0*	+ 1*
	4	-19	- 5	- 4*	0*
	6	-33	+13*	- 7*	-13*
D58	2	+ 2	+ 1	0	- 1
	4	- 8	-16	- 8	- 2
	6	-46	-76*	- 4*	-21*
D88	2	- 3	- 3	0*	0*
	4	+ 1	+ 5	- 1	0
	6	+ 7	+15	- 1*	- 3*

[a] Each score represents the difference (in msec) between the mean pre-CS IBT and the mean IBT during CS which differed maximally from mean pre-CS, and is the average of all pre or post-drug trials for the designated CS-US interval duration. Positive scores indicate cardiac deceleration, negative scores indicate cardiac acceleration.

* significantly different from pre-drug at $p < .05$.

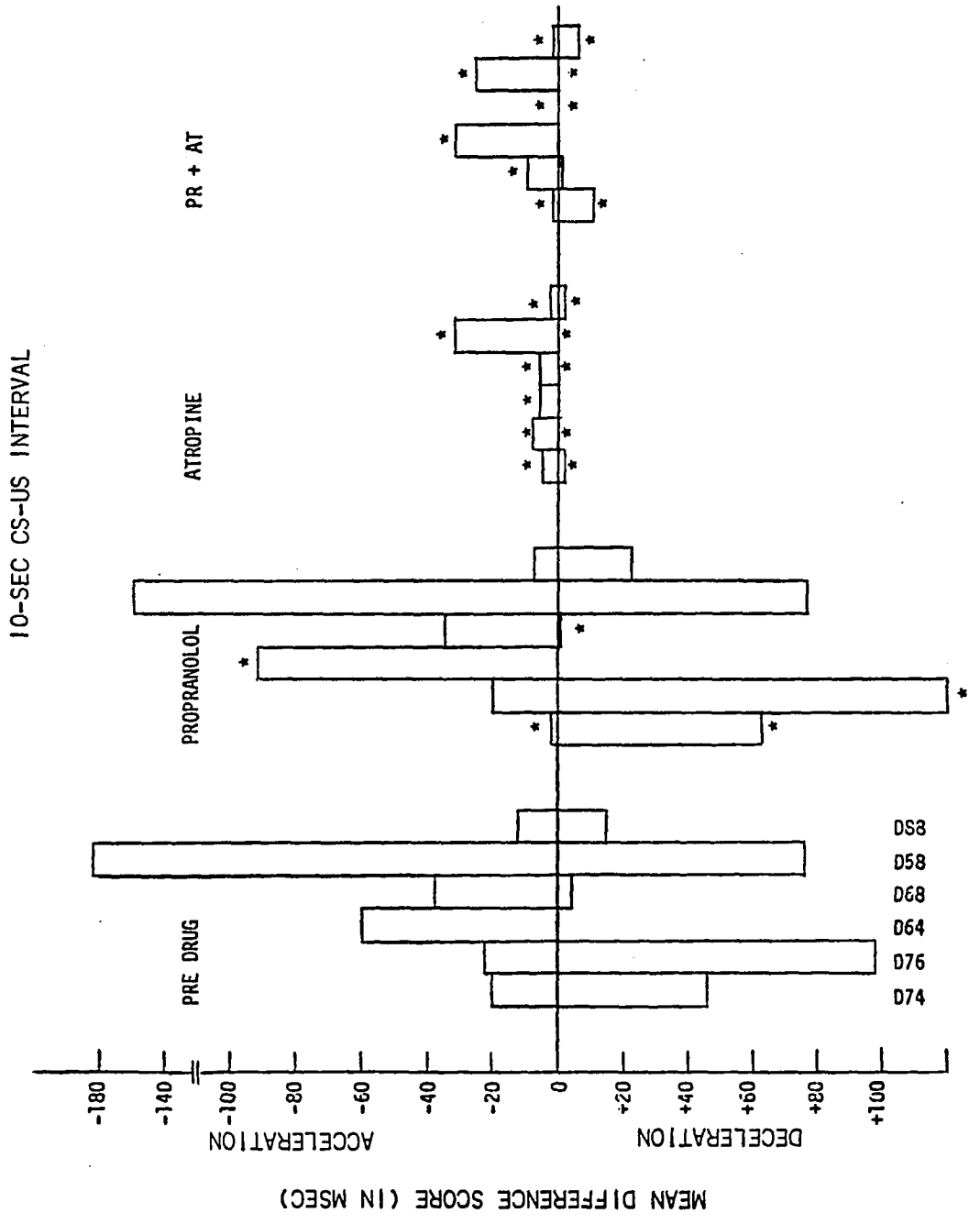
between the mean IBT of the 2-sec pre-CS period and the mean IBT of the 2-sec period within CS which differed maximally (either positively or negatively) from mean pre-CS. Each score is the average of all pre- or post-drug trials for the designated CS-US interval. Positive difference scores represent CR deceleration, and negative scores represent CR acceleration. Asterisks indicate statistically significant differences ($p < .05$) between pre- and post-drug scores, as determined by *t*-tests (two-tailed).

Table 6 shows that atropine and the combination of drugs significantly reduced CR magnitudes relative to pre-drug values, whether the pre-drug response was accelerative or decelerative. Propranolol did not affect CR magnitudes significantly in most cases, although it consistently facilitated decelerative responses above pre-drug values, as seen most dramatically in subject D76. Propranolol's effect on accelerative CRs was variable and consisted of either: (a) a facilitation of CR magnitudes relative to pre-drug; (b) a reduction of CR magnitudes relative to pre-drug; or, (c) a change in direction of response from HR acceleration to deceleration.

Figures 25-29 illustrate, for each subject, mean magnitudes of the accelerative and decelerative components of the biphasic HR CR under pre- and post-drug conditions, at CS-US intervals from 10-120 sec. Each figure contains the data for six subjects at a single CS-US interval, and is divided into four panels showing the data for pre-drug, propranolol, atropine, and the combination of propranolol and atropine. For each animal, the bar extending above the zero line represents the mean magnitude of the CR's initial accelerative component, and the bar extending downward

Figures 25-29. Mean magnitudes (difference scores) of accelerative and decelerative components of the biphasic CR before and after drug injection, for CS-US intervals of 10, 20, 40, 60, and 120 sec. Bars within each of the four figure panels represent from left to right: CR magnitudes for subjects D74, D76, D64, D68, D58, and D88. Bars projecting upward from the zero reference line represent magnitude of acceleration (negative difference scores); bars projecting downward represent magnitude of deceleration (positive scores). Asterisks indicate statistically significant differences ($p < .05$) between pre- and post-drug values, as determined by t-tests. Data shown for each subject are means, averaged over all pre- or post-drug trials at the designated CS-US interval.

Fig.25


10-SEC CS-US INTERVAL
PR + AT
ATROPINE
PROPRANOLOL
PRE DRUG
D58
D58
D68
D64
D76
D74
-180
-140
-100
-80
-60
-40
-20
0
+20
+40
+60
+80
+100
ACCELERATION
DECELERATION
MEAN DIFFERENCE SCORE (IN MSEC)

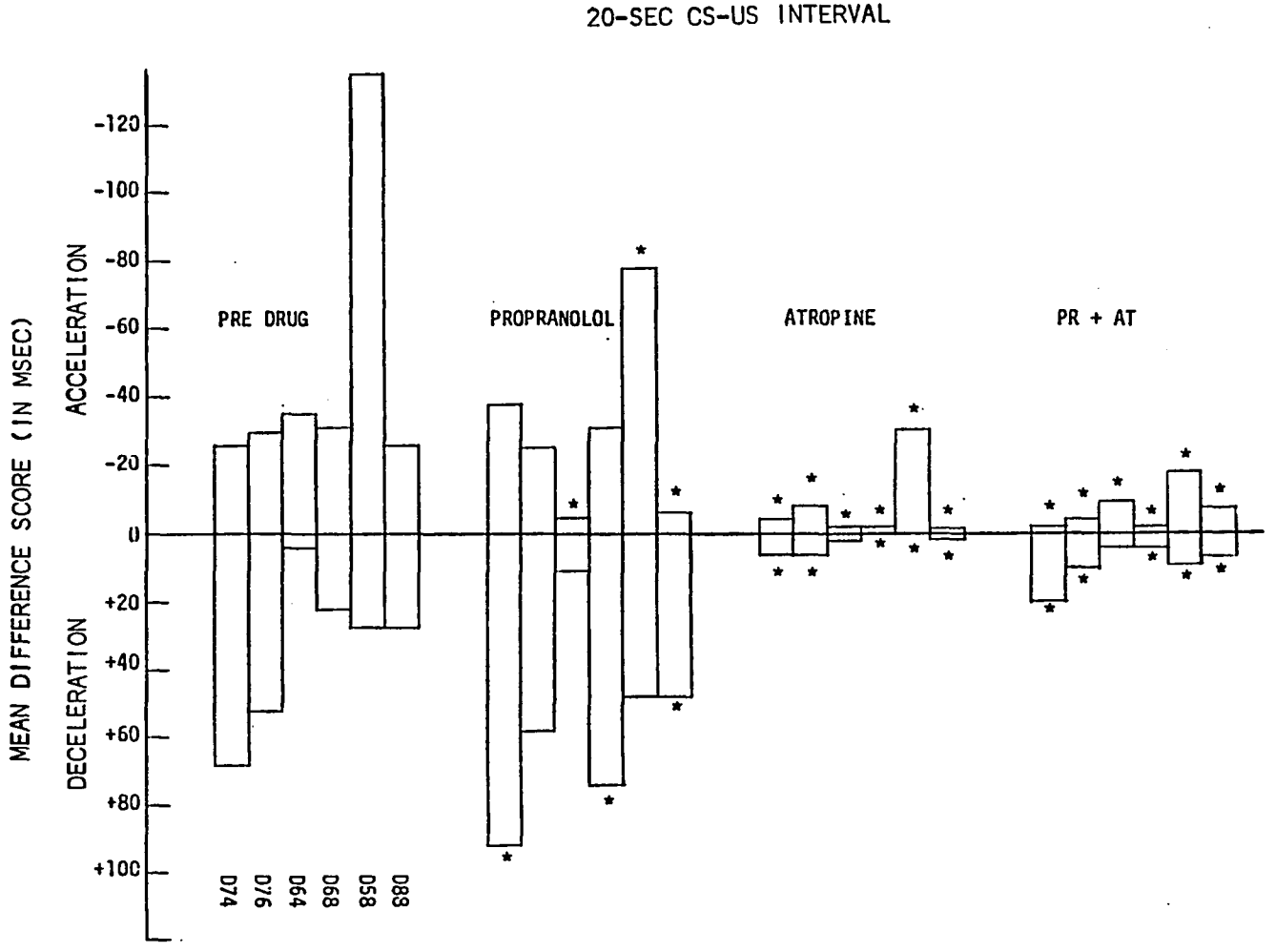
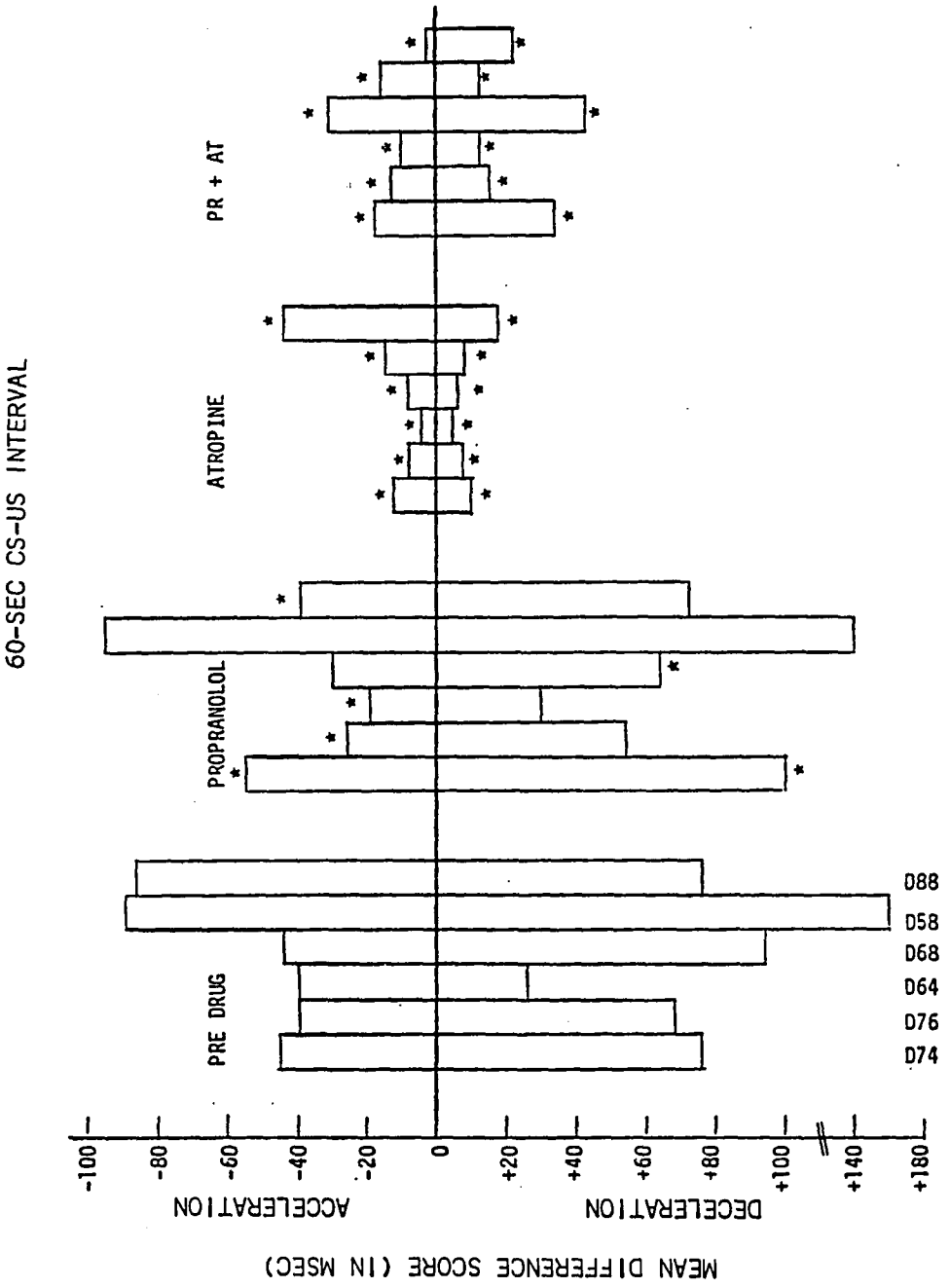

20-SEC CS-US INTERVAL
MEAN DIFFERENCE SCORE (IN MSEC)
ACCELERATION
DECELERATION
-120
-100
-80
-60
-40
-20
0
+20
+40
+60
+80
+100
PRE DRUG
PROPRANOLOL
ATROPINE
PR + AT
D74
D76
D64
D68
D58
D83

Fig.26 107

MEAN DIFFERENCE SCORE (IN MSEC)
DECELERATION
ACCELERATION
+140
+100
+80
+60
+40
+20
0
-20
-40
-60
-80
-100
-140
-180
PRE DRUG
PROPRANOLOL
ATROPINE
PR + AT
40-SEC CS-US INTERVAL

Fig.27

Fig.28


60-SEC CS-US INTERVAL
PR + AT
ATROPINE
PROPRANOLOL
PRE DRUG
D88
D58
D68
D64
D76
D74
-100
-80
-60
-40
-20
0
+20
+40
+60
+80
+100
+140
+180
ACCELERATION
DECELERATION
MEAN DIFFERENCE SCORE (IN MSEC)

120-SEC CS-US INTERVAL

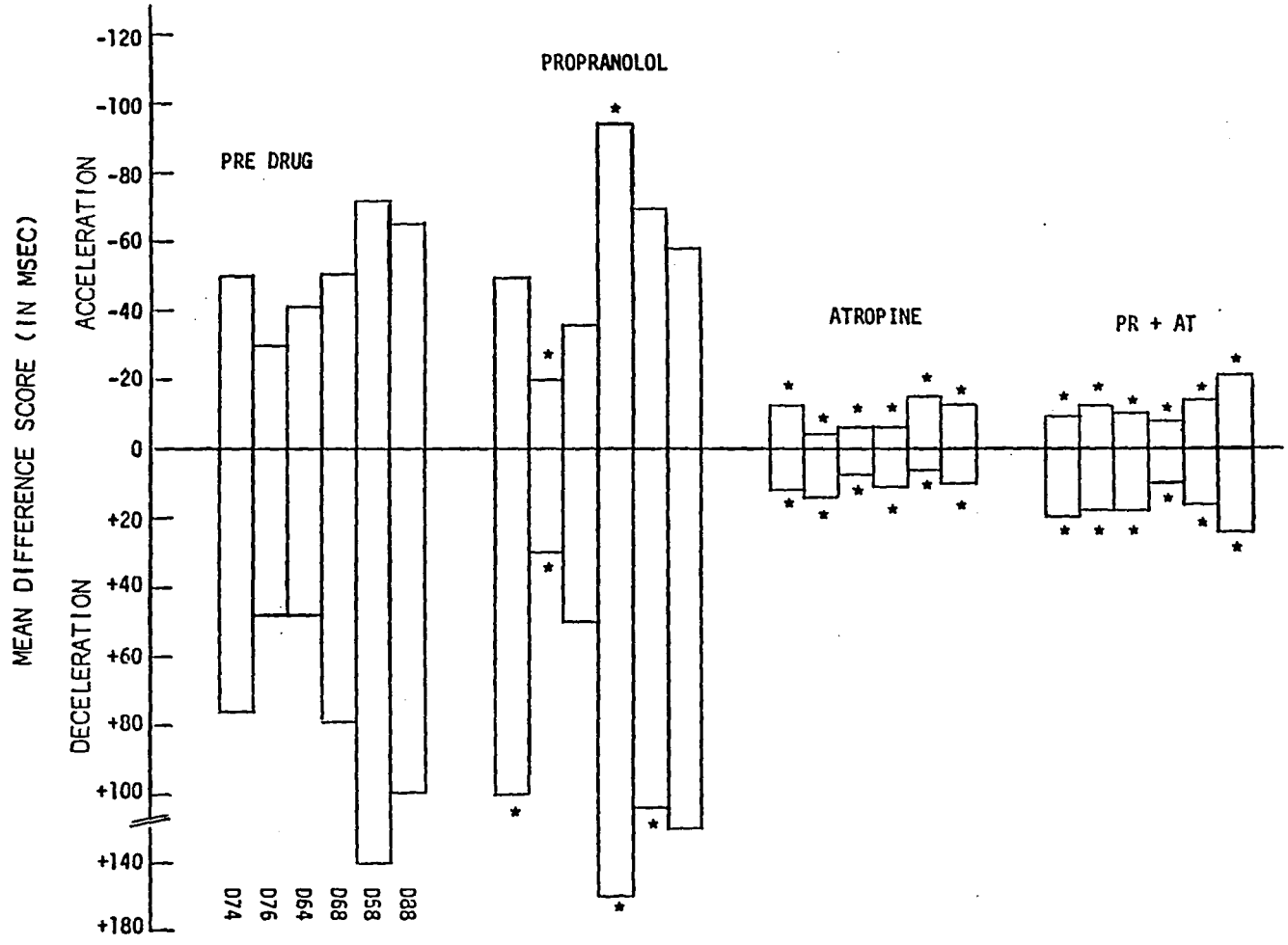


Fig.29

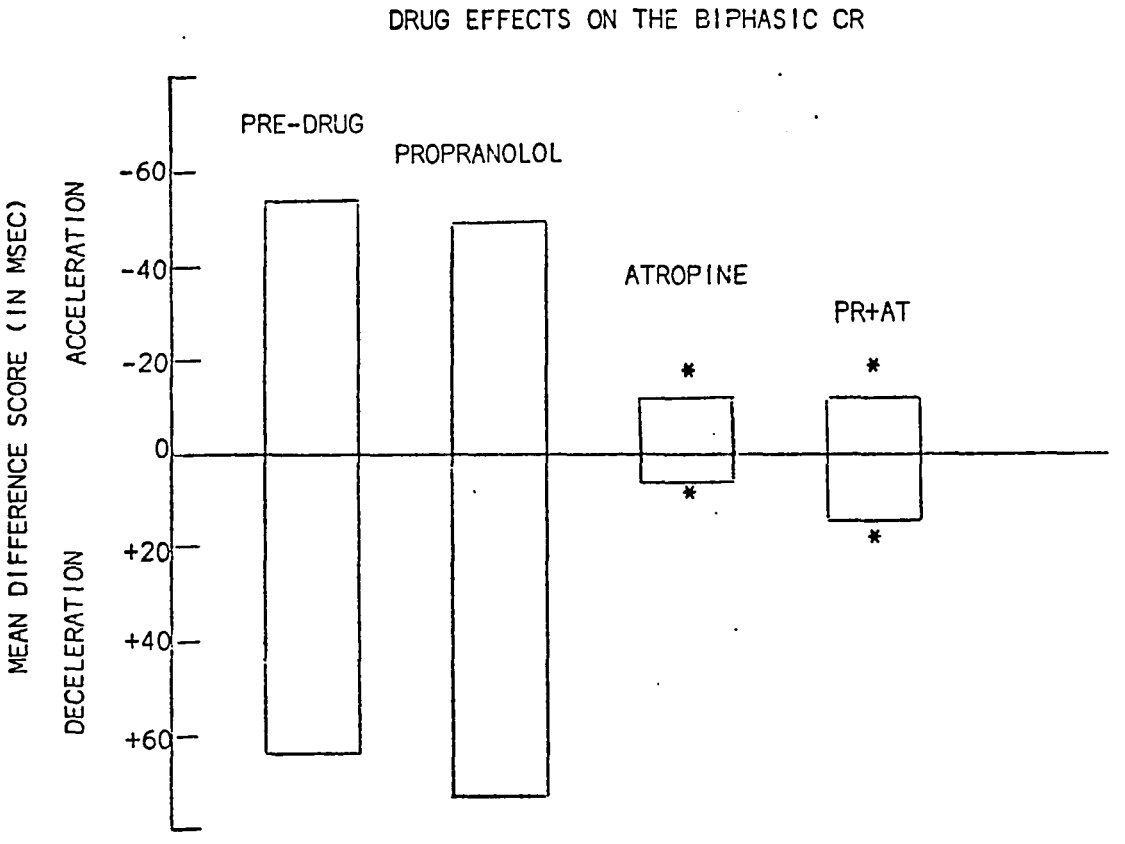
represents the mean magnitude of the CR's subsequent decelerative component. Each bar in Figs. 25-29 represents the mean of all pre- or post-drug trials at the designated CS-US interval. Asterisks denote statistically significant differences ($p < .05$) between mean pre- and post-drug magnitudes, as determined by t-tests.

Drug effects were similar across the five CS-US intervals (10-120 sec) and, therefore, the results will be described collectively.

Figures 25-29 show that atropine, as well as the combination of propranolol and atropine, severely reduced magnitudes of both the accelerative and decelerative components of the biphasic CR, relative to pre-drug magnitudes. In almost every case, differences between pre- and post-drug magnitudes were statistically significant. Propranolol's effects were less consistent, although in most cases it weakly attenuated the CR's accelerative component and facilitated the CR's decelerative component (consistent with the earlier findings at CS-US intervals of 2-6 sec).

Figure 30 summarizes the effects of the drugs on the biphasic CR, presenting mean magnitudes of the accelerative and decelerative components under pre- and post-drug conditions, averaged over the six subjects and over the five CS-US intervals (10-120 sec). (The means for CR acceleration are based on an N of 30 [six animals at each of five CS-US intervals] whereas the means for CR deceleration are based on an N of 29 since subject D64 showed no deceleration at the 10-sec CS-US interval.) Statistical comparison (t-tests) of the mean pre- and post-drug CR magnitudes, shown in Fig. 30, indicates that atropine significantly reduced the magnitude of both the accelerative ($t = -6.611$, df = 29,

Figure 30. Mean magnitudes (difference scores) of accelerative and decelerative components of the biphasic CR before and after drug injection, averaged over six subjects and CS-US intervals of 10, 20, 40, 60, and 120 sec. Bars above the zero line indicate magnitude of acceleration; bars directly below indicate magnitude of deceleration. Asterisks indicate statistically significant differences between pre- and post-drug means ($p < .05$), as determined by paired t-tests.

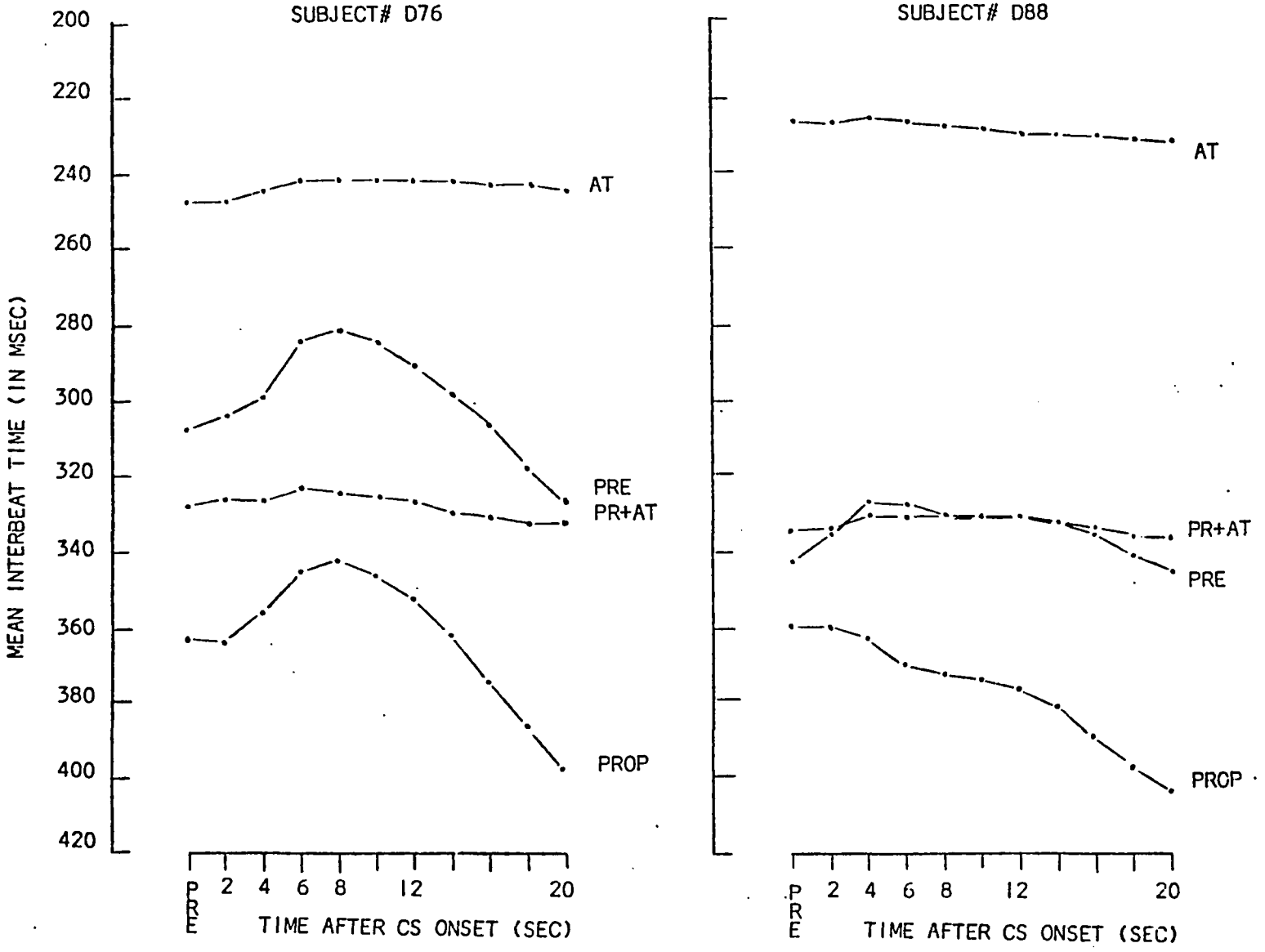

DRUG EFFECTS ON THE BIPHASIC CR
MEAN DIFFERENCE SCORE (IN MSEC)
ACCELERATION
DECELERATION
-60
-40
-20
0
+20
+40
+60
PRE-DRUG
PROPRANOLOL
ATROPINE
PR+AT
*
*
*
*

$p < .05$) and decelerative ($t = -7.499$, df = 28, $p < .05$) components of the biphasic CR, as did the combination of drugs (for acceleration: $t = -6.584$, df = 29, $p < .05$; for deceleration: $t = -6.948$, df = 28, $p < .05$), but that propranolol failed to significantly alter either portion of the response (for acceleration: $t = -1.647$, df = 29, $p > .05$; for deceleration: $t = +1.808$, df = 28, $p > .05$), although it tended to reduce the accelerative component and enhance the decelerative component.

Changes were evident not only in the magnitude but also in the form of the cardiac CR as a result of the drugs. For example, Fig. 31 presents pre- and post-drug CR functions for two subjects (D76 and D88) for the 20-sec CS-US interval. Figure 31 shows, for both subjects, that following atropine injection baseline HR levels were high and CR functions were essentially flat. Following combined propranolol and atropine, flat CR functions were again evident, although at much lower HR levels. In subject D76, the normally-occurring biphasic CR remained wholly intact following an injection of propranolol, whereas in D88 the initial accelerative component was selectively eliminated leaving a HR pattern of monophasic deceleration across the entire CS-US interval.

Thus, changes in pre-CS heart rate and in the form and magnitude of the cardiac CR were evident at each CS-US interval from 2-120 sec, as a result of sympathetic blockade by propranolol, parasympathetic blockade by atropine, and double blockade by a combination of the two drugs. Atropine markedly raised baseline heart rate, relative to pre-drug, whereas propranolol lowered it. The combination of drugs generally lowered heart rate, but not to the levels seen under propranolol.

Figure 31. Mean pre- and post-drug cardiac CR functions (20-sec CS-US interval) for subjects D76 (left) and D88 (right). Each datum point represents mean interbeat time (msec) for 2 sec, averaged over all pre- or post-drug trials.


SUBJECT# D76
SUBJECT# D88
MEAN INTERBEAT TIME (IN MSEC)
200
220
240
260
280
300
320
340
360
380
400
420
AT
PRE
PR+AT
PROP
PRE
2
4
6
8
12
20
TIME AFTER CS ONSET (SEC)

At CS-US intervals of 2-6 sec, CR magnitudes were drastically reduced, relative to pre-drug values, following atropine or the combination of propranolol and atropine, whether the pre-drug CR was accelerative or decelerative. Propranolol consistently enhanced CR magnitudes relative to pre-drug in those cases where the pre-drug CR was decelerative, but had variable effects on accelerative CRs. At CS-US intervals of 10-120 sec, where the pre-drug CR was biphasic, propranolol only slightly reduced the initial accelerative component of the CR and facilitated the subsequent decelerative component, relative to pre-drug values. Both components of the biphasic CR were reduced severely by atropine and by the combination of propranolol and atropine, leaving CR functions that were almost entirely flat.

Adjusted CR magnitude data

The problem of comparing response magnitudes when pre-stimulus levels differ was discussed earlier, and regression analysis was used to counteract the confounding of cardiac CR magnitudes with pre-CS heart rate. In the case of pre- vs. post-drug comparisons of CR magnitudes, statistical adjustment of data again became necessary because of the large changes in heart rate produced by the drugs. For instance, since CR magnitude depended upon the immediately preceding heart rate level, one might at first think that the post-drug changes in CR magnitude were due solely to induced changes in HR level. But it is also possible that these observed changes in CR magnitude resulted from the drug's

blockade of neural activity which contributed to the original (pre-drug) CR. What seems to be called for here is a statistical technique that would separate the effects of drug action on CR magnitude, as distinct from indirect effects on CR magnitude arising from drug action on heart rate level. Analysis of covariance would have been the method of choice for this purpose, but its application was precluded in the present case by heterogeneity of regression coefficients between subjects, between CS-US intervals, and between pre- and post-drug conditions.

As an alternative solution, a regression technique was again used. In this instance, the technique aimed to answer the question of whether CR magnitude under the drugs differed significantly from the CR predicted from the pre-drug regression relationship between CR magnitude and heart rate level. Toward this end, the previously computed regression equations, for each subject, relating cardiac CR magnitudes to preceding heart rate levels (slope values listed in Table 3) at each CS-US interval, were used to compute predicted pre-drug CR magnitude scores at heart rate levels as low and as high as those obtained under the drugs. The predicted pre-drug CR magnitudes were then compared statistically with the actually obtained post-drug CR magnitudes for each drug condition.

The regression analysis was performed on the data of each subject at each CS-US interval from 2-120 sec, as follows. Using the pre-drug regression equation relating CR magnitudes to heart rate levels (for the particular subject and CS-US interval under consideration), a predicted pre-drug CR magnitude was computed at the mean post-drug heart rate level by substituting the numerical value of the mean post-drug

HR level (X) into the regression equation, $Y' = bX + a$, where $\underline{b}$ is the slope of the regression line, $\underline{a}$ is the Y-intercept, and Y' is the predicted pre-drug magnitude score in msec. For CS-US intervals of 10-120 sec, two predicted pre-drug scores were obtained for each of the three different drug conditions: one for the initial accelerative component of the CR, and the other for the subsequent decelerative component. For the decelerative component, predictions were made from the immediately preceding maximum CS HR level rather than from pre-CS HR level.

To determine whether an actually obtained post-drug CR magnitude score differed significantly from its corresponding predicted pre-drug CR score, 95% confidence limits were established around the pre-drug regression line, using the $\underline{t}$-formula presented in Appendix A (this formula was derived by methods described in Snedecor & Cochran, 1967). The difference between the actually obtained post-drug mean CR magnitude score ($\overline{Y}_{post}$) and the predicted pre-drug score (Y') is divided by a pooled error estimate which contains standard error terms for the mean of the actually obtained pre-drug CR score, the mean of the actually obtained post-drug CR score and, the variability of the slope of the pre-drug regression line. The result is tested against Student's $\underline{t}$-distribution, with $df = N_{pre} + N_{post} - 3$. This test indicates, at the 95% confidence level, whether the obtained post-drug CR magnitude was drawn from the same population as the predicted pre-drug CR; i.e., whether the drug significantly modified the magnitude of the CR over and above its modification of baseline heart rate. (A similar application of regression techniques is reported by Myers & Honig, 1969).

Comparisons of predicted and actually obtained CR magnitude scores were made for each of the three different drug conditions at every CS-US interval from 2 through 120 sec. The results obtained at CS-US intervals of 2, 4, and 6 sec are presented in Table 7. Positive values represent increases in IBT from pre-CS level (decelerative CRs), negative values represent decreases in IBT from pre-CS level (accelerative CRs). An asterisk marks those instances where the obtained post-drug score differed significantly from the predicted pre-drug score at the 95% confidence level, based on the *t*-formula presented in Appendix A.

The data in Table 7 show, with few exceptions, that atropine reduced the magnitude of the cardiac CR relative to the CR predicted at the high post-atropine heart rate, although the difference between predicted and actually obtained values was not statistically significant. Propranolol significantly reduced the magnitude of accelerative CRs, relative to predicted pre-drug values at the low post-propranolol heart rates, and facilitated the magnitude of decelerative CRs but not significantly. The combination of propranolol and atropine significantly reduced CR magnitudes, relative to predicted pre-drug values, in all cases but one.

Table 8 compares predicted pre-drug and actually obtained post-drug scores for the accelerative and decelerative components of the biphasic CR at CS-US intervals from 10-120 sec. These data show that relative to predicted pre-drug values: (a) propranolol significantly reduced the magnitude of the accelerative but not the decelerative component of the biphasic cardiac CR; (b) atropine significantly reduced

Table 7

Predicted pre-drug (Y') and obtained post-drug (Y)[a] cardiac CR magnitude scores[b] (in msec) for propranolol, atropine, and the combination of drugs (PR + AT), for each subject, at CS-US intervals of 2, 4, and 6 sec.

		Propranolol		Atropine		PR + AT	
		Y'	Y	Y'	Y	Y'	Y
S#	[c]						
	2	+16	+15	- 2	- 1	+12	- 1*
D74	4	+ 9	+14	+ 9	0	+ 9	- 6*
	6	+16	+29	+28	- 4*	+11	- 3*
	2	+61	+62	+ 7	+ 1*	+31	+ 1*
D76	4	+44	+20	- 9	0*	+18	- 1*
	6	+11	+ 9	- 2	- 1	+ 8	- 5*
	2	-20	- 4*	+ 2	0	-10	+ 1*
D64	4	-60	-22*	- 2	- 2	-38	- 2*
	6	-80	-25*	- 4	- 3	-56	- 7*
	2	-16	+16*	- 6	0	- 8	+ 1*
D68	4	-50	- 5*	+ 3	- 4	-30	0*
	6	-47	+13*	+12	- 7	-43	-13*
	2	- 5	+ 1	+ 8	0	+ 1	- 1
D58	4	-46	-16*	+ 4	- 8*	-16	- 2*
	6	-127	-76*	+ 8	- 4	-61	-21*
	2	-11	- 3*	0	0	- 7	0*
D88	4	-21	+ 5*	+17	- 1*	+10	0*
	6	+18	+15	+ 3	- 1	+ 8	- 3*

[a] each Y value is the mean of all post-drug trials for the designated subject, drug condition, and CS-US interval duration.

[b] positive scores indicate cardiac deceleration; negative scores indicate cardiac acceleration.

[c] each number in this column indicates CS-US interval duration (sec).

* obtained post-drug score is significantly different from predicted pre-drug score at $p < .05$.

Table 8

Predicted pre-drug (Y') and obtained mean post-drug (Y) CR magnitude scores[a] (in msec) for the accelerative (ACC) and decelerative (DEC) components of the biphasic CR, at CS-US intervals of 10, 20, 40, 60, and 120 sec.

		Propranolol				Atropine				PR + AT			
		ACC		DEC		ACC		DEC		ACC		DEC	
S#		Y'	Y	Y'	Y	Y'	Y	Y'	Y	Y'	Y	Y'	Y
	10	-24	- 2*	+47	+63*	+ 1	- 5	+43	+ 2*	-15	- 1*	+46	+11*
	20	-35	-36	+39	+92*	-23	- 5*	+81	+ 6*	-31	- 2*	+45	+20*
D74	40	-54	-64	+73	+139*	-30	- 6*	+84	+10*	-40	-11*	+78	+18*
	60	-75	-55	+52	+100*	-30	-13*	+81	+10*	-49	-17*	+64	+34*
	120	-83	-49*	+ 6	+101*	-25	-13	+105	+12*	-60	- 9*	+26	+20
	10	-42	-20	+207	+121	- 1	- 8	+ 4	0	-27	- 9*	+143	+ 1*
	20	-50	-25*	+116	+58*	- 6	- 7	+ 8	+ 5	-34	- 4*	+97	+11*
D76	40	-61	-21*	+141	+43*	-15	-16	+36	+10*	-45	- 7*	+116	+19*
	60	-57	-26*	+80	+54	+ 9	- 8	+51	+ 7*	-38	-13*	+73	+15*
	120	-44	-20*	+60	+30*	- 9	- 4	+33	+14*	-42	-13*	+60	+17*
	10	-153	-92*			-11	- 5			-87	-32*		
	20	-90	- 5*	-14	+11*	- 5	- 2	+ 4	+ 1*	-80	- 9*	-11	+ 4*
D64[b]	40	-68	-42	+ 9	+27*	- 9	- 9	+21	+ 3*	-64	- 7*	+10	+ 2*
	60	-80	-19*	+30	+30	- 2	- 5	+25	+ 5*	-69	-10*	+30	+12*
	120	-63	-36*	+74	+50	-25	- 6*	+37	+ 6*	-47	-10*	+61	+18*
	10	-61	-35*	+14	0*	-18	- 5	+ 1	0	-45	0*	+11	+ 2*
D68	20	-174	-31*	+ 5	+74*	+13	- 3	+22	+ 1*	-107	- 2*	+ 9	+ 4
	40	-97	-23*	+21	+33	+ 2	-16	+64	+11*	-75	- 2*	+30	+ 5*
	60	-101	-30*	+58	+63	+12	- 8	+103	+ 6*	-100	-31*	+59	+43
	120	-136	-95*	+116	+157	- 9	- 7	+72	+11*	-80	- 7*	+120	+10*
	10	-230	-160*	+142	+75	+ 4	-32	+38	0*	-37	25	+82	0*
	20	-103	-77*	+21	+47*	+40	-30	+38	+ 1*	-47	-18*	+18	+ 9*
D58	40	-264	-195*	+214	+116*	-44	-44	+109	+ 6*	-117	-52*	+176	+29*
	60	-111	-95	+200	+138*	-58	-15*	+132	+ 8*	-80	-16*	+175	+13*
	120	-113	-69*	+110	+111	+ 4	-15	+173	+ 6*	-43	-14*	+139	+16*
	10	-18	- 7*	+19	+23	+ 5	- 3	+ 7	+ 2	- 7	- 1	+13	+ 6*
	20	-29	- 5*	+27	+47	+14	- 1	+22	+ 6*	-20	- 7*	+26	+ 7*
D88	40	-102	-47*	+160	+127	+14	-18*	+ 7	+ 2	- 4	- 3	+40	+16*
	60	-100	-39*	+52	+73	0	-44*	+94	+17*	-10	- 3*	+82	+22*
	120	-110	-58*	+218	+121*	+18	-13*	+10	+ 7	-53	-21*	+148	+24*

[a] Positive scores indicate cardiac deceleration; negative scores indicate cardiac acceleration

[b] No decelerative component at the 10-sec CS-US interval

* obtained post-drug score differs significantly from predicted pre-drug score at $p < .05$.

the magnitude of the decelerative but not the accelerative component of the CR; and, (c) the combination of propranolol and atropine significantly reduced both portions of the biphasic CR. Note particularly the small predicted pre-drug scores for atropine, which show that if baseline HR level had been as high pre-drug as it actually was post-atropine, little or no CR acceleration, or in some cases even deceleration, would have been found during the early portion of CS.

Additional drug manipulations

The post-drug data presented thus far were obtained using .16 mg/kg dosages of propranolol and of atropine. These data raised questions about the role of the dosage factor in determining the observed drug effects. Foe example, following .16 mg/kg propranolol, the magnitude of the cardiac CR was reduced, but large changes in HR often remained within the CS-US interval. This observation suggested that the .16 mg/kg dosage may have been insufficient to achieve complete (or nearly complete) sympathetic blockade. Perhaps a much larger dosage, such as 1.0 mg/kg would result in greater attenuation of the cardiac CR. In the case of atropine, a dosage of .16 mg/kg appeared to raise HR levels so high as to make it impossible to tell whether the absence of HR acceleration during CS was due merely to a "ceiling" effect. Perhaps a smaller dosage of atropine would reveal flat CR functions at lower baseline heart rates, thereby giving some indication that atropine's attenuation of CR acceleration was not due merely to a ceiling effect. Another

question was whether extraneural (i.e., hormonal) factors contributed to HR acceleration during CS. It has been reported, for example, that cardiac denervated monkeys display a significant HR acceleration beginning approximately 12 sec after the onset of a pre-shock stimulus, with the conclusion that this long-latency "residual" response is attributable to the secretion of catecholamines (e.g., epinephrine and norepinephrine) from the adrenal medulla (Randall, Kaye, Randall, Brady, & Martin, 1976). Pharmacologic denervation can be achieved by means of a ganglionic blocking agent, such as chlorisondamine or hexamethonium, which occupies cholinergic receptor sites at the level of the autonomic ganglia (cf. Goodman & Gilman, 1975). Since complete ganglionic blockade would eliminate both sympathetic and parasympathetic post-ganglionic transmission simultaneously, it would allow any residual HR acceleration during CS to be attributed to secretion of catecholamines.

In an attempt to obtain information relevant to the above questions, a variety of pharmacological manipulations were conducted with each animal, during re-exposure to the 20-sec CS-US interval. Additionally, data for both the CR and UR were subjected to analysis so that the neural substrates of the two responses could be compared. A description of the experimental procedure follows.

In an effort to maximize data collection, subjects were given increasing dosages and sometimes two different drugs within the same experimental session. For example, in some sessions animals received increasing dosages of propranolol which were then followed by an injection of atropine. In other sessions the sequence was reversed; i.e., increasing dosages of atropine were followed by an injection of propranolol.

This was done in order to see the effects of adding a parasympathetic blocking agent to a sympathetic blocking agent, and vice versa. The effects of ganglionic blockade were assessed through the use of chlorisondamine (Ciba-Geigy). All drugs were given by intravenous injection in the leg. Dosages, in mg/kg, ranged from .16 to 2.0 for propranolol, .02 to 2.0 for atropine, and .08 to 1.0 for chlorisondamine. Subjects were tested in pairs: the first pair tested was D74 and D76, the second D64 and D68, the third D58 and D88. Drug treatments were the same for members of a pair, but differed among pairs. Since D74 and D76 were the first animals tested, they received the greatest number and variety of drug dosages. Based on their results, the dosages which appeared to provide the most information were used with other animals. Subjects D74 and D76 received a total of six drug sessions and the remaining four subjects each received three drug sessions. In all cases, consecutive drug sessions were separated by at least 48 hrs to prevent cumulative drug effects.

As in earlier phases of the study, sessions began with a 10-min waiting period in the chamber, followed by 10 pre-drug trials. The subject was then removed from the chamber and injected with a drug. After replacement in the chamber, and another 10-min waiting period, five post-drug trials were given, followed by an injection of the same drug (higher dose) or by an injection of a different drug. This sequence of drug injection, waiting period, and five post-drug trials, was repeated until as many as five drug injections had been administered.

Figures 32-37 present, for each subject, pre- and post-drug cardiac response functions for all drug sessions at 20-sec II. Each function is composed of mean IBT values (in msec) for successive 2-sec

Figures 32-37. Individual-subject pre- and post-drug HR functions for all drug sessions at 20-sec II. Each HR function consists of mean IBTs (in msec) for successive 2-sec averaging periods beginning 2 sec before CS onset and ending 14 sec following US onset. Arrows denote the onset of US. No datum point is shown for the 2 sec immediately following the onset of US, because of movement artifacts induced by the shock. Each pre-drug function (upper left panel) is the mean of all pre-drug trials administered to that subject during all drug sessions at 20-sec II. Each post-drug function is the mean of five post-drug trials for the designated drug and dosage. Numbers directly above each HR function indicate drug dosages in mg/kg. Abbreviations: PR = propranolol; AT = atropine; CH = chlorisondamine.

Figure 32

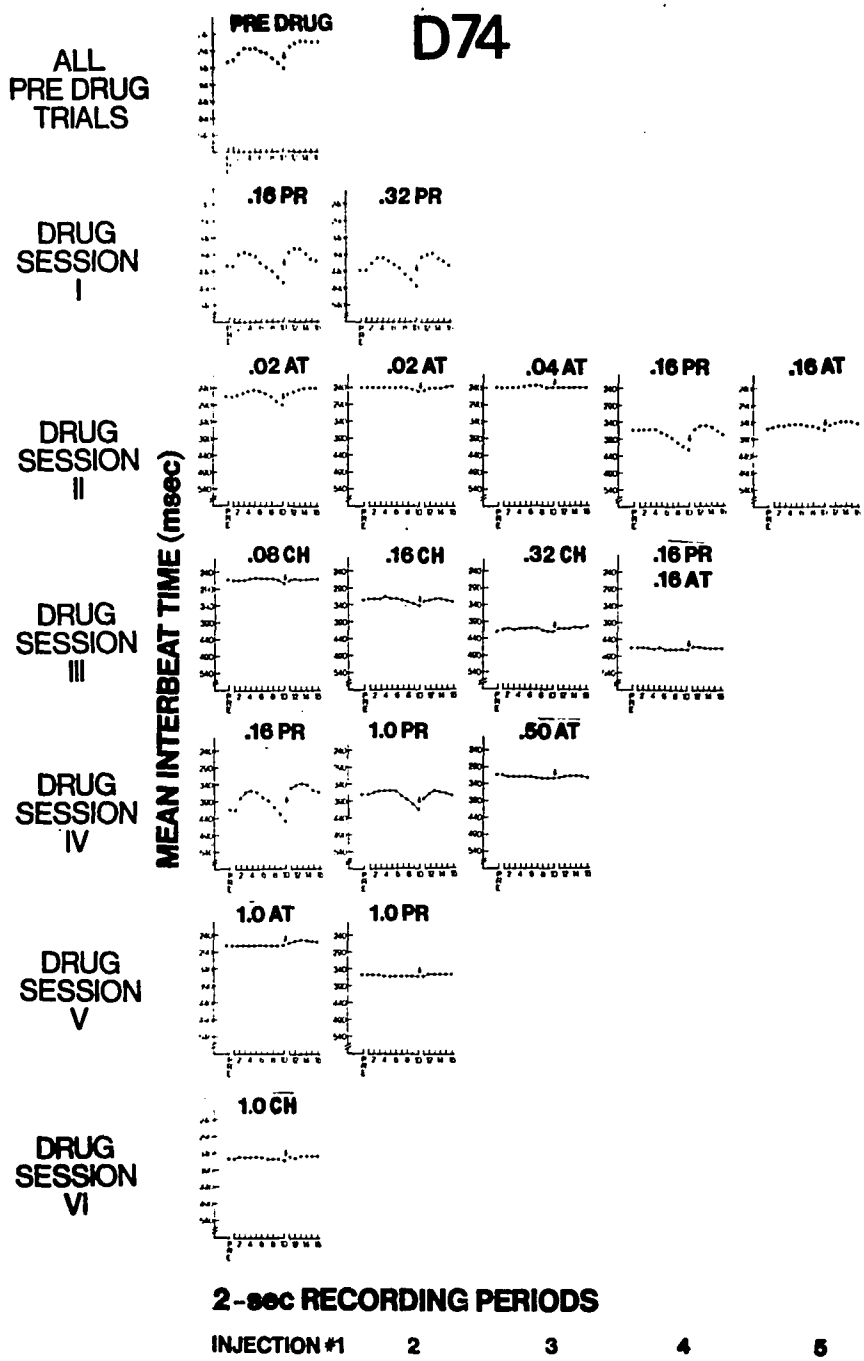
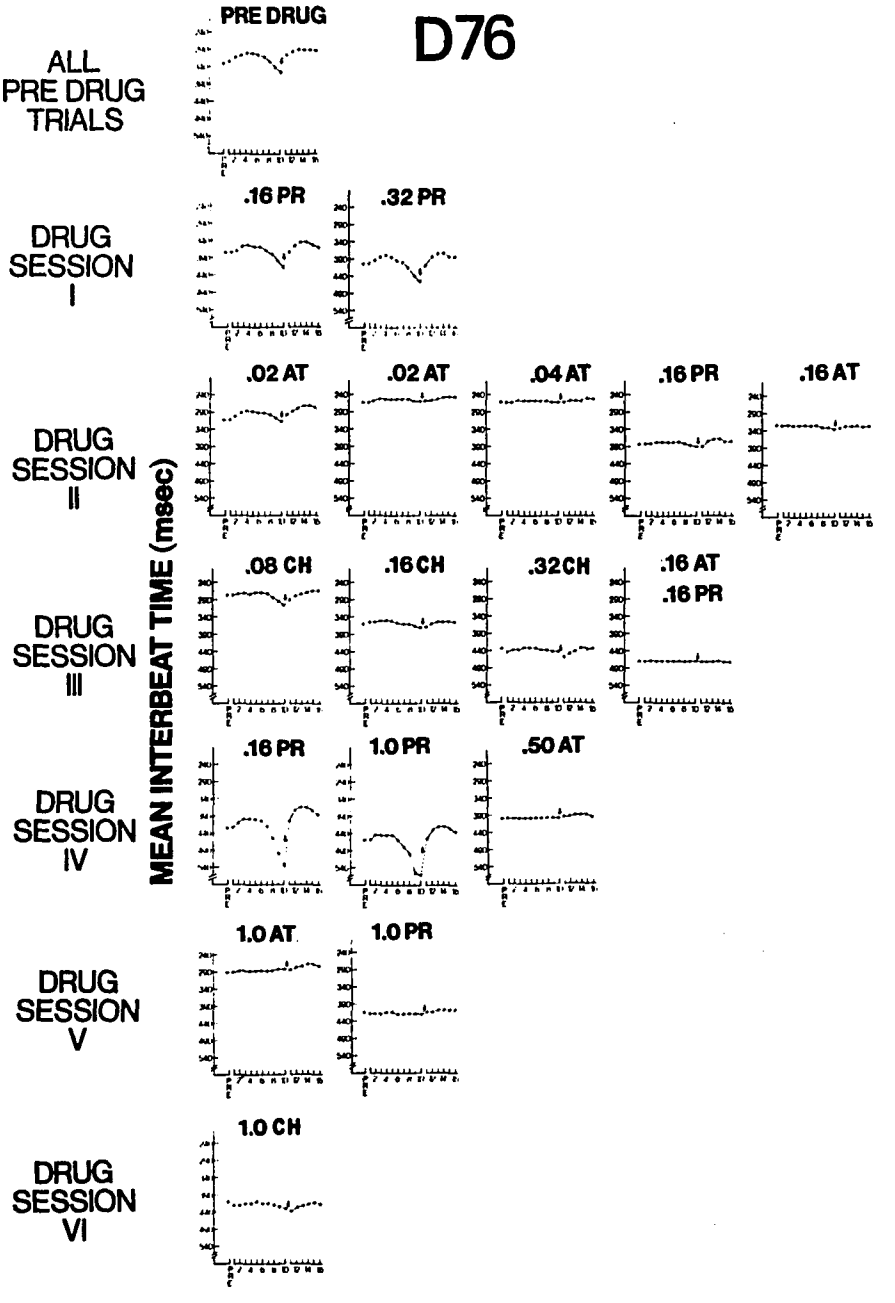
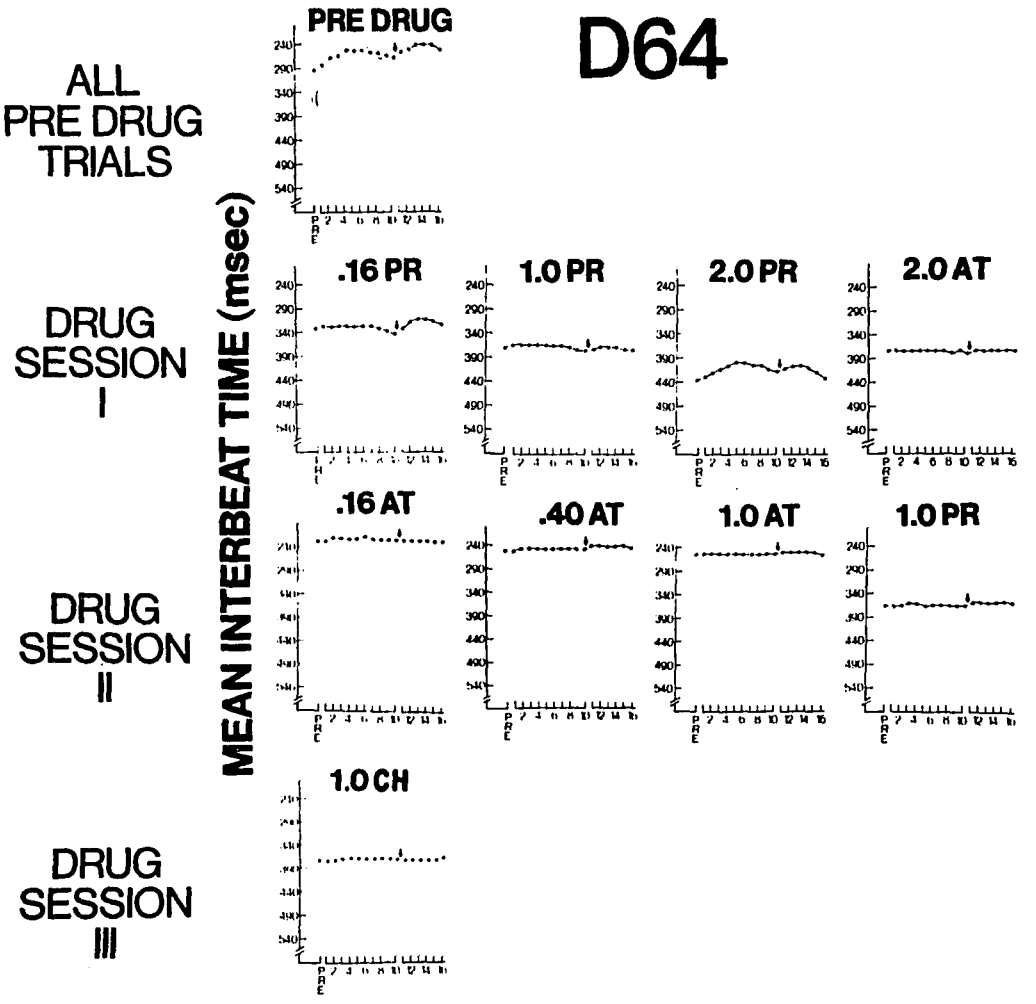
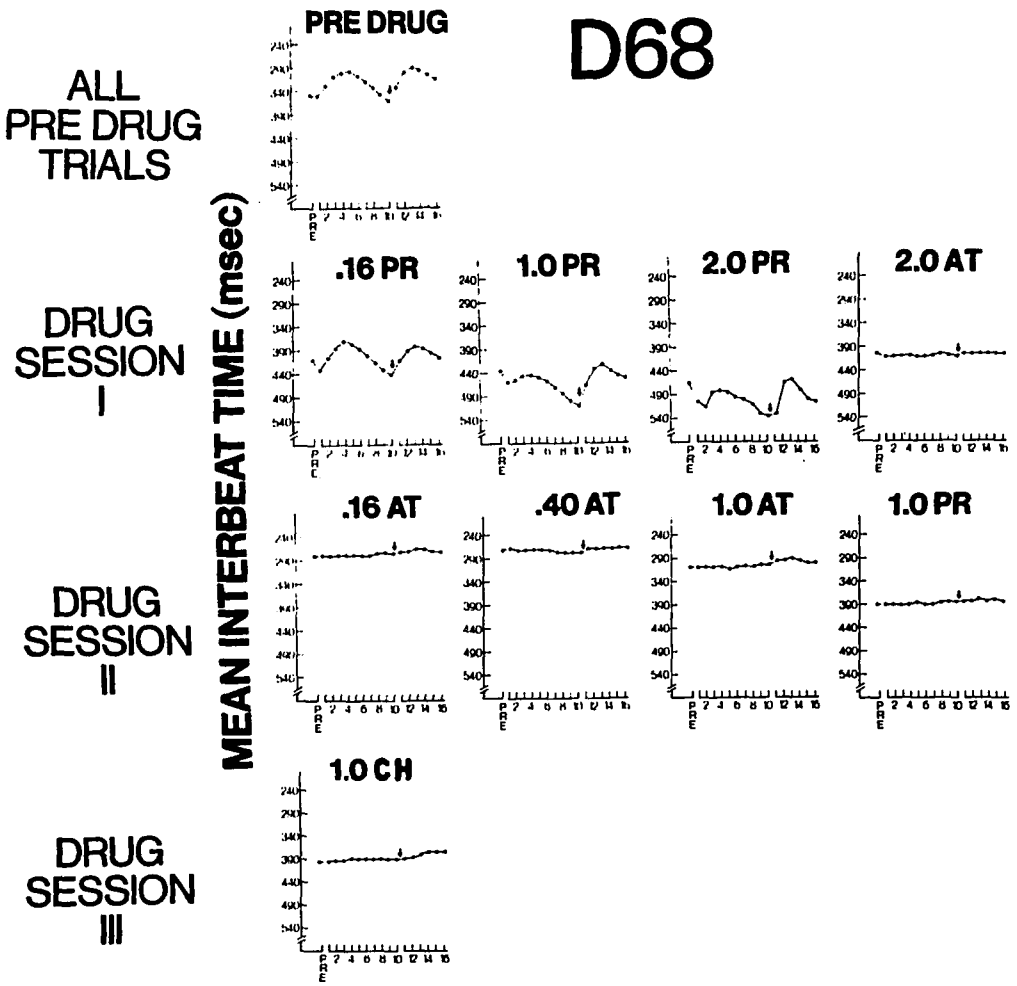
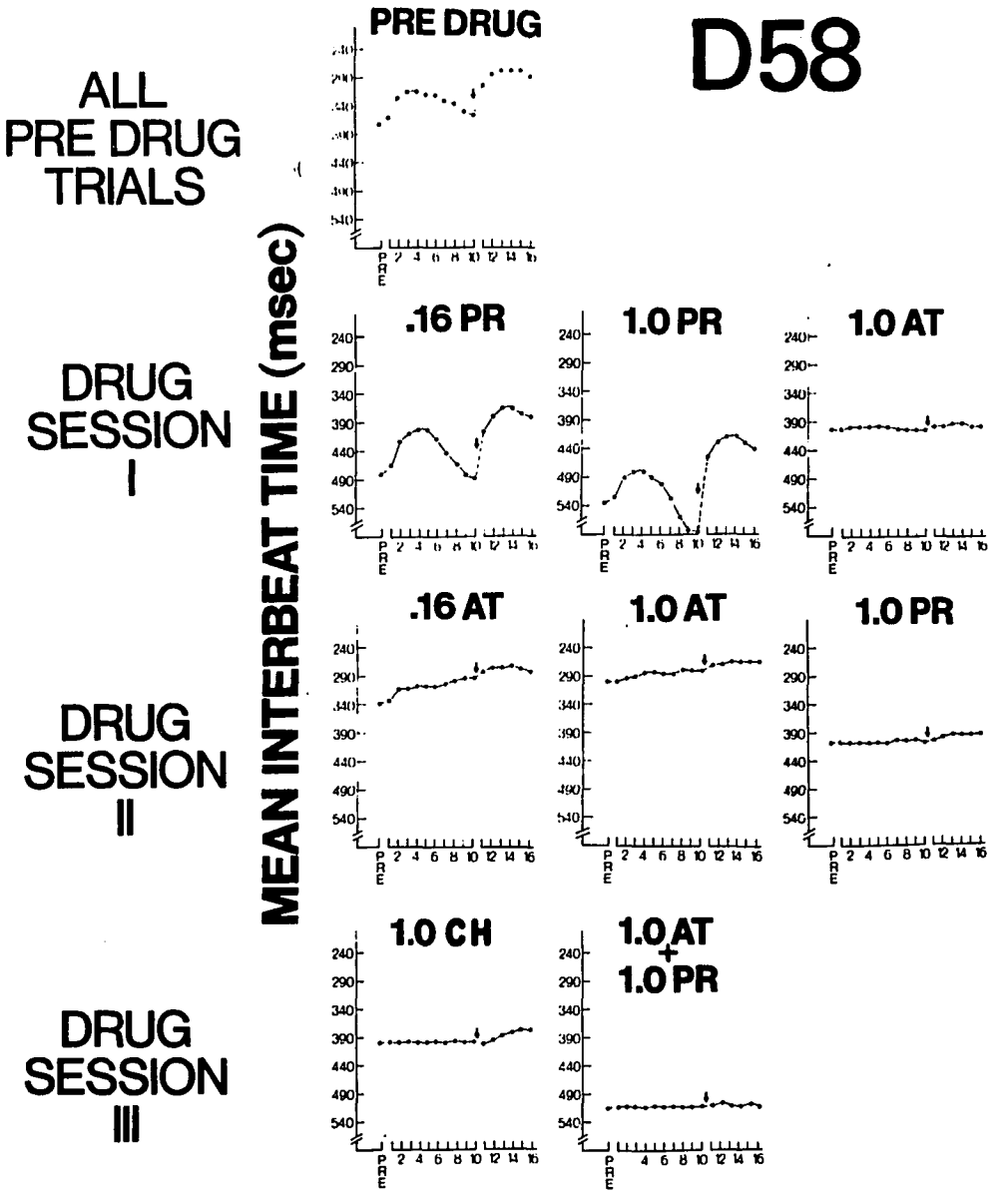

D74
ALL PRE DRUG TRIALS
PRE DRUG
DRUG SESSION I
.16 PR
.32 PR
DRUG SESSION II
.02 AT
.02 AT
.04 AT
.16 PR
.16 AT
DRUG SESSION III
.08 CH
.16 CH
.32 CH
.16 PR
.16 AT
DRUG SESSION IV
.16 PR
1.0 PR
.50 AT
DRUG SESSION V
1.0 AT
1.0 PR
DRUG SESSION VI
1.0 CH
MEAN INTERBEAT TIME (msec)
2-sec RECORDING PERIODS
INJECTION #1
2
3
4
5

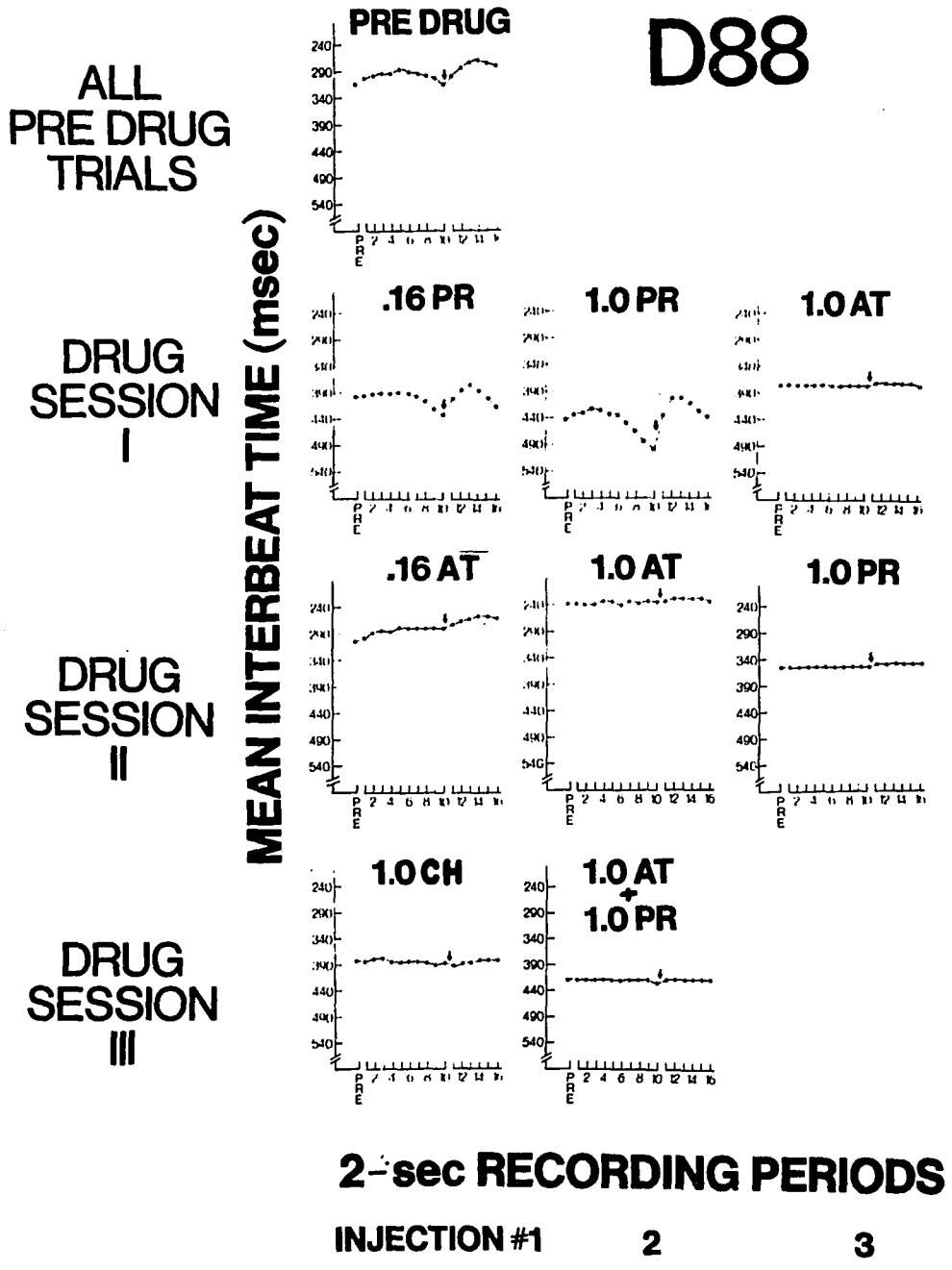
Fig. 33


D76
ALL PRE DRUG TRIALS
PRE DRUG
DRUG SESSION I
.16 PR
.32 PR
DRUG SESSION II
.02 AT
.02 AT
.04 AT
.16 PR
.16 AT
DRUG SESSION III
.08 CH
.16 CH
.32 CH
.16 AT
.16 PR
DRUG SESSION IV
.16 PR
1.0 PR
.50 AT
DRUG SESSION V
1.0 AT
1.0 PR
DRUG SESSION VI
1.0 CH
MEAN INTERBEAT TIME (msec)
2-sec RECORDING PERIODS
INJECTION #1
2
3
4
5


D64
ALL PRE DRUG TRIALS
DRUG SESSION I
DRUG SESSION II
DRUG SESSION III
MEAN INTERBEAT TIME (msec)
PRE DRUG
.16 PR
1.0 PR
2.0 PR
2.0 AT
.16 AT
.40 AT
1.0 AT
1.0 PR
1.0 CH
2-sec RECORDING PERIODS
INJECTION #1
2
3
4


D68
PRE DRUG
ALL PRE DRUG TRIALS
.16 PR
1.0 PR
2.0 PR
2.0 AT
DRUG SESSION I
.16 AT
.40 AT
1.0 AT
1.0 PR
DRUG SESSION II
1.0 CH
DRUG SESSION III
MEAN INTERBEAT TIME (msec)
2-sec RECORDING PERIODS
INJECTION #1
2
3
4


D58
PRE DRUG
ALL PRE DRUG TRIALS
DRUG SESSION I
.16 PR
1.0 PR
1.0 AT
DRUG SESSION II
.16 AT
1.0 AT
1.0 PR
DRUG SESSION III
1.0 CH
1.0 AT + 1.0 PR
MEAN INTERBEAT TIME (msec)
240
290
340
390
440
490
540
PRE
2 4 6 8 10 12 14 16
2-sec RECORDING PERIODS
INJECTION #1 2 3


D88
PRE DRUG
ALL PRE DRUG TRIALS
DRUG SESSION I
.16 PR
1.0 PR
1.0 AT
DRUG SESSION II
.16 AT
1.0 AT
1.0 PR
DRUG SESSION III
1.0 CH
1.0 AT + 1.0 PR
MEAN INTERBEAT TIME (msec)
240
290
340
390
440
490
540
PRE
2 4 6 8 10 12 14 16
2-sec RECORDING PERIODS
INJECTION #1 2 3

averaging periods beginning 2 sec before the onset of CS and ending 14 sec after the onset of US. Because data recording was suspended during the .30 sec shock-US and for 1.7 sec thereafter, no datum point is shown for the 2-sec period immediately following US onset. Each datum point in pre-drug HR functions is the mean of all pre-drug trials administered at 20-sec II. Each point in post-drug functions is the mean of five post-drug trials for the designated drug and dosage. The actual order of drug administrations within a session is preserved in the figures (left to right).

With regard to the CR, Figs. 32-27 show that in most subjects a 1.0 mg/kg injection of propranolol was followed by lower baseline heart rates and greater attenuation of the CR's initial accelerative phase, than a .16 mg/kg injection given earlier during the same experimental session. Note subject D68 who, following the 1.0 mg/kg injection of propranolol, showed HR deceleration at CS onset and no subsequent acceleration above baseline HR levels for the remainder of CS. Note also D64 who displayed flat CR functions following the 1.0 mg/kg injection, indicating that HR changes within the CS-US interval had been eliminated almost entirely. In subjects D58 and D88, on the other hand, 1.0 mg/kg propranolol produced no further attenuation of the CR relative to .16 mg/kg.

For all animals, whatever changes in HR remained under propranolol were obliterated entirely by a subsequent injection of atropine within the same session. Note especially that baseline HR levels increased when atropine was added to propranolol, but still remained lower than pre-drug levels, thus indicating that elimination of the CR by atropine

could not be attributed in this case to a "ceiling" effect.

Chlorisondamine (1.0 mg/kg) lowered baseline HR levels relative to pre-drug, but not to the levels seen under propranolol. Without exception, chlorisondamine eliminated both the accelerative and decelerative components of the pre-drug biphasic CR, leaving HR functions that were almost entirely flat. In subjects D74 and D76 (session III), who were tested under several dosages of chlorisondamine, the drug's effects on baseline HR levels and CR form were clearly dose-dependent within the range of .08 to 1.0 mg/kg.

Although occurring at much higher heart rates, flat CR functions were also consistently evident following 1.0 mg/kg atropine.

Subjects D74 and D76 were the only ones tested with dosages of atropine smaller than .16 mg/kg. This attempt to dissociate atropine's effect on CR magnitude from its effect on baseline HR level was, however, unsuccessful: the degree to which atropine attenuated CR magnitude was directly related to the degree to which it raised baseline HR level, and both were a function of the amount of atropine in the system. As shown in Figs. 33 and 34 (session II), an initial injection of .02 mg/kg atropine had minimal effects on baseline HR level and CR form, relative to pre-drug, whereas an additional .02 mg/kg markedly raised baseline HR and obliterated the CR almost entirely. A third injection of atropine (.04 mg/kg) produced no further effects.

With regard to the UR, Figs. 32-37 show drug effects similar to the CR, although the UR appears to have been less suppressed by the drugs. For example, in some cases, a discernable HR acceleration remained at US onset following a 1.0 mg/kg injection of atropine or chlorisondamine,

despite complete elimination of the preceding CR. Also, in most cases, the UR's initial accelerative component was facilitated, rather than suppressed, by propranolol. As with the CR, however, whatever changes in HR remained under propranolol were eliminated entirely by a subsequent injection of atropine during the same session.

CR and UR magnitude

Computations were made of the magnitude of the initial accelerative and subsequent decelerative components of the biphasic CR and UR, from the data obtained following the 1.0 mg/kg injections of propranolol, atropine, and chlorisondamine. The results for the CR are presented in Fig. 38. As in previous figures, bars projecting above the zero line represent the magnitude of the accelerative component of the response and bars projecting downward represent the magnitude of the decelerative component. Asterisks denote instances where the pre- and post-drug means differed significantly from one another ($p < .05$), based on the usual t-tests.

Figure 38 shows that atropine, as well as chlorisondamine, significantly reduced the magnitude of both components of the biphasic heart rate CR in all six subjects. Propranolol significantly reduced the initial accelerative component of the CR in four subjects and significantly enhanced the subsequent decelerative component in three subjects.

The results for the UR are presented in Fig. 39. The magnitude of the initial accelerative component of the UR was computed by subtracting

Figure 38. Mean magnitudes of accelerative and decelerative components of the CR before and after 1.0 mg/kg injections of propranolol, atropine, and chlorisondamine, at 20-sec II. Bars in each set of six represent, from left to right: CR magnitudes for subjects D74, D76, D64, D68, D58, and D88. Bars extending above the zero line represent magnitude of acceleration; bars extending directly below represent magnitude of deceleration. Asterisks indicate statistically significant differences between pre- and post-drug values ($p < .05$), as determined by t-tests. Data for pre-drug are means of all pre-drug trials administered to that subject at 20-sec II. Data for post-drug are means of five post-drug trials.

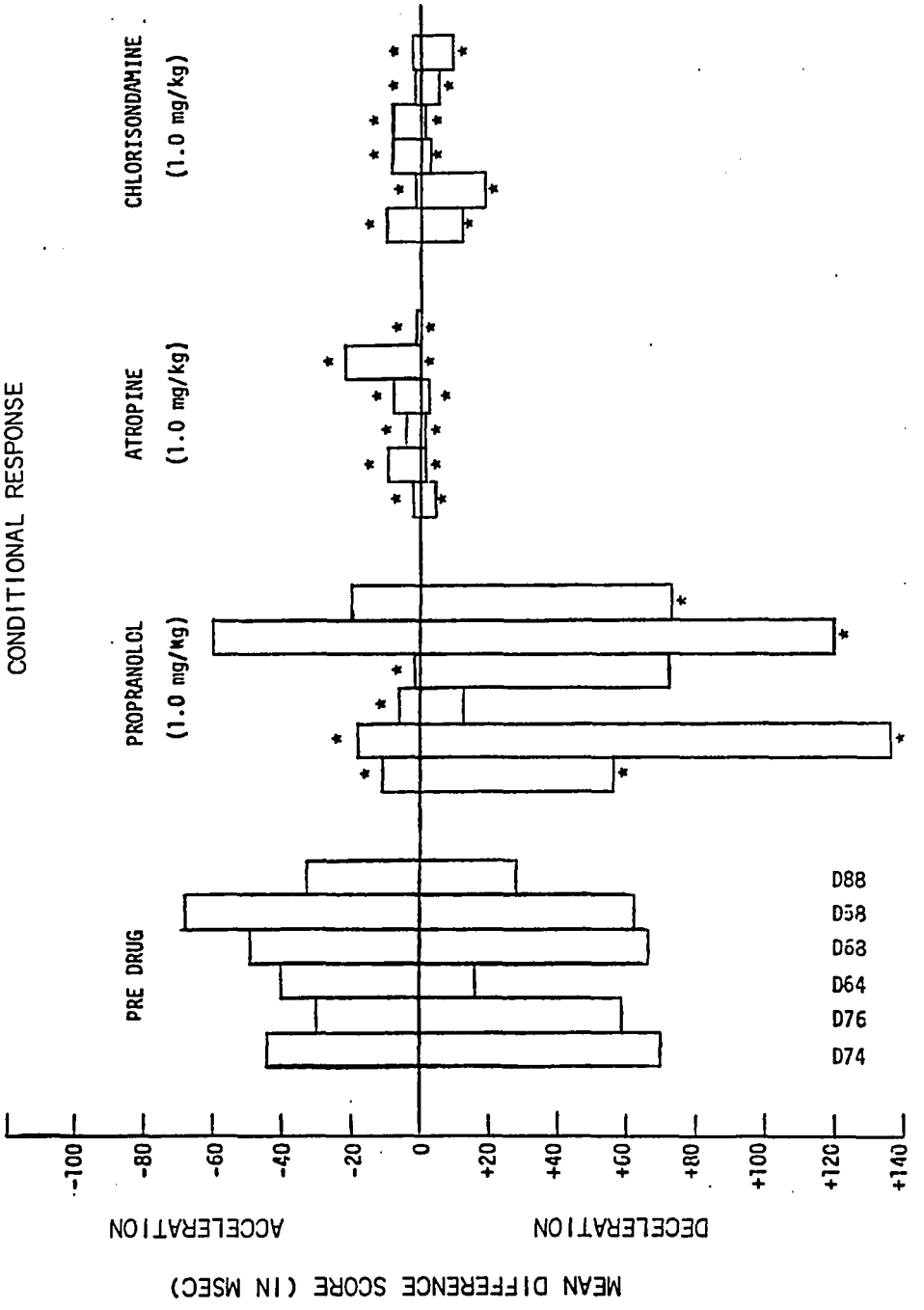
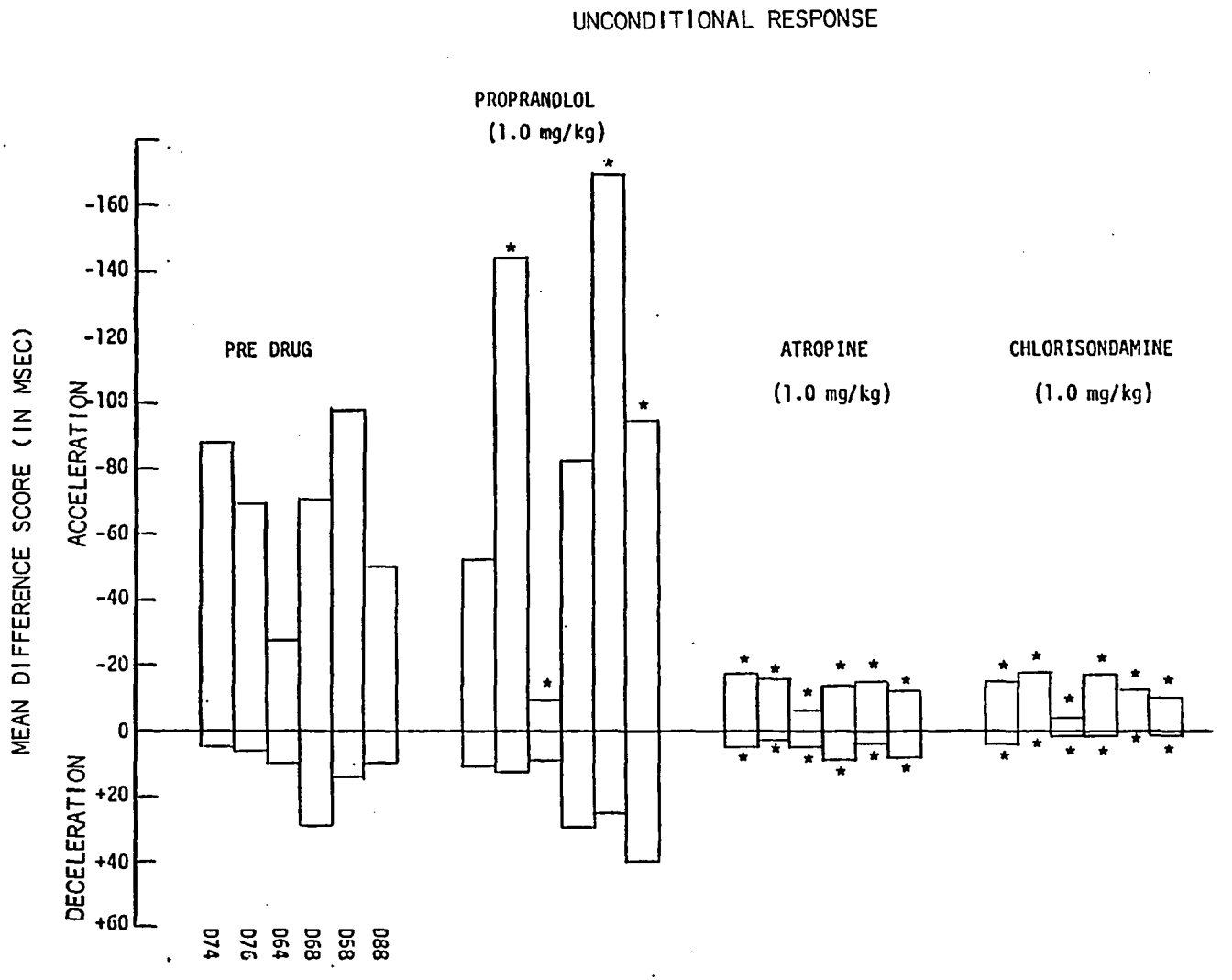

CONDITIONAL RESPONSE
CHLORISONDAMINE (1.0 mg/kg)
ATROPINE (1.0 mg/kg)
PROPRANOLOL (1.0 mg/kg)
PRE DRUG
D88
D58
D68
D64
D76
D74
-100
-80
-60
-40
-20
0
+20
+40
+60
+80
+100
+120
+140
ACCELERATION
DECELERATION
MEAN DIFFERENCE SCORE (IN MSEC)

Figure 39. Mean magnitude of the initial accelerative and subsequent decelerative components of the biphasic cardiac UR, before and after drug injections at 20-sec II. Details same as in Fig. 38.


UNCONDITIONAL RESPONSE
PROPRANOLOL
(1.0 mg/kg)
PRE DRUG
ATROPINE
(1.0 mg/kg)
CHLORISONDAMINE
(1.0 mg/kg)
MEAN DIFFERENCE SCORE (IN MSEC)
ACCELERATION
DECELERATION
-160
-140
-120
-100
-80
-60
-40
-20
0
+20
+40
+60
D74
D76
D64
D68
D58
D88

the mean IBT of the 2-sec period just prior to US onset (final 2 sec of CS) from the preceding smallest mean IBT (highest HR) within the 12-sec post-US recording period. The magnitude of the subsequent decelerative component of the UR was computed by subtracting that same smallest IBT value from the subsequently observed largest mean IBT (lowest HR) toward the end of the post-US recording period.

Figure 39 shows that, as with the CR, both components of the biphasic UR were reduced significantly by atropine and by chlorisondamine. Unlike the CR, however, the UR's initial accelerative component was significantly enhanced by propranolol in some subjects. Propranolol resulted in no significant effects on the UR's decelerative component.

Because of the large changes in HR levels produced by the drugs, the regression technique described earlier was again used to compare the actually obtained post-drug response magnitudes (for both the CR and UR) with those predicted by the pre-drug regression relationships between response magnitude and preceding heart rate level. First, to determine the extent of LIV in the accelerative and decelerative components of both the CR and UR, regression and correlation coefficients were computed between: (a) the magnitude of the initial accelerative component of the CR and pre-CS heart rate level; (b) the magnitude of the subsequent decelerative component of the CR and preceding maximum CS heart rate level; (c) the magnitude of the initial accelerative component of the UR and pre-shock (last 2 sec of CS) heart rate level; and, (d) the magnitude of the subsequent decelerative component of the UR and preceding maximum heart rate level in the post-shock recording period.

The results of these computations (Table 9) show that the LIV relationship was operating in the initial accelerative component of both the CR and UR, as evidenced by negative slope values and product-moment correlations significantly greater than zero ($p < .05$). Both the regression and correlation coefficients for the accelerative component of the UR were larger than corresponding values for the CR, indicating that the dependency of the magnitude of HR acceleration on preceding heart rate level was greater for the UR than the CR. The UR's decelerative component consistently showed a reverse LIV effect: all slope values were positive and all but one correlation coefficient were statistically significant, indicating that the magnitude of UR deceleration decreased with higher heart rate levels. Consistent with earlier results (Table 3), the magnitude of the CR's decelerative component showed no consistent relationship to preceding maximum CS heart rate level.

A comparison of response magnitudes actually obtained post-drug with those predicted by the pre-drug regression equation for the accelerative and decelerative components of the CR and UR is presented in Table 10. Asterisks denote those instances where the actually obtained post-drug score (Y) differs significantly ($p < .05$) from the predicted pre-drug score (Y'), based on the t-formula provided in Appendix A.

Regarding the CR, the data in Table 10 show that propranolol significantly reduced the magnitude of the initial accelerative component in all six subjects, and significantly facilitated the magnitude of the subsequent decelerative component in three subjects, relative to the predicted pre-drug value. Atropine significantly reduced the decelerative component of the CR in every case; it also reduced the accelerative

Table 9

Product-moment correlations (r) and regression coefficients (b) of: (1) pre-CS heart rate levels with magnitude of CR acceleration; (2) maximum CS HR levels with magnitude of CR deceleration; (3) pre-US HR levels with magnitudes of UR acceleration; and, (4) maximum post-US HR levels with magnitudes of UR deceleration

			CR		UR		
			r	b	r	b	N[a]
Subject	D74	ACC	-.69*	-.34	-.82*	-.55	40
		DEC	+.19	+.23	+.90*	+.34	
	D76	ACC	-.84*	-.38	-.98*	-.89	40
		DEC	+.11	+.29	+.11	+.06	
	D64	ACC	-.60*	-.66	-.81*	-.50	24
		DEC	+.22	+.15	+.47*	+.30	
	D68	ACC	-.68*	-.63	-.93*	-.81	24
		DEC	-.14	-.20	+.58*	+.87	
	D58	ACC	-.83*	-.43	-.98*	-.81	30
		DEC	+.23	+.32	+.90*	+.81	
	D88	ACC	-.95*	-.51	-.94*	-.69	32
		DEC	-.40*	-.17	+.38*	+.38	

[a] Number of pre-drug trials upon which the coefficients are based

* statistically significant at $p < .05$

Table 10

Predicted pre-drug (Y') and obtained post-drug (Y) magnitude scores[a] (in msec) for accelerative (ACC) and decelerative (DEC) components of the cardiac CR and UR, for 1.0 mg/kg doses of propranolol, atropine, and chlorisondamine

		Propranolol				Atropine				Chlorisondamine			
		ACC		DEC		ACC		DEC		ACC		DEC	
S#		Y'	Y	Y'	Y	Y'	Y	Y'	Y	Y'	Y	Y'	Y
D74	CR	-59	-11*	+87	+56	-26	- 2*	+66	+ 5*	-56	-10*	+84	+12*
	UR	-118	-53*	+35	+11*	-46	-17*	+ 2	+ 6	-93	-15*	+32	+ 4*
D76	CR	-78	-18*	+98	+136*	-15	- 9	+53	+ 1*	-61	- 1*	+90	+19*
	UR	-253	-144*	+15	+13	- 6	-16	+ 6	+ 3	-136	-18*	+15	0*
D64	CR	-91	- 6*	+31	+13	-17	- 4	+15	+ 1*	-95	- 8*	+32	+ 3*
	UR	-79	- 9*	+47	+ 9*	-18	- 6	+11	+ 5	-76	- 4*	+46	+ 1*
D68	CR	-103	- 3*	+38	+73*	-23	- 7	+64	0*	-77	- 8*	+47	+ 1*
	UR	-187	-85*	+140	+29*	-22	-14	+26	+ 9*	-91	-17*	+97	+ 1*
D58	CR	-137	-60*	+117	+120	-36	-22	+54	0*	-79	- 1*	+93	+ 5*
	UR	-273	-169*	+130	+25*	-20	-15	+ 2	+ 4	-121	-13*	+105	0*
D88	CR	-97	-20*	+ 5	+73*	+ 7	- 1	+36	0*	-65	- 3*	+13	+ 9
	UR	-177	-95*	+62	+40	0	-12	- 4	+ 8	-101	-10*	+53	+ 1*

[a] Positive scores indicate cardiac deceleration; negative scores indicate cardiac acceleration.

* Obtained post-drug score differs significantly from predicted pre-drug score at $p < .05$.

component, but the difference between predicted and actually obtained values was statistically significant in only one subject. Chlorisondamine significantly reduced both components of the biphasic CR in all subjects except D88, whose decelerative component was not significantly affected by chlorisondamine.

As with the CR, in every case, the magnitude of the initial accelerative component of the UR was significantly smaller under propranolol than predicted by the pre-drug regression equation. Also, under atropine, the UR's accelerative component was smaller than predicted, though not significantly (except in D74). Unlike the CR, however, the UR's decelerative component was only minimally affected by atropine, and reduced (rather than facilitated) by propranolol, relative to predicted pre-drug values. In all cases, chlorisondamine significantly reduced both portions of the biphasic UR.

In summary, although 1.0 mg/kg propranolol was followed by greater attenuation of CR acceleration than .16 mg/kg, it still left larger HR changes within the CS-US interval than either atropine or chlorisondamine. Both the initial accelerative and subsequent decelerative components of the normally-occurring biphasic HR CR were eliminated almost entirely following a 1.0 mg/kg injection of atropine, which raised baseline HR levels relative to pre-drug, or, following a 1.0 mg/kg injection of chlorisondamine, which lowered baseline HR levels relative to pre-drug but not to the levels seen after propranolol injection(s). Also, the large HR changes which remained after propranolol injection(s) were obliterated entirely by a subsequent injection of atropine within the same experimental session. Drug effects on the biphasic UR were similar

to those for the CR although the UR tended to be more resistant to suppression by the drugs: facilitation of UR acceleration was noted under propranolol, when compared with pre-drug.

As was the case for earlier results obtained with the .16 mg/kg dosages of drugs, comparisons of predicted pre-drug and actually obtained post-drug response magnitude scores revealed a somewhat different picture of drug effects: propranolol was found to significantly reduce the accelerative but not the decelerative component of the biphasic HR CR, whereas atropine was found to significantly reduce the decelerative but not the accelerative component of the response. Chlorisondamine, however, significantly reduced both components of the biphasic CR, whether compared with actual or predicted pre-drug magnitudes. Results for the biphasic UR were similar to those for the CR, although the UR's decelerative component was reduced by propranolol and minimally affected by atropine, relative to predicted pre-drug values.

Discussion

The experimental design and parameter values chosen for study here represent an effort toward clarifying the role of the CS-US interval variable in cardiac conditioning. Systematic and broad manipulation of the CS-US interval yielded orderly changes in the waveform, latency, and magnitude of cardiac rate CRs within individual organisms. The present results can be discussed with respect to several areas of interest in the literature: (a) the importance of temporal variables in controlling the cardiac rate effects of a CS; (b) the definition of a cardiac rate CR; (c) the Pavlovian "inhibition of delay" phenomenon; and, based on findings with the autonomic blocking agents, (d) the underlying ANS contributions to cardiac rate CRs and UCRs.

An overview of the present data suggests that a CS-US interval of at least 10 sec is critical for obtaining large and consistent cardiac rate CRs. At CS-US intervals shorter than 10 sec, the CR was small and labile, demonstrating marked inconsistency across and within subjects, from one trial to the next. At CS-US intervals longer than 10 sec, a large and consistent biphasic HR response of initial acceleration followed by deceleration was uniformly observed during CS. This biphasic response pattern is the one typically reported for rhesus with CS-US intervals ranging from 10-60 sec and, therefore, present findings complement a steadily growing literature which speaks of the uniformity and replicability of rhesus cardiac CR forms. For example, Snapper et al. (1969) reported of the replicability of rhesus cardiac CR forms across a

variety of aversive conditioning procedures (each of which involved a visual CS and an electric-shock US), and CS-US intervals of 12, 30, and 60 sec. These investigators found that, during initial Pavlovian delay conditioning sessions, intermittent pairings of CS and US, cued escape of US, cued avoidance of US, and CS-US pairings superimposed upon an avoidance baseline schedule, their rhesus subjects invariably displayed a biphasic HR pattern of initial acceleration followed by deceleration over the course of CS. A biphasic CR pattern in rhesus has also been observed: (a) on CS^+ trials of discrimination procedures (e.g., Kadden et al., 1975; Ramsay, 1971); (b) with control of pre-CS heart rate by a cardiac pacemaker (Snapper, Kadden, & Schoenfeld, 1971); (c) with food as the US (e.g., Randall, Brady, & Martin, 1975; Randall et al., 1976); and, (d) during signalled periods of an exercise task (Randall & Smith, 1974). This uniformity and stability of cardiac rate waveform is rather unusual in the cardiac conditioning literature where, for the most part, much greater variability of response patterning has been customarily reported both within and across species (cf. Harris & Brady, 1974). However, the literature for species other than rhesus has concentrated primarily on short CS-US intervals, usually in the range of 0 to 10 sec, and the most common method for assessing the cardiac CR has been to compare pre-CS and post-CS heart rate averages. The present findings indicate that constancy of cardiac CR forms may be demonstrable only when a long CS-US interval is used and the time course of HR changes across the whole of CS is monitored. Short CS-US intervals and/or averaging methods can obscure the waveform and magnitude of the basic response because of its biphasic course.

Because previous studies in rhesus have employed long CS-US intervals, almost always in the range of 10-60 sec, exact precedents for the present findings at short CS-US intervals are lacking. Nevertheless, there is some evidence in the available literature to support the notion that a CS-US interval of at least 10 sec is critical for the biphasic response. This evidence consists of the observation that studies which have used a 10-sec CS-US interval report biphasic response patterns in some monkeys and wholly accelerative response patterns in others (e.g., Kadden et al., 1975; Schoenfeld et al., 1974; Schoenfeld et al., 1975), while studies which have used longer CS-US intervals, such as 30 or 60 sec, report biphasic response patterns without exceptions (e.g., Nathan & Smith, 1968; Ramsay, 1970; Snapper, Kadden, & Schoenfeld, 1971).

It is not clear why cardiac CR forms were inconsistent at the short CS-US inetrvals. Although having started at the short CS-US intervals in a within-subjects design might account for it, such an argument is refuted by finding that each subject recovered his original accelerative or decelerative CR form during re-exposure to the 2-sec CS-US interval at the end of the experiment, despite intervening exposure to much longer interval durations. Wilson (1969) has stated, in a similar context, that during short CS-US intervals, the initial accelerative and subsequent decelerative components of the basic biphasic response are simply "jammed together" so as to produce a "spasmodic mixed response."

The notion that short CS-US intervals simply truncate the course of the biphasic heart rate response (Dronsejko, 1972) is not entirely supported by the present findings. The data for monkeys D64 and D68

(Figs. 3 and 4) corroborate the averaged response patterns reported by Dronsejko (1972) for humans: both animals displayed an initially monophasic HR acceleration at CS-US intervals from 2-10 sec which evolved into a biphasic rate pattern of acceleration followed by deceleration at CS-US intervals longer than 10 sec. On the other hand, the data for subjects D74 and D76 (Figs. 1 and 2), who showed primarily decelerative rather than accelerative CR forms at the short intervals, contradict the notion that response patterns during short CS-US intervals represent the initial portions of longer-interval responses. As Dronsejko's findings were based on averaged response patterns for 60 subjects, it is not possible to determine whether response patterns for all her subjects were similar, or, as in the present findings, some subjects showed different patterns. It can be noted, however, that Figure 5 of Dronsejko's article discloses marked between-subject variability of CR form within a 4-sec CS-US interval.

Although a biphasic HR response has been observed in species other than monkeys, some authors assert that either the accelerative or decelerative component of this pattern is not part of the CR. For example, Wilson (1969) regarded the initial accelerative component of human biphasic responses as an "orienting reflex," and the subsequent decelerative component as the "true" conditioned response. The decelerative component has often been excluded from analyses of conditioning effects, based on assumptions that it is a reflexive return from preceding acceleration and thus not a true conditioning effect (e.g., Fitzgerald & Walloch, 1966; Fehr & Stern, 1965). Given present observations that both components of the biphasic rate function were

lawfully affected by changes in CS-US interval length, the designation of either component as not part of the CR seems unwarranted. Moreover, that the slope of the decelerative component changed with the duration of the CS-US interval, refutes the argument that this portion of the biphasic response is merely secondary to preceding acceleration, and further suggests that more attention be paid to the decelerative component in future analyses of biphasic responses.

Present findings indicate that the CS-US interval is a powerful variable in determining the temporal distribution of cardiac responding during CS. Locations of maximum and minimum HR in the biphasic CR function, as well as the rate of change from maximum to minimum (i.e., the slope of the decelerative component of the CR), were lawfully related to the duration of the CS-US interval. These findings are at odds with the results of Dronsejko (1972), who manipulated the CS-US interval within-subjects and from short to longer intervals, as in the present design. Dronsejko found that the biphasic CR pattern of human subjects was "time-locked" to CS onset, since it peaked consistently at 5 sec into the interval and then declined at a relatively fixed rate, despite lengthening of the CS-US interval from 8 to 12 sec. Her findings indicate that although the cardiac rate CR is initiated by CS onset, its temporal properties are not under control of the variable of CS-US interval length: an invariant biphasic response pattern is merely "triggered" by CS onset and continues its course until truncated by US. The lack of control over temporal patterning in Dronsejko's study can be attributed to her rather unusual procedure of increasing the CS-US interval in steps of .5 sec every two trials within a single experimental

session (each subject received all CS-US interval values within one session). It seems unlikely that two trials would be sufficient for response patterns to adjust to each new interval. In the present study, 160 trials were given at each CS-US interval and, in addition, a much wider range of interval durations was explored (maximum of 120 sec as compared with 12 sec in Dronsejko's experiment).

A comparison of present findings with those of a related study conducted in this laboratory (Turkkan, 1977), points to an important procedural variable in the control of cardiac response patterning at long CS-US intervals. Highly consistent cardiac waveforms of initial acceleration followed by deceleration were obtained, in the present experiment, even at CS-US intervals of 2 min. Using the same species, equipment, stimuli, and comparable CS-US intervals, but with a trace procedure (and fixed inter-US intervals), Turkkan found that cardiac CR patterns became increasingly variable (unpredictable) as the CS-US interval was lengthened and longer and longer trace periods ("gaps") were introduced between CS termination and US onset. Although it has often been suggested, in comparisons of trace and delay procedures, that the continued presence of an external cue during long time intervals facilitates the formation of a "temporal discrimination" (e.g., Fitzgerald & Teyler, 1970; Manning et al., 1969), it is not entirely clear why a CS that does not vary with the passage of time in a long interval (delay) results in more consistent cardiac response patterning than a shorter CS followed by a gap (trace). A study by Kamin (1965) suggests that the temporal proximity between CS termination and US onset, rather than CS duration per se, may be a critical determiner of conditioning

effectiveness at long CS-US intervals. Using a conditioned emotional response (CER) procedure with rats, Kamin systematically varied the duration of CS within a constant 180-sec CS-US interval. (In this case, longer CS durations are synonymous with shorter gaps between CS termination and US, and vice versa.) He found that CS durations ranging from 1.5 to 120 sec did not differ from one another and produced almost no effects on bar-pressing behavior. As CS duration was increased further, so as to narrow the gap between CS termination and US to 5 sec or less, strong conditioning effects suddenly appeared. Moreover, as the gap decreased from 5 sec to 0 sec, conditioning effects increased markedly. Kamin concluded that "literal contiguity of CS and US seems to be a very important factor" (p. 140). The importance of a close temporal relation between CS and US during long time intervals has also been demonstrated by Farmer and Schoenfeld (1966), who found that a CS introduced at varying temporal placements within a 60-sec fixed-interval schedule for food (US) could maintain discriminative control over responding (key-pecking of pigeons) at much longer temporal separations from US when, in addition to being removed in time from US, the CS also occurred just prior to US delivery; i.e., at the end of the 60-sec interval. In the present delay procedure, therefore, it may be that the fixed and close relation to US enabled CS to maintain strong control over HR patterning at long temporal separations between CS and US onsets.

The term "inhibition of delay" was applied by Pavlov (1927) to his observations of a progressive delay in the onset of the salivary CR with longer and longer CS-US intervals. He stated: "this delay is proportional to the length of the interval between the two stimuli and may

even extend to several minutes" (p. 88). Pavlov postulated that the early portions of long CSs acquired inhibitory properties through a process similar to experimental extinction (i.e., lack of reinforcement), which acted to delay initiation of the CR until later in CS. In the present study, no evidence was found of delayed cardiac CRs: heart rate changes began immediately at CS onset and continued throughout the entire duration of CS, even at the longest CS-US intervals employed. Moreover, it appears that observations similar to Pavlov's have never been reported in the cardiac conditioning literature. This disparity may reflect inherent differences between the salivary and cardiac response systems. For example, unlike salivation, HR is acutely sensitive to almost any abrupt change in the environment (Gantt, 1960; Stern, 1972) and, in addition, conditional HR responses are extremely resistant to extinction (e.g., Gantt, 1960; Schoenfeld, Kadden, & McMillan, 1974).

One study possibly demonstrating "inhibition of delay" in the cardiac rate CR was reported by Kadden, Washton, McMillan, and Schoenfeld (1975), in rhesus monkeys. These experimenters introduced a CS^- stimulus signalling the omission of US (shock) on that trial, at varying temporal placements during a 10-sec CS which was otherwise followed immediately by US. They found that when the CS^- stimulus was introduced toward the end of CS, cardiac responding during the early portions of CS was eliminated almost entirely. (A similar finding had been obtained by Bersh, Notterman, & Schoenfeld, 1956, in human subjects.)

Since Pavlov's time, the definition of inhibition of delay seems to have been expanded arbitrarily to include instances where there is no delay in the onset of the CR per se, but where there is a progressive

shift in the temporal locus of peak CR amplitude toward US onset as the CS-US interval is lengthened (cf. Dykman, 1967; Gormezano & Moore, 1971; Stern, 1972). Although such shifts have been widely observed in a variety of response systems (e.g., for HR, Church & Black, 1958; for GSR, Kimmel, 1965; for eyeblink, Ebel & Prokasy, 1963; for salivation, Ellison, 1964; for nictitating membrane, Gormezano, 1972), they do not necessarily relate to the theoretical significance Pavlov attributed to his own observations; namely, that the early segments of long CSs acquire inhibitory properties which act to delay initiation of the conditional response. In any event, while present findings are consistent with the literature, over part of the range of CS-US intervals employed (10-40 sec), a problem remains with the observation that latency to peak HR acceleration in the biphasic CR decreased at the two longest CS-US intervals of 60 and 120 sec. This latter finding appears to have been an artifact of continued training, as suggested by reports that a decrease in peak CR latency often occurs with repeated exposure to a fixed CS-US interval (e.g., Ebel & Prokasy, 1963; Gormezano, 1972). This explanation is supported by the re-exposure functions at 20-sec II which show shorter latencies to peak HR as compared with original exposure functions at the 20-sec interval. Turkkan (1977) also found shorter latencies to peak HR at re-exposure intervals of 10 and 20 sec, as compared with original exposure.

Ebel and Prokasy (1963) have hypothesized that a shift in the temporal locus of the CR peak toward US is "instrumentally shaped." That is, CR-US overlap is differentially reinforced because the occurrence of the CR mitigates the effects of US, as when an appropriately

timed eyeblink response prevents an airpuff US from reaching the surface of the eye. Present findings do not support such an analysis. For example, latency to peak HR increased with longer CS-US intervals even though there was an accompanying increase in the temporal proximity of peak HR to US. Similarly, if temporal proximity between peak HR and US were the sole determiner of CR peak location, then how can the observed decrease in latency at the two longest CS-US intervals be explained? Moreover, while the possible "reinforcing" effects of blinking to avoid an airpuff are obvious, it is difficult to imagine how HR changes might mitigate the effects of electric shock.

In the absence of simple explanatory concepts which can adequately handle the data on peak CR latency shifts, it may be more heuristically valuable to view the temporal pattern of responding as fundamentally determined by the temporal relationships among stimuli under which it is observed. As Schoenfeld and Cole (1972) have pointed out, the temporal relationships among stimuli can be as important to a particular pattern of responding as the physical properties of the stimuli themselves.

The magnitude of the cardiac rate CR, in present rhesus subjects, increased as the CS-US interval increased from 2 to 20 sec, and remained relatively constant thereafter, despite further lengthening of the interval to as much as 2 min. It appears that there is a minimum rather than an "optimum" CS-US interval, at least in the present design, beyond which subjects exhibit their largest cardiac CRs. The present findings corroborate and extend previous studies which have found the magnitude of cardiac rate CRs to increase with the duration of the CS-US interval, as in the case of Hastings and Obrist (1967), who examined the CR of

humans at CS-US intervals from .8 to 13 sec, and Fitzgerald and Martin (1971), who examined the CR of rats at intervals ranging from 0 to 6 sec. How far can the CS-US interval be extended before cardiac CRs diminish or disappear entirely? The answer to this question cannot be obtained from the available literature. Successful HR conditioning has been demonstrated at CS-US intervals of 3 min in rhesus (Brady, Kelly, & Plumlee, 1969), and at intervals of 12 min in humans (Breznitz, 1967).

Neural control of the cardiac CR and UR

Results of the pharmacological manipulations suggest that the sources of ANS control over the cardiac rate CR remained essentially unchanged across the range of CS-US intervals employed. The effects of the drugs on the cardiac CR were independent of the CS-US interval except insofar as the interval duration determined the waveform and direction of the pre-drug response. Drug effects on CR acceleration were the same whether this acceleration constituted the entire CR at a short CS-US interval or was part of a biphasic CR at a long interval. This was also true for CR deceleration. Such pharmacological evidence appears to be inconsistent with the view of some authors that CRs at different points along the CS-US continuum reflect different underlying behavioral processes (e.g., Dykman, 1967; Stern, 1972).

Results of the drug-dosage manipulations performed during re-exposure to the 20-sec CS-US interval (20-sec II) showed that effects on baseline heart rate and cardiac CR magnitude of propranolol, but not atropine,

were dose-dependent within the range of .16 to 1.0 mg/kg, similar to reports from other investigations in rhesus (Klose et al., 1975; Schoenfeld et al., 1975). Because these findings suggested that the .16 mg/kg dosage of propranolol, used across earlier phases of the experiment, was probably inadequate to achieve complete (or nearly complete) blockade of sympathetic activity, the present discussion will focus exclusively on data obtained with the 1.0 mg/kg dosages of the drugs at 20-sec II. This affords a more meaningful characterization of the ANS contributions to observed HR responses. It also affords a more integrated discussion of pharmacological findings, since it was only at 20-sec II that data for both the conditional and unconditional heart rate response were obtained, and the effects of ganglionic blockade by chlorisondamine were explored.

Results of the pharmacological manipulations can be discussed with regard to: (a) which branch of the ANS exerts the controlling influence over resting heart rate of rhesus subjects during experimental sessions; (b) whether extraneural (hormonal) factors contribute to the cardiac rate CR; and, (c) the underlying sympathetic and parasympathetic contributions to the cardiac CR and UR.

Pharmacological denervation by chlorisondamine indicated that the intrinsic rate of the rhesus heart is approximately 155 bpm (the mean pre-CS heart rate of all six subjects following 1.0 mg/kg chlorisondamine), which is identical to the value reported by Klose et al. (1975) for restrained rhesus subjects after pharmacological denervation by combined administration of 3.0 mg/kg propranolol and 1.0 mg/kg atropine. A comparison of baseline heart rates before and after ganglionic blockade allows inferences as to which branch of the ANS exerts

the controlling influence over resting heart rate in the intact organism. In the present study, baseline heart rate prior to drug administration (mean of 185 bpm) was significantly higher than that after ganglionic blockade by chlorisondamine (mean of 155 bpm). Since the sympathetic and parasympathetic systems exert "mutually antagonistic" effects on heart rate (Rushmer, 1970), this finding indicates that the sympathetic system exerted the controlling influence over resting heart rate during conditioning sessions (also concluded by Klose et al., 1975).

Pharmacological denervation by chlorisondamine also indicated that extraneural factors did not contribute to observed HR changes during a 20-sec CS-US interval, as evidenced by complete elimination of the normally-occurring biphasic CR after administration of chlorisondamine. This finding is at odds with Randall et al. (1976) who found a long-latency HR acceleration during a 60-sec CS-US interval in cardiac-denervated rhesus subjects, and concluded that this "residual" HR response was due to a conditional secretion of catecholamines from the adrenal medulla. However, the 20-sec CS-US interval in the present study may have been too short to allow observation of a long-latency hormonal response. An inspection of data from Randall et al. (their Fig. 4) shows almost no changes in HR during the first 20 sec of their 60-sec CS-US interval in denervated subjects.

Parasympathetic blockade by atropine resulted in baseline heart rate levels significantly higher than pre-drug levels, confirming previous reports in various species where such a finding has been taken to indicate that the vagus normally maintains a restraining influence on resting heart rate (e.g., in rhesus, Klose et al., 1975; for squirrel monkeys,

Kelleher, Morse, & Herd, 1972; for dogs, Dykman & Gantt, 1959; for rats, Fitzgerald, Martin, & O'Brien, 1973; for rabbits, Schneiderman, 1972). Sympathetic blockade by propranolol significantly lowered baseline heart rate levels, as also reported by other experimenters (e.g., Klose et al., 1975; Sampson et al., 1974; Schoenfeld et al., 1975).

The large difference between pre- and post-drug heart rate levels complicate the data analysis and interpretation of the drugs' effects on cardiac CR magnitudes. This is especially true for the accelerative component of the CR since its magnitude was significantly correlated with pre-CS heart rate level in every case (Table 9). If only the raw data (Figs. 32-38) are considered, ignoring any effects of the drugs on heart rate level, one could conclude that both the accelerative and decelerative components of the biphasic CR were mediated primarily by changes in parasympathetic activity. Such a conclusion is supported by the observations that although propranolol reduced the initial accelerative component and facilitated the subsequent decelerative component, atropine eliminated both components of the biphasic CR almost entirely. If, on the other hand, the drugs' effects on heart rate level are not ignored, but rather eliminated statistically, a somewhat different picture emerges. Comparisons between the magnitude of the actually obtained post-drug CR and the magnitude that would have been predicted for the CR had the heart levels observed under the drug been obtained in the pre-drug session (Table 10), indicated that sympathetic blockade by propranolol selectively reduced the initial accelerative component of the CR while parasympathetic blockade by atropine selectively reduced the subsequent decelerative

component. Although each drug yielded a significant reduction in a particular portion of the CR, relative to predicted pre-drug values, it did not eliminate that portion entirely. These findings differ from the raw data in one major respect: they show propranolol as having a much stronger effect on the CR's accelerative component, seemingly pointing to a predominant sympathetic influence over the initial HR increase.

Some overall conclusions can be offered which take into account both the raw data and the the results of the regression analysis: The initial accelerative component of the CR is probably the combined result of an increase in sympathetic activity accompanied by a decrease in parasympathetic activity, as suggested by other investigators for various species (e.g., for rhesus, Klose et al., 1975; Randall & Smith, 1974; Schoenfeld et al., 1975; Turkkan, 1977; for dogs, Dykman & Gantt, 1959; Obrist & Webb, 1967; for pigeons, Cohen & Pitts, 1968). As for the subsequent decelerative component, it appears to be due primarily to an increase in parasympathetic activity, as also suggested by other investigators (e.g., Downs et al., 1972; Hein, 1969; Schneiderman, 1972). Since the sympathetic and parasympathetic systems restrain each other's effects on heart rate, the facilitation of the decelerative component under propranolol suggests that the sympathetic system normally checked the strong decelerative action of the vagus. The present conclusion that both branches of the ANS played at least some role in both portions of the biphasic CR is supported by observations that only complete autonomic blockade, whether by combined action of propranolol and atropine or by ganglionic blockade with chlorisondamine, totally eliminated both portions of the CR.

The above conclusions for the CR can also be applied to the cardiac UR, which was not only similar in form to the CR, but also affected similarly by the drugs. However, the UR was less suppressed by the drugs than the CR, suggesting that ANS input to the heart may have been more strongly activated by the shock-US than by the light-CS. A similar finding was obtained by Turkkan (1977), also in rhesus.

For both the CR and UR, the effects of propranolol on the initial heart rate increase were greatly strengthened when the regression relationship between the magnitude of the increase and pre-stimulus HR level was taken into account. This use of a regression relationship to statistically eliminate the confounding effects of a covariate is a common procedure, and has been applied by other investigators to cardiovascular data (Myers & Honig, 1969). However, the use of a linear regression model to test extreme values, where the regression relationship was not actually tested pre-drug, involves a critical assumption; namely, that the same linear function which describes the data actually obtained pre-drug, would have also described the data in the regions of extrapolation, if such data were obtained under the original set of experimental conditions. Significant departures from linearity would, therefore, compromise any conclusions based solely on the present regression analysis.

Since propranolol hydrochloride and atropine sulfate both cross the blood-brain barrier (cf. Goodman & Gilman, 1975), one might ask whether the observed effects of these drugs on the cardiac responses of present rhesus subjects was due to their pharmacological actions

on the autonomic nervous system, or, to their actions on the central nervous system. Although this question is not answerable from the present data, Schoenfeld et al.(1975) compared the effects on rhesus cardiac CRs of; (a) propranolol hydrochloride with other drugs that interfere with sympathetic nervous system activity, but presumably do not cross the blood-brain barrier (e.g., sotalol), and (b) atropine sulfate with other drugs that interfere with parasympathetic nervous system activity, but presumably do not cross this barrier (e.g., atropine methyl nitrate). These investigators found that drugs which interfered with sympathetic activity, whether or not they crossed the blood-brain barrier, all shared the same effect on the cardiac rate CR. Similarly, drugs which interfered with parasympathetic activity all shared the same effect on the CR. Their findings suggest that the effects of the drugs observed in the present study were of peripheral rather than of central origin.

Summary

The present study examined Pavlovian conditioning of heart rate in rhesus monkeys under systematic manipulation of the variable of CS-US interval length from 2 to 120 sec. Additionally, the underlying ANS contributions to cardiac rate CRs and URs were assessed by administration of selective pharmacological blocking agents.

Cardiac CR waveforms were least consistent both within and across subjects at CS-US intervals of 2-6 sec, where instances of accelerative, decelerative, and biphasic HR patterns were observed during CS, with the direction of response changing from trial-to-trial depending upon the level of heart rate just prior to CS onset. At CS-US intervals from 10-120 sec, a stable biphasic HR pattern of initial acceleration followed by deceleration was uniformly observed during CS, with the form of the response showing consistency within subjects (across trials) despite continued wide fluctuations in pre-CS heart rate. During re-exposure to the 20-sec CS-US interval, the biphasic CR pattern was retained, and three of the six subjects fully recovered their original rates of HR acceleration and deceleration during CS. During re-exposure to the 2-sec CS-US interval, where the experiment began, each subject recovered his original CR form of monophasic acceleration or deceleration.

The latency to peak HR in the biphasic CR function increased as the CS-US interval was lengthened from 10 to 40 sec, and then decreased at the two longest CS-US intervals of 60 and 120 sec. Shorter latencies to peak HR were found during re-exposure to the 20-sec CS-US interval

as compared against original exposure. The rate of cardiac deceleration from the preceding peak of acceleration in the biphasic CR pattern was inversely related to the length of the CS-US interval: the longer the interval the slower the decline from maximum to minimum heart rate during CS.

The magnitude of peak HR change during CS increased linearly as the CS-US interval was lengthened from 2 to 20 sec, and then remained essentially unchanged with further lengthening of the CS-US interval to 120 sec.

The law of initial value (LIV) was consistently evident in the initial accelerative but not the subsequent decelerative component of the biphasic CR. Correlation and regression coefficients relating cardiac CR magnitudes to pre-CS HR levels assumed increasingly negative values as the CS-US interval increased.

Baseline heart rate levels were highest during vagal blockade by atropine, lowest during sympathetic blockade by propranolol, and similar to but lower than pre-drug during double blockade by combined propranolol and atropine. Ganglionic blockade by chlorisondamine lowered baseline HR levels relative to pre-drug.

Both accelerative and decelerative HR changes within the CS-US interval were eliminated almost entirely by parasympathetic blockade, ganglionic blockade, or combined sympathetic and parasympathetic blockade. Sympathetic blockade alone left large HR changes within the CS-US interval, with CR deceleration often facilitated relative to pre-drug. These effects were obtained across all CS-US intervals (2-120 sec), and whether the entire pre-drug CR form was monophasic or biphasic.

The unconditional heart rate response to shock was similar in form to the CR, consisting of an initial accelerative and subsequent decelerative component, and was affected similarly by the pharmacological blocking agents, although the UR tended to be less suppressed by the drugs.

It was suggested that a CS-US interval of at least 10 sec is critical for obtaining large and consistent cardiac rate CRs. Constancy of cardiac CR forms may be demonstrable only when a long CS-US interval is employed and the entire time course of HR changes across the CS-US interval is measured. Short CS-US intervals and/or averaging methods can obscure the waveform and magnitude of the basic response because of its biphasic course. The whole biphasic rate function should be regarded as the conditional response, and segmenting it into separable parts does not appear warranted. Reasons for the response variability at short CS-US intervals are unclear. A fixed and close temporal relation between CS termination and US onset in the present delay conditioning procedure may have been the factor which enabled CS to maintain strong control over cardiac response patterning even at long CS-US intervals. There appears to be a minimum rather than an "optimum" CS-US interval beyond which subjects display their largest cardiac CRs. The duration of the CS-US interval is a powerful variable in determining the temporal distribution of cardiac rate changes during CS.

Resting heart rate in the rhesus subjects was under greater control of the sympathetic system from evidence of lower heart rates after complete autonomic blockade. The underlying ANS contributions to the cardiac rate CR remained unchanged across the range of CS-US intervals

employed. The initial accelerative component of the biphasic CR is the combined result of an increase in sympathetic outflow coupled with a decrease in vagal restraint. The subsequent decelerative component is due primarily to an increase in vagal restraint. The biphasic UR is mediated by similar changes in autonomic nervous system activity as the CR.

Appendix A

t-formula for testing the significance of differences between predicted pre-drug (Y') and obtained mean post-drug ($\overline{Y}$) HR response magnitude*:

$$t = \frac{\overline{Y}_{post} - Y'}{\sqrt{\frac{s^2_{Y \cdot X\ post}}{N_{post}} + \frac{s^2_{Y \cdot X\ pre}}{N_{pre}} + \frac{(s^2_{Y \cdot X\ pre})(\overline{X}_{pre} - \overline{X}_{post})^2}{\sum(X - \overline{X})^2_{pre}}}}$$

where: $s^2_{Y \cdot X}$ = standard error for predicting Y (HR response magnitude) from X (initial heart rate level)

N = number of X,Y pairs (trials).

* tested with df = $N_{pre} + N_{post} - 3$

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