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VARYING TEMPORAL LOCATION OF A CS IN A FIXED INTER-US INTERVAL IN HEART RATE CONDITIONING IN *MACACA MULATTA*

by

Jaylan S. Turkkan

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.

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Abstract

VARYING TEMPORAL LOCATION OF CS IN A FIXED INTER-US INTERVAL IN HEART RATE CONDITIONING IN MACACA MULATTA

by

Jaylan Turkkan

Adviser: Dr. William N. Schoenfeld

An investigation of the temporal distribution of a stimulus serving as "CS" for its effects on heart rate conditioning in six rhesus monkey subjects was conducted, with an additional investigation of the autonomic nervous system contributions to such conditioned heart rate changes.

A 10 sec light (CS) was introduced at varying temporal locations during periodic 231 sec intervals between presentations of electric shock (US). This procedure corresponds to an "intruded stimulus" paradigm, and incorporates such designs as delay, trace, safety-signal, backward, and temporal conditioning as CS is first introduced close to a subsequent US, , and is then moved further back in the inter-US interval. Eight locations of CS were used, with three locations repeated. They were, as timed from CS onset to onset of the subsequent US: 10, 20, 30, 50, 80, 120, 170, and 230 sec, in that order for all six subjects. CS-US intervals of 50, 20, and 10 sec were re-examined. Each CS location during original exposure was examined for six sessions (20 trials each), fol-

lowed by two sessions where US was delivered alone at periodic intervals of 231 sec. The dependent variable was mean cardiac interbeat interval (in msec) averaged in either 2 sec or 10 sec successive periods.

During re-examination of each CS location, three pharmacological blocking agents were administered. Atropine sulfate (a parasympathetic blocking agent), propranolol hydrochloride (a sympathetic blocking agent), and chlorisondamine (a ganglionic blocking agent) were injected i.v. at a strength of 1 mg/kg to evaluate the sources of autonomic control (sympathetic or parasympathetic) over the form and magnitude of conditioned and unconditioned heart rate responses. Each drug's effects on heart rate changes in the CS-US and US-US intervals were examined during conditioning sessions.

Results of the behavioral and pharmacological manipulations were:

1. A biphasic heart rate function (rate acceleration followed by deceleration) developed during the CS-US interval at the first CS-US interval of 10 sec, followed by polyphasic (i.e., several maxima and minima) and more variable waveforms at longer CS-US durations.

2. Latency to the peak heart rate change in the CS-US interval, and the variability of the location of peak heart rate change increased proportionally to the duration of the CS-US interval.

3. Heart rate during a pre-CS interval was deceleratory at the first location of CS (10 sec CS-US), and acceleratory at subsequent locations of CS, including re-exposure, with the exception of 120 sec CS-US. In sessions where CS was not presented, heart rate in a comparable measurement period was deceleratory. Sessions subsequent to 50 sec CS-US showed acceleratory trends in this period.

4. Cardiac conditioned response (CR) magnitude increased significantly during the first three locations of CS (10-30 sec CS-US), decreased

over the next two locations (50 and 80 sec CS-US), and increased once again from 120 to 170 sec CS-US.

5. Atropine raised heart rate levels, and eliminated conditioned heart rate changes in the CS-US interval. Propranolol lowered heart rate levels, reduced the acceleratory component of the biphasic CR, and enhanced the magnitude of the decelerator component. Chlorisondamine raised heart rate levels in most cases, and eliminated conditioned heart rate changes entirely.

The relevance of the obtained results was discussed in terms of the specification of basic response units in cardiac conditioning, the differing effects of CS depending upon its temporal proximity to US, whether in a temporally forward or backward direction, and, the probable autonomic innervations of the cardiac CR.

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The author wishes to express her gratitude to her sponsor, Dr. William N. Schoenfeld for his role as the proverbial gadfly. I hope that his stylistic and conceptual rigor is at least partly reflected in these pages. Dr. Ronald M. Kadden, head of the Psychology Research Laboratory at the FDR VA Health Care Facility, Montrose, N.Y., where this experiment was conducted, provided the kind of day-to-day guidance that was invaluable in the shaping of this dissertation.

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INTRODUCTION

When the primitive operation of introducing an unconditioned stimulus (US) during the ongoing activity of an organism is periodically repeated, one might find systematic changes during the interstimulus interval in various response systems as a result of the time elapsed since the previous stimulus delivery. In Pavlovian terminology this procedure is known as temporal conditioning (Pavlov, 1927), and, in the operant system, it is termed "superstitious" conditioning (Skinner, 1948). Pavlov, and later investigators who extended Skinner's superstition experiment, noted an increase in the frequency of US-related behaviors as a function of time elapsed between presentations of the US. For example, in Pavlov's laboratory, an increase in salivation was observed in dogs toward the end of 30 min periods between food presentations; similarly, Staddon & Simmelhag (1971) noted consistent increases in pigeons' activity around a food hopper toward the end of 12 sec inter-food intervals.

If another previously neutral stimulus is paired with the unconditioned stimulus, this extra stimulus (hereafter termed a "CS") can be demonstrated to exercise control over behavior as a result of pairings with US. Skinner (1938) described, for the operant case, the differing functions that this stimulus could assume as, (a) discriminative, in that its presence, by being correlated with US (reinforcement) availability, sets the occasion for responding, (b) "emotional" in that a group of behaviors are either increased ("facilitated") or decreased

("inhibited") by its presentation, or, (c) reinforcing, in that it could change the frequency of a response, similar to a primary reinforcer. Furthermore, Skinner demonstrated that a stimulus could assume more than one function simultaneously. For instance, a discriminative stimulus may also act as a conditioned positive or negative reinforcer.

It is recognized that the temporal relationship between the CS and US is an important variable in determining the functions of CS. In this regard, Libby (1951) examined the inhibitory or depressive function acquired by a CS as a result of its temporal proximity to US. He found that as CS-US intervals (where US was an electric shock) increased from 0 sec to 10 sec, rate of responding in the presence of CS, later introduced during a regular reinforcement schedule for bar-pressing in rats, was systematically reduced.

Studies conducted by Farmer & Schoenfeld (1966 a,b), and by Rescorla and co-investigators, have also shown that the function of a CS is determined by temporal parameters (Moscovitch & LoLordo, 1968; Rescorla, 1969 a,b; Rescorla & Solomon, 1967). Rescorla & Solomon (1967) distinguished between "warning" and "safety" effects of CS in terms of its temporal proximity to shock (US). At short CS-US intervals, CS was shown to act as a warning signal, resulting in increased avoidance responding, or reduced positively reinforced responding. Long CS-US intervals resulted in the CS acquiring safety-signal properties, as evidenced by effects opposite to the above (attributed to the inhibition of fear).

Farmer & Schoenfeld (1966 a,b), through the introduction of what they termed an "intruded" or "added" stimulus design, forced the recognition that various functions of stimuli can be ordered along a temporal continuum. The intruded stimulus procedure consists of a baseline

reinforcement schedule maintaining a steady state of behavior, into which initially "neutral" stimuli are introduced. Farmer & Schoenfeld (1966 b) demonstrated, for key-pecking rate of pigeons, that a CS introduced at varying temporal placements in a 60 sec fixed-interval baseline schedule for food assumed, (a) a positive discriminative stimulus function (S^D) when the temporal separation between CS and US (reinforcement) was short, and (b) a negative function (S^Δ) when the CS-US separation was long. Also, at long CS-US intervals, the intruded stimulus was shown to act as a conditioned positive reinforcer for the pattern of responses preceding its occurrence in the inter-US interval.

Another intruded stimulus study demonstrating the ordering of stimulus functions along a temporal continuum was that of Snapper, Kadden, Shimoff, & Schoenfeld (1975). These investigators, by additionally manipulating the intensity of CS (electric shock), made contact with "aversive" schedules. They showed, in rats, that when the intensity of a CS introduced at varying temporal locations in a fixed-interval food baseline was low (approximately 0.5 mA), response rate patterning pre and post CS replicated the findings of Farmer & Schoenfeld (1966 b). When CS intensity was high (approximately 1.6 mA), responding was suppressed, resembling punishment or avoidance, with the amount of suppression dependent upon the temporal separation of CS and US.

It has also been recognized from studies in the Pavlovian tradition that a CS has differing effects depending upon its temporal proximity to US. The intruded stimulus design is Pavlovian conditioning when presentations of CS and US are response-independent. These Pavlovian procedures can be generally classified as "forward" and "backward". The

forward case can be further subdivided into: (a) procedures where CS overlaps a subsequent US, termed as "simultaneous" when CS duration is less than 5 sec, and "delay" at longer durations, and (b) where CS does not overlap with US onset, termed "short-trace" conditioning when the CS-US interval (onset to onset) is less than 5 sec, and "long-trace" conditioning at longer CS-US intervals. The backward conditioning case is specified by the occurrence of CS immediately after a previous US, with the CS-US interval equal to the inter-trial interval (Pavlov, 1927; Terrace, 1973).

Responses mediated by the autonomic nervous system, typically the dependent variables of the Pavlovian procedures outlined above, are apparently under the control of temporal variables, and extensive experimental efforts have been directed in the search for the "optimal" CS-US interval, i.e., that interval which results in the largest magnitude of conditioned responses (CRs) during the CS-US interval (e.g., for salivation, Ellison, 1964; galvanic skin response [GSR], White & Schlosberg, 1952; nictitating membrane, Schneiderman, 1972; heart rate [HR], Black & Black, 1967; eyeblink, Ebel & Prokasy, 1963). Jones (1962), after a review of the literature on optimal CS-US interval (not including heart rate responses), concluded that "no single optimum exists". She proposed that the magnitude of CRs depends on the duration of training, and the latency of the response system measured.

Cardiovascular responses of the autonomic nervous system, heart rate in particular, are of special interest because of their long association with "emotional", or "motivational" states. Heart rate changes have been said to reflect "anxiety" (e.g., Church & Black, 1958;

Notterman, Schoenfeld, & Bersh, 1956), "fear" (Breznitz, 1967; Cannon, 1923; Deane & Zeaman, 1958), "arousal" (e.g., Dronsejko, 1972), "pain" (e.g., Lewinsohn, 1956), and "uncertainty" (Higgins, 1971; Miller & Caul, 1969). The magnitude of heart rate changes during Pavlovian conditioning procedures have long been thought to depend importantly upon the CS-US interval. However, apart from a consensus among most authors that heart rate can be conditioned at longer intervals than such short-latency, punctate autonomic responses as eyeblink and nictitating membrane (e.g., Black & Black, 1967; Black, Carlson, & Solomon, 1962; Hastings & Obrist, 1967; Schneiderman, 1972), there is little agreement as to what CS-US interval is optimal for the largest possible cardiac CR magnitudes. Typically, studies examining cardiac CR magnitude as a function of CS-US interval have compared two or three intervals in a rather restricted range of 0 sec to 30 sec, with one group of subjects per interval. Results from these studies follow.

No differences in the magnitudes of conditioned cardiac responses of dogs were found with comparisons of intervals of 5 sec and 20 sec (Church & Black, 1958), or with intervals ranging from 2.5 sec to 10 sec (Black et al., 1962). However, other investigators have found large differences among CS-US intervals for facilitation of cardiac CR magnitudes. For example, Hastings & Obrist (1967) compared, with human heart rate, CS-US intervals of .8, 7, and 13 sec and found CR magnitudes to increase with the CS-US interval. Also, Fitzgerald & Martin (1971) found the magnitude of cardiac CRs in rats to increase with the CS-US interval (0 sec to 6 sec). Occasionally, investigators have found optimal conditioning at some intermediate value of their CS-US interval range. For instance, VanDercar & Schneiderman (1967) found an interval

of 2.25 sec optimal for rabbits when the CS-US interval varied between .25 sec and 6.75 sec. Black & Black (1967) with rats, and Lockhart & Steinbrecher (1970) with rabbits, found 5 sec optimal when the CS-US intervals in both studies ranged between .5 sec and 10 sec.

Breznitz (1967) examined longer CS-US intervals than the above in a variant of Pavlovian conditioning. Human subjects were told to expect shock at the termination of either 3, 6, or 12 min (one group of subjects per interval). They were provided with clocks, and HR measures were taken in the interval between the threat and time of expected shock (no subjects were shocked). Breznitz found that tha largest HR magnitudes occurred at the longest (12 min) interval. Vardaris (1971) examined acquisition and extinction of HR CRs in a procedure which alternated long CS-US interval trials (85-90 sec) with short ones (6 sec). He found that CR magnitudes during acquisition and extinction were reduced in those sessions employing short and long intervals when compared with sessions employing a constant, short CS-US interval.

All in all, the findings relating optimal cardiac CR magnitudes to the CS-US interval are difficult to interpret, possibly due to the differing ranges on intervals and step sizes employed. Moreover,this is only one of the many research areas in cardiac conditioning where generalizations seem difficult. In part, conflicting findings result when conventions of measurement, transformation, and graphic presentation of data differ so widely among laboratories, sometimes due to separate aspects of the cardiac CR under study. For example, when investigators are interested primarily in the cardiac CR magnitude they employ difference scores as their dependent measures, defined as the

difference between peak rate during the CS-US interval (or average rate during the entire CS-US interval) and pre-CS rate. Investigators who look at changes in the temporal patterning of heart rate during the CS-US interval, i.e., the "form" of the cardiac CR, sometimes record successive interbeat intervals (e.g., Newton & Perez-Cruet, 1967; Wilson, 1969), or, count beats within a specified time interval (e.g., Lynch, 1973; Miller & Caul, 1969). Often, interbeat intervals (IBIs) are recorded, and then converted to a rate measure such as beats per minute (BPM) (e.g., Geer, 1964; Zeaman, Deane, & Wegner, 1954). It should be mentioned, however, that the transformation of IBI to BPM is non-linear and changes the mean, variance, and skewness of the raw data frequency distribution (Jennings, Stringfellow, & Graham, 1974; Khachaturian, Kerr, Kruger, & Schachter, 1972).

Apart from differences in collecting and transforming the data, investigators employ various "correction" procedures on successive HR or IBI values during the CS-US interval. For instance, in the HR discrimination designs of some studies, values from the CS- function are subtracted from values of the CS+ function (e.g., Lockhart & Steinbrecher, 1970). In addition, the pre-conditioned response to CS is sometimes subtracted from the subsequent conditioned response function (e.g., Deane, 1965). There have also been procedures where, within each trial, the pre-CS mean rate or IBI is subtracted from successive rate or IBI values in the CS-US interval, thereby producing a "difference curve" (Hastings & Obrist, 1967); occasionally, pre-CS values are divided into successive values in the CS-US interval (Schneiderman, Smith, Smith, & Gormezano, 1966).

The above diversity in correction procedures has partly contributed to the diversity of cardiac CR forms in the literature. Cardiac CRs also take on differing forms depending upon, (a) which trial in a session is examined (Black & Black, 1967; Jaworska & Soltysik, 1962), (b) which subject in an experiment is examined (Cohen & Durkovic, 1966; Newton & Perez-Cruet, 1967), or, (c) whether early or late stages in an experiment are examined (Lynch, 1973; McDonald, Stern, & Hahn, 1963). Moreover, several independent variables have been seen to affect CR form. For example, the resulting form can depend upon whether a trace or delay (Black et al., 1962; Fitzgerald & Martin, 1971) or backward conditioning (Fitzgerald & Walloch, 1966) paradigm is employed, upon the mode or intensity of CS and US (Gantt, 1960; Lynch & McCarthy, 1969), upon the species of subjects (Cohen & Obrist, 1975), upon whether the organism subsequently makes an instrumental response (Schoenfeld, Matos, & Snapper, 1967), upon the pre-CS baseline heart rate (Ramsay, 1970), and, upon the CS-US interval (Dronsejko, 1972; Hastings & Obrist, 1967). Thus, according to the results of their individual experiments, investigators have described the cardiac CR form as (a) a monotonic acceleration of heart rate from CS onset to the end of the CS-US interval (e.g., Cohen & Pitts, 1968; Obrist & Webb, 1967), (b) as a monotonic deceleration over the course of the CS-US interval (e.g., Hein, 1969; McAllister, Farber, & Taylor, 1954; VanDercar & Schneiderman, 1967), or, (c) as a phasic response with distinguishable acceleratory and deceleratory components (Geer, 1964; Wilson, 1969). Most frequently, an acceleratory phase has been observed to precede a deceleratory phase in the CS-US interval, although, occasionally, the deceleratory phase precedes

(Fitzgerald & Martin, 1970; Newton & Perez-Cruet, 1967). Finally, polyphasic responses, i.e., of more than one cycle of acceleration and deceleration, have been noted (Bowers, 1971; Gatchel & Lang, 1974).

Apparently dismayed by the disparity of findings in cardiac conditioning, Harris & Brady (1974), after a review of the literature, were led to remark that for both appetitive and aversive conditioning, "all possible outcomes can be observed under some conditions". Further, they state that few generalizations regarding the conditioning of autonomic responses are justified, despite the large number of research reports devoted to this topic.

This view seems overly pessimistic, as some generalizations are possible. At least some of the variability in cardiac response form has been seen to result from differing data treatments, and, in addition, can be explained by species differences. For example, in primates the cardiac rate CR has almost always been reported as biphasic, i.e., an acceleration followed by a deceleration in the CS-US interval (e.g., for the rhesus, Nathan & Smith, 1968; Ramsay, 1970; Snapper, Pomerleau, & Schoenfeld, 1969; for humans, Geer, 1964; Wilson, 1969; Zeaman, Deane, & Wegner, 1954). Moreover, other species which have demonstrated monotonic acceleration or deceleration at CS-US intervals less than 4 sec sometimes revealed a biphasic CR form in studies which examined longer intervals (e.g., in dogs, Brown & Peters, 1967; in rabbits, Deane, 1965, Kosupkin & Olmsted, 1943; in rats, Schoenfeld, Matos, & Snapper, 1967).

A study by Dronsejko (1972) helps to clarify the role of CS-US interval in the reporting of diverse CR forms in the literature. Dronsejko, in a rare within-subjects manipulation of CS-US interval, examined

the cardiac CRs of human subjects between a warning signal and shock. She found that by increasing the CS-US interval in steps of.5 sec every two trials, an initially monotonic rate acceleration at 5 sec CS-US developed into a biphasic (acceleration followed by deceleration) rate function at CS-US intervals from 8 sec to 12 sec. In addition, she found that the acceleratory portion of the biphasic rate response was "time-locked", with the peak of acceleration occurring consistently at 5 sec into the interval, thereby leaving the rate of deceleration as the changing component of the biphasic waveform at CS-US intervals longer than 8 sec. Dronsejko's experiment demonstrates that the biphasic cardiac response in human subjects is truncated by US onset at CS-US intervals of 5 sec or less. Brown & Peters (1967) also reported truncated biphasic CRs of dogs at intervals less than 15 sec, and found consistent biphasic responses peaking at 15 sec for a CS-US interval of 29 sec.

At variance with Dronsejko and Brown & Peters, who emphasize a fixed latency of maximum heart rate at longer CS-US intervals, are those studies employing comparable or longer CS-US intervals than those used by the above investigators (with the same species) which show that peak heart rate occurs closer to US as the CS-US interval increases (e.g., for humans, Breznitz, 1967; Hastings & Obrist, 1967; in dogs, Church & Black, 1958), a phenomenon which Pavlov termed "inhibition of delay". Inhibition of delay has been frequently observed in other responses of the autonomic nervous system (e.g., for salivation, Ellison, 1964; for nictitating membrane, Schneiderman, 1966).

In addition to major sources of variability in cardiac CR form being attributable to methodology, species variables, or the minimum

CS-US interval employed, movement artifacts have also been seen to affect CR form. For example, Black et al. (1962) noted the relative stability of the CR forms in curarized dogs when compared with undrugged dogs. Also, Randall & Smith (1974) noted, for rhesus monkey CRs, that in trials when activity was present during a one minute CS, monotonic heart rate accelerations were observed. In trials where activity was absent, the CRs were biphasic.

The heart rate response of the rhesus monkey has been reported to be "very complex and very sensitive to changes in experimental procedure" (Miller & Caul, 1969). There is a report from a group of investigators, however, of the relative stability of the biphasic CR form of the rhesus monkey across a variety of aversive conditioning procedures (shock as the US) and three durations of CS (Snapper et al., 1969). Throughout, (a) Pavlovian delay conditioning sessions, (b) cued "Sidman" avoidance, (c) cued escape, and, (d) CS-US pairings superimposed on an avoidance baseline (the conditioned emotional response or "CER" procedure) at CS durations of 12, 30, and 60 sec, the restrained rhesus subjects continued to exhibit cardiac CR forms of initial acceleration followed by deceleration.

The present study proposes to examine stimulus control of heart rate in the rhesus by use of a response-independent intruded stimulus design. By systematically moving the location of CS from close temporal proximity to a subsequent US to successively earlier portions of a periodic inter-US interval, the disparate procedures outlined thus far, such as delay, trace, warning, safety, forward, and backward procedures, with their accompanying behavioral effects, may be seen to

fall at successive points along a temporal continuum. Intrusion of CS close to a subsequent US generates such designs as warning signal, delay, and trace conditioning. As CS moves further back in the inter-US interval, long-trace and safety-signal procedures result. Finally, when CS occurs immediately after the preceding US, backward conditioning results, concurrent with the ideal case for safety-signal training by CS predicting the longest shock-free interval (cf. Moscovitch & LoLordo, 1968).

A comparison of delay and trace conditioning is afforded in the beginning of the study: the delay case where CS offset is contiguous with US onset merges into the trace case when CS moves back in the inter-US interval. With respect to CR magnitude, investigators comparing delay and trace (with a group design) have found them to be comparable at shorter CS-US intervals, but have superior conditioning with delay at longer intervals (for HR, Black et al., 1962; Fitzgerald & Martin, 1971; Meredith & Schneiderman, 1967; for salivation, Ellison, 1964; for nictitating membrane, Schneiderman, 1966). Pavlov (1927) also found long-trace conditioning to be inferior to long delay, both in ease of acquisition, and susceptibiltiy to extraneous stimuli. He noted, however, that when dogs were begun at simultaneous conditioning and then shifted to progressively longer trace intervals, long-trace conditioning was facilitated. The present procedure was similar to Pavlov's and may result in stable long-trace cardiac CRs by having begun at a shorter interval delay case.

Apart from a comparison of trace and delay for cardiac CR magnitude, the present design also allows examination of the latency characteristics of the cardiac CR as the CS-US interval is lengthened. Inhibition of

delay, as defined earlier, has been attributed by Pavlov to extinction of the early segments of the CR from lack of reinforcement. He states, "this delay [of the CR] is proportional to the length of the interval between the two stimuli and may even extend to several minutes" (p. 88).

Ebel & Prokasy (1963), moreover, stated that when the delayed CR (in their case, eyeblink) overlaps with the US, reinforcement is maximized. The CR-US overlap is "instrumentally shaped" because the occurrence of the CR mitigates the effects of the US, as when an eyelid closure mitigates the effects of an airpuff. As the CS-US interval is lengthened, subjects have increasing difficulty in overlapping their CR with US, reflected in an increase in the variance of response latencies. It is not immediately clear, in the present context, how heart rate changes might mitigate the effects of shock. Schneiderman (1972) explained that the preparatory HR CRs might allow the organism to "cope" with the forthcoming shock. He cites evidence from investigators who show that subjects choose signalled over unsignalled shock (e.g., Perkins, Seyman, Lewis, & Spencer, 1966). Also, shocks that are preceded by a CS have been shown to result in smaller unconditioned responses (URs) (e.g., for GSR, Lykken, 1962). The present study will not only examine CR latencies and their variability as the CS-US interval increases, but will, in an additional procedure of unsignalled, periodic presentations of US alone, examine the magnitude of URs to signalled and unsignalled shock presentations.

Within the context of warning and safety signals and their effect on cardiac CR form, it is also not clear how one might interpret obtained heart rate accelerations or decelerations as "warning" or "safety" effects since directionality of heart rate changes to a CS has not been reliably

linked to specific emotional states of organisms such as "fear" or "relief" (Martin, 1961). As noted earlier, the form of the CR depends importantly upon a combination of several factors which include the species employed, and the CS-US interval. It has been suggested, for other response systems, that a reduction in "excitatory" conditioning be a measure of the inhibitory or safety properties of a CS (Hammond, 1968; Rescorla, 1969 a,b; Rescorla & Solomon, 1967). Thus, Moscovitch & LoLordo (1968) defined the effects of a fear-arousing stimulus as an increase in "Sidman" avoidance shuttle-box performance as a response to a safety-stimulus. They demonstrated that if a CS closely followed US (the traditional backward conditioning procedure) and, moreover, signalled a long shock-free period, avoidance rates declined during and following CS.

A study possibly demonstrating safety-signal effects on heart rate of the rhesus by Kadden, Washton, McMillan, & Schoenfeld (1975) showed that intruding a stimulus which indicated a shock omission trial during the progress of a conditioned response, shifted HR acceleration to deceleration, or slowed acceleration of the CR. Another method of demonstrating safety-signal effects on heart rate might be at the backward conditioning phase of the present experiment, i.e., when CS occurs immediately after a previous US. Since the CS coincides temporally with the UR to shock, and is also followed by a long shock-free interval, attenuation of the UR magnitude may be found (cf. Rescorla, 1969 a,b).

It will be recalled that the present design incorporates sessions where US is signalled and sessions where US is unsignalled, with the same inter-US interval in both cases. Many investigators of Pavlovian con-

ditioning have employed irregularly spaced trials (CS-US pairings) to avoid attributing obtained conditioned responses to anticipation of regularly timed US presenations, rather than to effects of their independent variables of interest. Successful temporal conditioning with the periodic delivery of shock has been demonstrated with GSR as the measured response (reported in Hull, 1943; Lockhart, 1966 b), and, with the periodic delivery of both CS and US for heart rate (Dykman & Gantt, 1959; Gantt, Gakenheimer, & Stunkard, 1951). Dmitriev & Kochigina (1959), and other investigators (Dyman & Gantt, 1959; Gantt et al., 1951) have included in the definition of temporal conditioning the case where CS-US pairings are repeated at regular intervals. Thus, in the present study, temporal conditioning under both signalled and unsignalled procedures can be examined. However, some question has been raised concerning temporal conditioning, leading Graham (1973) to conclude that there is ambiguity in the available evidence for such conditioning. Any positive evidence confirming temporal conditioning would have to take one or both of these forms: anticipatory responding just prior to stimulus presentation, and response occurrence at the time US would have been delivered on omission trials. Both methods have been employed in the literature, but with equivocal results. Dmitriev & Kochigina (1959) provide a lengthy review of the Russian work in temporal conditioning in a variety of organisms and response systems. They find that, in the course of "time reflex" acquisition, both forms of evidence are provided. The beginning phases of conditioning are characterized by generalized responding throughout the inter-US interval. In later phases, responses come at increasing delay in the interval until, after much training, responses come at the time of stimulus occurrence in trials

where the US is omitted. When both CS and US are presented, temporal conditioning is evidenced by pre-CS responding.

Many investigators of heart rate conditioning who have employed regularly timed presentations of both CS and US (e.g., Newton & Perez-Cruet, 1967; Schoenfeld, Matos, & Snapper, 1967; VanDercar & Schneiderman, 1967) or US alone (e.g., Schneiderman, VanDercar, Yehle, Manning, Golden, & Schneiderman, 1969)might have found evidence for temporal conditioning had they examined patterning of heart rate during the entire inter-trial interval (and especially the pre-CS interval). It is interesting to note that none of the studies which employed periodic presentations of US alone and examined evidence for cardiac temporal conditioning found such evidence (Katkin & Nelson, 1973; Snapper, Schoenfeld, Ferraro, & Locke, 1965). The only experiments demonstrating cardiac temporal conditioning have periodically presented CS and US, as referenced above. This suggests, perhaps, that temporal conditioning is facilitated with the addition of a CS, also discussed by Dmitriev & Kochigina (1959). They cite a study in Pavlov's laboratory where unstable temporal conditioning of salivation with regularly timed presentations of meat powder was improved with the addition of a tone CS.

Pharmacological manipulations

It has long been known that the autonomic nervous system (ANS) is the major source of control over heart rate (Rushmer, 1970); however,

the relative contributions of the sympathetic and parasympathetic branches to heart rate changes have remained unresolved. Cannon (1923) attributed increases in heart rate which accompanied the "major emotions" such as pain, fear, rage, and great excitement to the sympathetic branch of the ANS. The parasympathetic branch was relegated to the function of "building up reserves". Specifically, the vagus nerve was said by Cannon to decrease heart rate primarily to provide rest periods for the heart. Since Cannon's time investigators have sought, through surgical and pharmacological interventions, to determine which of the two branches of the ANS is the major contributor to heart rate changes during such experimental conditions as exercise (e.g., Robinson, Epstein, Beiser, & Braunwald, 1966), operant avoidance (Wynne & Solomon, 1955), aversive Pavlovian conditioning (Dykman & Gantt, 1959), "startle" reactions (Bond, 1943), and aversive reaction-time tasks (Obrist, Lawler, Howard, Smithson, Martin, & Manning, 1974). The literature with respect to autonomic innervations of the Pavlovian cardiac CR in particular, is large and equivocal. The observation of deceleratory CRs in aversive Pavlovian paradigms played havoc with the notion of the sympathetic system initiating HR acceleration as an "emergency" response (e.g., Hastings & Obrist, 1967). Especially vexing were observations that acceleratory cardiac CRs were unaffected by sympathetic blockade (e.g., Obrist & Webb, 1967). These findings reflect the fact that HR increases or decreases can be independently effected by either branch of the ANS (e.g., Robinson et al., 1966). For example, cardiac acceleration can occur either through an increase in sympathetic activity, or, through a decrease in vagal restraint. The vagus nerve exerts a controlling and restraining influence on resting heart rate in mammals

(Johansen & Reite, 1964); thus, when vagal firing is blocked or decreased, heart rate increases (Rushmer, 1958).

Apart from neural regulation of heart rate, there are also hormonal contributions (Cohen, 1974). The adrenal medulla secretes adrenalin and noradrenalin (collectively termed catecholamines). These hormones are documented to cause HR increases when the organism is under various forms of stress (Bond, 1943; Cannon, 1923; Randall, Kaye, Randall, & Brady, 1973).

Cohen (1974) has offered the view that relative contributions of the sympathetic and parasympathetic systems to the cardiac CR depend upon the particular form of the cardiac CR under study. His method of organizing a literature review by accelerative, decelerative, or biphasic CR forms will be followed here; first, however, the experimental procedures employed in these studies will be outlined below.

Typically, subjects undergo Pavlovian pairings with shock as the US. After stable HR CRs are acquired, either or both branches of the ANS are blocked (surgically and/or pharmacologically), and subsequent changes in the cardiac CR are assessed.

Surgical procedures to eliminate the parasympathetic system involve severing the vagus nerve whereby the sympathetic nervous system is surgically eliminated by removal of the stellate ganglia and part of the sympathetic chain. Pharmacological interventions are more common, perhaps due to ease of administration. This procedure employs blocking agents which antagonize neurotransmitter substances at receptor sites of sympathetic or parasympathetic nerve endings in the heart. Based on the selective effects of these blocking agents, autonomic innervation of the cardiovascular system has been pharmacologically clas-

sified as cholinergic, alpha-adrenergic, or beta-adrenergic . Cholinergic blocking agents, such as atropine and scopolamine, antagonize acetylcholine at receptor sites of parasympathetic fibers in heart muscle, among other sites. Adrenergic blocking agents such as phentolamine and propranolol, block, respectively, sympathetic innervation of the arterioles ("alpha" receptors),and sympathetic nerve endings in the heart ("beta" receptors).

Cohen (1974) has warned that in the use of these surgical and pharmacological procedures, eliminating one branch of the ANS may change the contribution of the other branch to the regulation of heart rate. He suggests that, ideally, studies should eliminate each nerve supply to assess the effects on the other. Although most studies conducted in this area have blocked only one branch of the ANS, they have also mostly implicated the action of both branches in the intact cardiac CR. Theories as to the major contributor are, however, divided. A review follows.

Cardiac CRs of monotonic acceleration are often observed in dogs, pigeons, and sometimes cats. Those studies which present evidence for parasympathetic control of the acceleratory CR include Obrist & Webb (1967) and Obrist, Sutterer, & Howard (1972) who showed, in dogs, that beta-adrenergic (sympathetic) blockade by propranolol resulted in either small, or no response decrements during Pavlovian trials. They concluded that the CR must have been mostly of vagal origin. Dykman & Gantt (1959) also concluded that the greater contributor to an acceleratory CR in dogs was parasympathetic after observing a greatly diminished response with atropine-block. Because the response was not completely eliminated, however, they hypothesized some sympathetic input.

Evidence for primarily sympathetic mediation of acceleratory CRs

can be found in a study conducted by Bond (1943). He concluded almost total sympathetic control of the HR increases of dogs and cats to the sound of a pistol shot, because acceleration still occurred when the vagus nerves were cut and the adrenals removed. Bergamaschi & Longoni (1973), in an unusual procedure of injecting propranolol after the peak of an acceleratory CR in dogs during a 5 min CS, demonstrated a lowering of heart rate 3 min after injection, toward the end of CS. They therefore attributed the CR to activation of the sympathetic nervous system.

Some evidence suggests that the length of training may influence the amount of sympathetic involvement in the acceleratory cardiac CR, with sympathetic effects more evident early in training (Cohen & Pitts, 1968; Obrist, Howard, Lawler, Sutterer, Smithson, & Martin, 1972). In this regard, Cohen & Pitts demonstrated that beta-adrenergic block by propranolol of an acceleratory CR in pigeons was more effective than vagotomy in reducing response magnitude early in training. The vagal contribution increased as training progressed, as seen in larger response magnitudes in later trials, even when the sympathetics were blocked.

There appears to be greater agreement among studies examining deceleratory CRs. Most conclude that the deceleratory response is vagally mediated after observations that atropine block or vagotomy abolished the reponse (for the cat, Flynn, 1960; Hein, 1969; for the rat, Fitzgerald, Martin, & O'Brien, 1973; for the rabbit, Downs, Cardozo, Schneiderman, Yehle, VanDercar, & Zwilling, 1972; Fredericks, Moore, Metcalf, Schwaber, & Schneiderman, 1974; Sampson, Francis, & Schneiderman, 1974; Schneiderman, VanDercar, Yehle, Manning, Golden, & Schneiderman, 1969). An exception is a study conducted by Kazis, Milligan, & Powell (1973). They

found that the magnitude of the decelerative rabbit CR was decreased by administration of either propranolol or atropine, but only eliminated completely by combined injection. These authors, therefore, suggest that the deceleratory CR in intact rabbits results from combined parasympathetic discharge and inhibition of sympathetic tone.

There have been relatively few studies conducted on the biphasic CR in classical conditioning paradigms. In two experiments conducted with dogs (Katcher, Solomon, Turner, LoLordo, Overmier, & Rescorla,1969; Obrist, Howard, Lawler, Sutterer, Smithson, & Martin, 1972) the authors have described the CR as mainly acceleratory but with a slight fall in rate at the end of CS; these CRs are here considered as biphasic. Both studies employed sympathetic blockade, with Katcher et al. having used sympathectomy, and Obrist et al. having used propranolol. In both cases the acceleratory and deceleratory portions of the CRs were reduced after sympathetic block, although the conclusions reached by the authors are different. Katcher et al. concluded major contributions from the sympathetic system, while Obrist et al. concluded mainly vagal mediation. It seems probable that both the vagus and the sympathetics contributed to both portions of the response, in keeping with physiologists' emphasis of "reciprocal innervation" of heart rate by both sympathetic and parasympathetic branches (e.g., Rushmer, 1970).

Another study demonstrating this reciprocal innervation, although only reported for the acceleratory portion of a biphasic response in rhesus monkeys (Klose, Augenstein, Schneiderman, Manas, Abrams, & Bloom, 1975),found that neither atropine methlynitrate (a form of atropine which does not affect the central nervous system) acting alone, nor

propranolol alone, eliminated the initial acceleratory portion, although their combined administration did. Their data were interpreted to suggest greater sympathetic involvement in that propranolol diminished the response more than did atropine, although this finding was not statistically significant (their Table 4).

An experiment by Kadden, Schoenfeld, & Bindler (1975) stands alone in having assessed both the acceleratory and deceleratory components of a biphasic CR with sympathetic, parasympathetic, and combined blockade. Employing rhesus monkey subjects in a classical conditioning paradigm, they obtained results suggesting that a) the initial acceleratory portion of the biphasic CR is largely under sympathetic control, as evidenced by the selective reduction of acceleration after propranolol injection, and b) the subsequent deceleratory portion is largely under parasympathetic control, as evidenced by reduction after atropine. These observations seem to be confirmed by the fact that combined administration of atropine and propranolol completely eliminated the biphasic CR.

Obrist and collaborators (Obrist, Lawler, Howard, Smithson, Martin, & Manning, 1974; Obrist, Wood, & Perez-Reyes, 1965), working with biphasic or multi-phasic human cardiac CRs in classical conditioning and aversive reaction-time tasks, have suggested that sympathetic influences on the heart are minimal unless evoked by severe stress (Obrist et al., 1965) and, moreover, in those paradigms where subjects can avoid impending shock (Obrist et al., 1974).

Some overall conclusions may be stated. Those studies examining CRs with an acceleratory component, whether the entire response form is monotonic or biphasic, find contributions from both branches of the ANS, although it seems probable that the sympathetic system is the larger con-

tributor (e.g., Bond, 1943; Kadden et al., 1975; Klose et al., 1975). Those studies examining CRs with a deceleratory component, whether monotonic or biphasic, seem to point mostly to an increase in vagal restraint on the heart as the primary source of heart rate deceleration. Again, however, both branches can be seen to contribute (Kazis, Milligan, & Powell, 1973). Perhaps the most striking evidence for both vagal and sympathetic contributions to the form of the CR, whether the CR is acceleratory, deceleratory, or biphasic, come from studies showing that either vagal or sympathetic blockade does not abolish the response, but combined blockade does (Cohen & Pitts, 1968; Kadden et al., 1975; Kazis et al., 1973; Klose et al., 1975).

Since there have been so few studies conducted with the classically conditioned biphasic CR where both acceleratory and deceleratory components are assessed after blockade of both sympathetic and parasympathetic branches of the ANS, the present study proposes to add information in this area. Additionally, a ganglionic blocking agent will be used to pharmacologically denervate the heart. Most studies examining the fate of the CR after cardiac denervation employ combined administration of atropine and propranolol. It is difficult, however, to determine the titration of dosages of one blocking agent against the other to achieve equal effectiveness of both. By the use of a single blocking agent such as chlorisondamine, the questions inherent in the titration of dosages are alleviated. A ganglionic blocking agent effectively denervates the heart by blocking acetylcholine transmission at the level of the ganglia. Occasionally, a ganglionic block is used to estimate "intrinsic rate", i.e., the resting rate of the denervated heart (e.g., Dews & Herd, 1974). Also, any contribution of cathecholamines to cardiac acceleration

can be assessed, since complete ganglionic block eliminates both branches of the ANS, allowing any observed HR changes during CS to be attributed to hormonal effects. It has been shown, for example, that cats startled by a pistol shot after complete cardiac denervation exhibited a slow HR acceleration 14 sec after the shot (Bond, 1943). In addition, Randall et al.(1973) observed HR acceleration in surgically denervated rhesus monkeys 20 sec after the onset of CSs preceding food or shock. Both Bond, and Randall et al. attributed the HR accelerations to the secretion of catecholamines.

Through the behavioral manipulation of moving CS temporal location in a regular inter-US interval, and pharmacological manipulations of selective and total autonomic blockade, the sources of control over conditioned and unconditioned cardiac changes may thus be illuminated.

Method

Subjects

Six experimentally naive, male rhesus monkeys (Macaca mulatta) served as subjects. Each animal weighed approximately 5 kg at the start of the experiment. Their diet consisted of ten primate biscuits (Wayne Monkey Diet) totalling approximately 160 gms, with 750 ml of water, distributed over three feedings daily. Every other day, 1/4 apple was added. Periodic tuberculin testing was carried out prior to the start of the experiment. In other respects, all animals were found to be healthy from visual inspection.

Apparatus

Subjects were confined to primate restraint chairs (BRS-Foringer Rhesus Test Chairs [No. PC-002]) with thoracic plates and attached cummerbund for added restraint, for the duration of the experiment. During each experimental session the restraint chairs were wheeled into individual wooden experimental chambers (No. PCH-002) lined with acoustic tile. Each chamber was equipped with an exhaust fan, a 7.5 watt blue overhead lamp, and a speaker on the inside rear wall driven by a Grason Stadler white noise generator (No. 901B) set at 10dB below 1.5V, which provided masking noise during sessions.

Visual stimuli consisted of two white indicator lights (Dialco, 24V, No. 327 bulbs) mounted on a metal minibox and attached to the restraint chair during experimental sessions. The lights were thus positioned approximately 20 cm from the subject's face at eye level. The two lights, arranged vertically 2 cm apart, center-to-center, served as the conditioned stimulus (CS); four other lights on the stimulus display panel were never used. CS duration was 10 sec throughout. The blue

overhead lamp was lit from the onset, and remained lit for the duration of the experimental session.

Electric shock was delivered through tail electrodes, each consisting of a 4 mm by 2.5 mm piece of brass shim stock (.004 in. thickness) riveted onto a strip of Velcro and connected to a rubber-jacketed wire. Five minutes before the start of each session the animal's tail was tied to the structure of the chair and two electrodes with electrode jelly were strapped to a shaved portion of the tail to insure good contact. The electrode wires, in turn, were attached to a cable in the chamber through which shock was delivered. Constant current AC shock was obtained by passing the output of a 650 V transformer through a set of matched capacitors (each .068 mF), and served as the unconditioned stimulus. Shock intensity was 9 $\pm$ 0.5 mA, as measured prior to each session by an ammeter in series with the shock source. Switching circuitry for the shockers, suggested by Ramsay, Knapp, & Zeiss (1970), eliminated large surges of current at shock onset and offset by a method which shorted the animal through normally closed contacts of a relay until shock delivery; the relay contacts were then opened, leaving the animal as the only path for current flow in the shock circuit. Switching transients were further reduced by a synchronous switch which allowed shock onset and offset to occur only at zero volts on the AC voltage cycle. Shock duration was 300 msec, $\pm$ 4 msec.

Each subject's EKG was monitored through two subcutaneous stainless steel electrodes (Siemens Aktiengesellschaft, Erlangen, Germany, No. 211140) the placement of which maximized the relative size of the R-wave of the EKG, and were implanted with the animal tranquilized by Vetalar (Parke-Davis). The animal's chest was shaved prior to implantation. A typical placement consisted of one electrode inserted subcutaneously at the sternum, with the other placed laterally, at approximately

15 cm to the left. The electrodes were attached by wires to a connector (Siemens , No. 2287985); the animals were prevented from pulling out the wires by being permanently dressed in a soft leather jacket which covered the electrodes and connector. During each session the connector was attached to a cable in the chamber; the EKG was amplified and displayed by a Beckman Type R Dynograph, and R-waves of the QRS complex were digitized by a Schmitt trigger circuit made from digital logic modules. All data were recorded, and all stimuli delivered, by a PDP-8 computer using a notation system and program devised by Snapper & Kadden (1973).

Procedure

All animals excepting subject E-18 were placed in restraint chairs for one month prior to the start of the experiment for adaptation. During this time they were removed from the chair once for implantation of EKG electrodes. For each day during the week preceding the first experimental session, each animal's tail electrodes were attached, and he was placed in the experimental chamber for one hour with only the overhead lamp and masking noise on. E-18's adaptation procedure differed from the above in that he underwent chair adaptation for only one week, concurrent with chamber adaptation.

The experimental sessions were conducted daily, excepting when a subject's EKG electrodes were re-implanted as a result of a deteriorating EKG signal. In order for effects of the tranquilizing agents used during re-implantation to diminish, sessions were not held for the following 24 hours. Also, sessions were not held for 48 hours after administration of the experimental drugs in the latter stages of the experiment.

The daily experimental routine was identical with the procedures described above for chamber adaptation, except that the experimental stimuli, CS and US, were delivered to the animal. Sessions began with a ten-minute adaptation in the chamber with masking noise and overhead lamp present, followed by CS onset.

Data Recording

Of twenty daily conditioning trials (CS-US pairings), data were collected from ten (Nos. 3,4,7,8,11,12,15,16,19, and 20), in recording groups of two consecutive trials. Groupings larger than two trials could not be done because of limitations of the computer's memory. Thus, for every two consecutive trials recorded, the following two were unrecorded, during which time data from the previous two trials were punched on paper tape. For each recorded trial, no data were take during the US, and not for 1 sec following the US because of noise in the cardiac signal during, and immediately after shock. One second after shock offset, the first R-wave of the QRS complex started the computer's time-phased recording in .01 sec units, and this recording continued until either two R-waves following the first had occurred, or, until a 2 sec time period had elapsed. Every alternate R-wave ended the counting of .01 sec time pulses and began the counting in a new recording area in memory. Thus, each area contained interbeat time, in 10 msec units, of two successive EKG cycles, sometimes referred to as the "double interbeat time" or "double R-R interval" (e.g., Wilson, 1969). One second after shock offset, a clock was started which, when 2 sec had timed out, stopped the counting of .01 sec units. A new count was begun in another counter upon detection of another R-wave. As a result of interrupting the count every 2 sec, one recording counter per 2 sec period had a value short of the full

duration between two successive R-waves; these counters were always eliminated from data analysis.

Trials had a duration of 231 sec. After a trial had ended, if the next trial was to be recorded, data recording was re-initiated at the detection of the first R-wave 1 sec after shock offset. If data were not to be collected from the following two trials, all scheduled stimuli were delivered to the subject, but recording was not re-initiated until the next two shocks had been administered, 1 sec had elapsed after the second shock delivery, and the first R-wave of the new trial was detected.

Figure 1 details the data recording scheme for a sample of four trials at an arbitrary CS-US interval. The 1.3 sec at the UCS arrow between trials 7 and 8 indicates the duration of interrupted data recording between two recorded trials: .3 sec during shock, and 1 sec following shock offset.

The experimental design employed eight temporal locations of CS with respect to US. Cycles of fixed duration (231 sec onset to onset) ran concurrently for CS and for US. The phase relationship of the two cycles determined CS-US intervals, as measured from CS onset to onset of the following US, of 10, 20, 30, 50, 80, 120, 170, and 230 sec. This order was the same for all six animals.

Each CS-US interval was used for six daily sessions, each session containing twenty CS-US pairings ("trials"); only trials from the final two days (days 5 and 6) of conditioning at each CS-US interval were analyzed. After each CS-US interval had been used for its six sessions, two successive sessions were held with US delivered alone at the 231 sec inter-US interval: 20 shocks were presented per session, and the data of both sessions were analyzed.

Figure 1. Data recording scheme for a sample of four trials. Asterisks at trials 7 and 8 indicate recording of double interbeat intervals in successive 2 sec periods for 230 sec. Note that no data recording occurred in the following two trials (9 and 10).

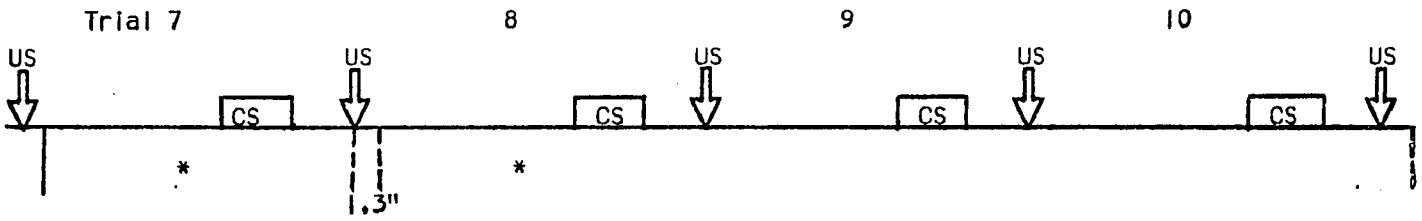


Fig. 1

The 10 sec and 230 sec CS-US intervals need further clarification. At the 10 sec CS-US interval, CS offset was coincident with US onset. Sessions at the 230 sec CS-US interval began with CS delivery, followed after 221 sec by US, followed by CS again after 1.3 sec, etc.

After two sessions with US alone were held following the 230 sec CS-US interval, three CS-US intervals were re-determined: 50, 20, and 10 sec, in that order for all six subjects.

Drugs were administered to each subject not only on the 6th day of conditioning at each re-determined CS-US interval, but two additional days (7 and 8) were also held, specified further below: the drugs consisted of chlorisondamine (Ecolid, Ciba-Geigy), propranolol hydrochloride (Inderal, Ayerst), and atropine sulfate (Atropine, Wyeth). The drugs were injected i.v. in the animal's leg. All dosages were 1 mg/kg, a strength found to produce marked effects relative to lower dosages (Randall & Smith, 1974). Interpolated sessions employing US alone were not administered until all drug sessions at a particular re-determined interval were completed: two sessions on two consecutive days were then held with US alone, followed by six days of conditioning at the next CS-US interval.

The method of drug administration at each re-determined interval follows: Immediately following the final twenty trials (day 6) of each interval, the animal was removed from the experimental chamber and injected with chlorisondamine. After replacement in the chamber, followed by a five-minute waiting period, eight further conditioning trials were given. On day 7 of each re-determined interval, only eight pre-drug conditioning trials were given, followed by an injection of propranolol. After a five-minute waiting period, eight conditioning trials were

delivered, followed by an injection of atropine, followed by eight conditioning trials after another waiting period. Day 8 consisted of the same procedure as day 7, except that atropine was administered first. Note that for each block of eight conditioning trials, four were recorded.

Table I lists the number of conditioning trials delivered to each subject at each stage of the experiment. In cases of discrepant column entries, they indicate the actual number of trials administered to that subject as a result of equipment malfunction. Entries for re-determined intervals (Roman II) are subdivided into: (a) number of conditioning trials with drugs, (b) conditioning trials without drugs, and, (c) trials with US alone.

Table I

Number of Conditioning Trials at Each Experimental Stage

	CS-US Interval (Sec.)																	
	10		20		30		50		80		120		170		230		50 II			20 II			10 II		
Subject	CS US	US only	CS US	US only	CS US	US only	CS US	US only	CS US	US only	CS US	US only	CS US	US only	CS US	US only	CS US	CS US(D)[a]	US only	CS US	CS US(D)	US only	CS US	CS US(D)	US only
E-28	120	40	120	40	120	40	120	40	100	40	120	40	120	40	93	40	160	40	40	136	40	40	136	40	40
E-34	120	37	120	40	120	40	120	40	100	40	120	40	120	40	120	40	160	40	40	136	40	40	136	40	40
E-40	120	40	120	40	120	40	120	40	120	40	120	40	120	40	120	40	160	32	40	136	40	40	136	40	40
E-38	120	40	120	40	120	40	120	40	120	40	120	40	120	40	120	40	160	40	40	136	32	40	136	40	40
E-32	120	40	120	40	120	40	120	40	120	40	120	40	120	40	120	40	160	40	40	128	24	38	136	40	40
E-18	120	40	120	40	120	40	120	40	120	40	120	40	120	40	120	40	136	48	40	136	40	40	136	40	40

[a] (D) indicates the number of conditioning trials with drugs

Rationale for Data Analysis

It has been widely observed in the field of psychophysiology that the magnitude of response to stimulation is inversely related to pre-stimulation response levels. This relationship was termed the law of initial value (LIV) by Wilder (1950, 1957) who was the first to emphasize its generality by pointing out numerous applications in biology, medicine, physiology, and neurology. Because Wilder urged caution in interpreting physiological response to stimulation without taking pre-stimulation response level into account, questions arose as to appropriate response measures, standardization, and statistical adjustment of data when individuals' pre-stimulation levels were not equivalent (Lacey, 1956, and others). Specifically, if the initial values of two individuals differ, apparently equal response magnitudes may not be equal. The law of initial value reflects the more general problem of comparing any individual or group performances when extraneous factors systematically affect the dependent variables under study.

Most researchers, and statisticians as well, recommend experimental, rather than statistical control of extraneous variables (e.g., Kirk, 1968; McGuigan, 1968; McNemar, 1955) through techniques such as elimination, constancy of conditions, and use of control groups. However, experimental control of initial level may in some cases be extremely difficult, if not impossible to achieve (Lacey, 1956). For their studies of cardiac conditioning, Snapper, Kadden, & Schoenfeld (1971) attempted to bring post-CS cardiac response levels under direct control by fixing pre-CS heart rate at pre-determined values with the use of an electrical pace-

maker. The heart was paced at varying pre-CS rates, and then released during CS. They were unable, however, to show control of post-CS HR level by pre-CS pacing rates. Since direct control of initial response level presents difficulties, one could revert to pre-experimental statistical procedures to match individuals and groups with respect to their initial levels, and then to conduct experiments with groups arranged by levels of pre-stimulation response measures. The power of statistical tests are increased when comparison groups are matched with respect to non-random extraneous variables (e.g., Kirk, 1968; McGuigan, 1968). Unfortunately, however, additional complexities surround the law of initial value: investigators have noted a consistent relationship between pre and post-stimulation response levels for an individual, but different degrees to which the LIV affects responses to stimulation from one individual to another (Block & Bridger, 1962; Bridger & Reiser, 1959; Lacey, 1956; Steinschneider & Lipton, 1965). Also, in the attempt to match individuals for initial response level, one might find that level to be in the upper portion of one individual's response range, and in the lower portion of the other's (Block & Bridger, 1962; Bridger & Reiser, 1959).

It appears that neither direct experimental control nor pre-experimental matching procedures reasonably counteract the confounding of initial level with response magnitudes. As a result, one must resort to post-experimental statistical adjustment of data.

There have been many attempts to define mathematically and to evaluate the Law of initial value. The LIV has been described as either a correlation or a regression: the observed negative correlation between pre and post-stimulation response magnitude (Benjamin, 1963, 1967; Wilder,

1965); or, the positive correlation between pre and post-stimulation response levels (Lacey, 1956). Regression models have also been proposed (Block & Bridger, 1962; Bridger & Reiser, 1959; Downer & Thompson, 1972; Surwillo & Arenberg, 1965), with the argument that a strong correlation between two variables, as measured by the Pearson r, conveys no information about the magnitude of their functional relationship. These authors suggest that the LIV be expressed by the slope of the best-fit regression of post-stimulation response level on initial response level, but do not agree on what value of the regression coefficient (slope) reflects maximal operation of the LIV. As a kind of compromise to the above confusion, Steinschneider & Lipton (1965) suggest use of correlation and regression coefficients when evaluating the LIV, rather than arbitrarily selecting one or the other.

There are many definitions of the LIV, and there are many proposals of how to eliminate it statistically; i.e., how to free response data from the confounding effects of initial level (see extensive review by Lacey, 1956). Benjamin (1963, 1967) has pointed out that the investigator's choice of analysis greatly affects interpretation of the data. In the 1963 paper she compared four major types of solutions to the problem of freeing the effect of initial response level on post-stimulus response magnitudes. Benjamin found that only scores adjusted by regression models, namely, Lacey's Autonomic Lability Score (ALS; 1956) and covariance adjustment resulted in zero correlation between the adjusted score and initial response level. After further demonstrating that Lacey's ALS is an equivalent, standardized form of covariance adjustment, she recommended Lacey's ALS for comparison of individuals and analysis of covariance for comparison of groups. Briefly, analysis

of covariance is a technique that combines components of analysis of variance and regression techniques (Snedecor & Cochran, 1967). The analysis of variance allows grouping of data to make comparisons of interest, for instance, between vs within groups comparisons. The regression component determines the linear dependency between response measures and some other variable, in this case, pre-stimulation level: the sums of squares from the analysis of variance are adjusted by an amount proportional to the magnitude of the observed linear dependency. Thus, the effect of initial response level on post-stimulation response measures is removed, allowing tests of significance of appropriate comparisons by the usual F ratios.

Before a statistical model for data analysis was chosen in the present study, it was necessary to determine the regression of response to stimulation on initial response level. Since it is not at all clear how to characterize the LIV relationship, the requirement for choosing a model that included pre-stimulation response measures in the analysis rested on some observed correlation between pre and post-CS response levels, and a regression coefficient greater than zero.

Results

The overall correlation between pre and post-CS IBI levels was found to be 0.92 and the regression of the pooled regressions for all CS-US intervals (excepting re-exposure) was 0.80. To the extent that the magnitude of these correlation and regression coefficients conform to many of the definitions of the law of initial value in the literature outlined previously, we can tentatively conclude the presence of the LIV in the present post-CS cardiac rate data. Other investigators have also shown that the LIV is present in the cardiac rate data of humans (Bridger & Reiser, 1959; Hord, Johnson, & Lubin, 1964; Lacey, 1956; Wilder, 1957), rhesus (Ramsay, 1970; Snapper, Kadden, & Schoenfeld, 1971), dogs (Black, et al., 1962), and pigeons (Cohen & Pitts, 1967). Based on Benjamin's (1963, 1967) demonstration that only covariance (synonymous with regression models) insure a score free of initial response level, and the values of the obtained regression and correlation coefficients, an analysis of covariance was performed.

There has been some disagreement regarding which dependent variable measure should be adjusted, whether difference scores (post minus pre) or level scores (post) (Lacey, 1956). Several authors have shown that results are identical regardless of which measure is adjusted (Benjamin, 1963, 1967; Block, 1964; Myers & Honig, 1969). Covariance adjustment of level scores was the method of choice for the present data.

Pre-stimulation level of cardiac activity, and response level after stimulation were determined as follows: pre-stimulation level was defined as the mean interbeat time (msec) 10 sec prior to CS onset and was termed

the covariate. It is the variable whose effects are to be removed from the dependent variable, and will be designated by "X". Response level after stimulation was the mean interbeat time (msec) during the CS-US interval maximally different from pre-CS level and was termed the variate: it is the dependent variable to be adjusted by covariance, and will be designated by "Y".

Variability in Y among subjects at each CS-US interval duration was large enough to warrant a design that also isolates the among-subjects variance from the error variance, therefore, a randomized block analysis of covariance was performed. Variation related to pre-CS response level is removed by covariance, and variation related to individual differences is removed by blocking. Each block (row) consisted of one subject, and columns consisted of the CS-US intervals 10, 20, 30, 50, 80, 120, and 170 sec. It should be noted that the 230 sec CS-US interval was not included in this analysis due to difficulties in distinguishing between the cardiac rate response to US and CS, since US coincided with CS onset.

The data from each criterion trial, (i.e., sessions 5 and 6 at each CS-US interval) consisting of a 230 sec recording period of double-interbeat times in 2 sec periods, were divided by two to provide an average single interbeat time, and 23 means of successive 10 sec periods were then calculated. X and Y values were determined for each subject for each trial; thus, a set of X,Y pairs was entered for each subject at each CS-US interval duration. A regression line was determined for each array of X,Y pairs by the method of least squares, resulting in 42 regression lines (six subjects by seven intervals). Regression coefficients and Pearson product-moment correlations are listed in

Table 2. In analysis of covariance, an important assumption to be satisfied is the requirement of homogeneity of regression between and within treatment levels (e.g., Evans & Anastasio, 1968; Kirk, 1968; Lacey, 1956; Snedecor & Cochran, 1967);i.e., the slope of regression for each treatment level must be equal to the slope of regression of all other treatment levels. Homogeneity of regression between and within CS-US interval durations (Table 2) was tested by a repeated measures analysis of variance. An F (df= 6,5) of 1.68 resulted (p >.05), confirming that between and within group regressions were not significantly different. Also, an F_{max} test on column variances of regression coefficients resulted in F_{max} (df= 7,5)= 16.71 (p >.05), thereby confirming that slope variances across treatments were not significantly different.

X and Y values in each array were then averaged, resulting in one mean X, mean Y pair for each subject at each CS-US interval duration. These values formed the basis for the analysis of covariance, and are listed in Table A of the Appendix. The Source Table is listed below:

SOURCE	ADJ. SS	DF	ADJ. MS	F	p
Between treatments (T)	38,127.96	6	6354.66	$\frac{MS(T)}{MS(R)}$ = 11.24	<.01
Between blocks (B)	40,027.80	5	8005.56	$\frac{MS(B)}{MS(R)}$ = 14.16	<.01
Residual (error; R)	16,392.99	29	565.28		

The obtained treatment F of 11.24 with 6,29 df is significant at p <.01. Therefore, it can be concluded that the duration of the CS-US interval influenced the value of maximum change in interbeat interval in the CS-US interval. Note also the significant blocks effect. This indicates

Table 2

Pearson product-moment correlations (r) and regression coefficients (b) for pre-CS interbeat interval level (X) and maximum change in interbeat interval (Y) in the CS-US interval

		CS-US Interval (Sec)													
		10		20		30		50		80		120		170	
		r	b	r	b	r	b	r	b	r	b	r	b	r	b
Subject	E-28	.88 (18)[a]	.80	.96 (16)	.94	.95 (16)	.86	.46 (19)	.46	0 (10)	.003	.56 (20)	.73	.85 (20)	.87
	E-34	.94 (19)	.67	.25 (20)	.13	.84 (20)	.57	.10 (20)	-.05	.88 (8)	.48	.78 (18)	.59	.70 (14)	.58
	E-40	.92 (14)	.73	.88 (19)	.76	.30 (17)	-.29	.14 (12)	.34	.78 (18)	1.11	.67 (12)	.63	.88 (13)	1.11
	E-38	.94 (10)	.81	.70 (19)	.48	.73 (18)	.61	.46 (18)	.32	.70 (19)	.50	.81 (15)	.81	.83 (19)	.67
	E-32	.88 (19)	.49	.91 (18)	.75	.81 (19)	.84	.30 (11)	-.29	.93 (15)	1.05	.75 (20)	.73	.47 (16)	.44
	E-18	.76 (20)	.63	.91 (14)	.65	.89 (18)	.52	.77 (20)	.66	.69 (10)	.83	.79 (15)	.64	.53 (17)	.51

[a] Numbers in parentheses represent the number of X,Y pairs upon which the coefficients above are based. They also correspond to the number of intact criterion trials at each CS-US interval for each subject.

that the row sums of squares (B) were large enough to warrant the use of randomized block analysis of covariance; the error variance was much reduced after extracting the row sums of squares.

Specific comparisons among CS-US interval durations were made after adjustment of column averages for Y (maximum change in rate from pre-CS) for differences in column averages of X (pre-CS rate; see Winer [1971] for a graphic representation and the adjustment formula). Unadjusted (closed circles) and adjusted (triangles) Y column means for each CS-US interval are plotted in Figure 2, along with associated values of mean IBI level pre-CS (X; open circles). Adjusted column means for Y were then compared for significant differences with the use of Tukey's a posteriori test. Results of all possible paired comparisons are shown in Table 3, and, indicate the following in conjunction with Figure 2:

As the CS-US interval duration increased from 10 to 30 sec, IBI values at peak change during the CS-US interval decreased significantly (smaller IBIs indicate higher heart rates, and vice-versa). Subsequently, and compared with the IBI value at 30 sec CS-US, IBI values at peak change significantly increased (i.e., lower HRs occurred) between the 50 sec and 80 sec CS-US conditions. These values were not significantly different from those at the first CS-US interval of 10 sec. After, and compared to the reduced heart rates at peak change for the 50 and 80 sec CS-US conditions, heart rates at peak change increased once again, and were significantly different from the 50 sec CS-US interval condition at 120 sec and 170 sec CS-US. These values at 120 and 170 sec were not significantly different from those at 30 sec CS-US.

It appears, then, that there were three CS-US intervals, 30, 120, and 170 sec which resulted in the highest heart rates within the CS-US

Figure 2. Adjusted (triangles) and unadjusted (filled circles) mean interbeat interval level at peak change in the CS-US interval, and mean interbeat interval during 10 sec pre-CS (open circles), as a function of CS-US interval duration. Each data point is the result of averaging over all criterion trials at each duration, averaged over six subjects.

Fig. 2

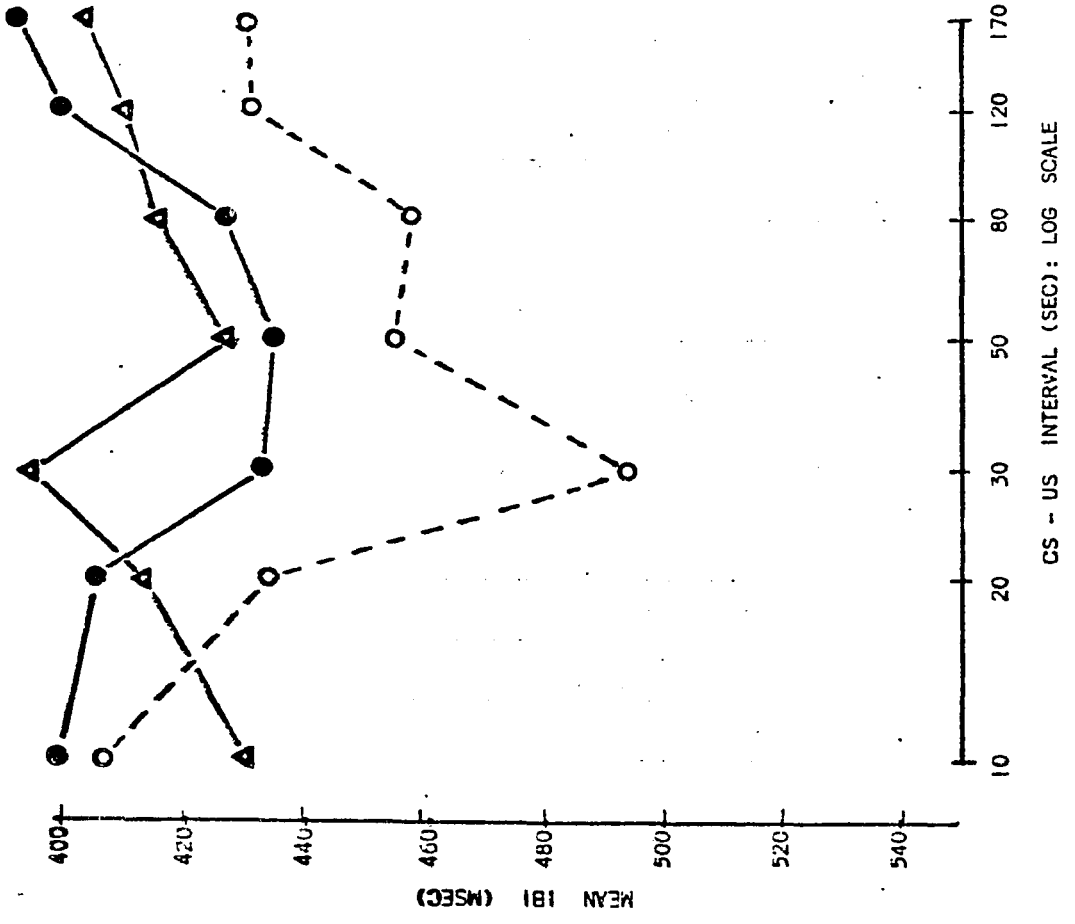

MEAN IBI (MSEC)
400
420
440
460
480
500
520
540
10
20
30
50
80
120
170
CS - US INTERVAL (SEC): LOG SCALE

Table 3

Results of a posteriori paired comparisons between group means for Y [a] using Tukey's q statistic

	CS-US Interval (Sec)						
	10	20	30	50	80	120	170
10		*	**	NS	NS	*	**
20			*	NS	NS	NS	NS
30				**	*	NS	NS
50					NS	*	**
80						NS	NS
120							NS
170							

[a] Y indicates mean IBI maximally different from pre-CS in the CS-US interval

NS= not significant ($p > .05$)

*= $p < .05$

**= $p < .01$

interval at the point of maximum change from pre-CS rates. Those CS-US intervals resulting in the lowest rates at the point of maximum change were the 10, 50, and 80 sec CS-US conditions.

CR Form

Although the law of initial value has been discussed above with regard to CR magnitude, it may appear in the form of the response as well. Investigators of the cardiac CR have noted changes in the form of the responses with changes in baseline heart rate (e.g., Black et al., 1962); similar changes are evident in the present data. For example, Figure 3 shows the cardiac rate CR in three trials (same session) for subject E-38 and demonstrates that CR form can change markedly as a function of pre-CS response level. The present finding, however, is that the form of the CR is not entirely determined by pre-stimulation heart rate, but is also a function of the CS-US interval duration (Figures 4 through 18). The data are plotted in three ways: (1) Figures 4-9 present individual-subject CRs composed of IBIs in successive 2 sec averaging periods, over the course of the CS-US interval. CS-US intervals of 10-50 sec are shown. (2) Figures 10-15 present individual-subject functions of IBIs in successive 10 sec averaging periods over the course of the US-US interval: filled-circle functions represent those conditions where the CS was presented. Open-circle functions at their right represent subsequent trials where the CS was omitted. CS-US intervals, with the interpolated sessions of US alone, are shown for 10 sec through 230 sec. (3) Figures 16-18 represent group functions (averages of six subjects) of IBIs in successive 10 sec averaging periods over the course of the US-US interval. CS-US intervals from 10-230 sec are shown. Filled

Figure 3. Three cardiac CRs during the same session (10 sec CS-US) for subject E-38. Each point represents mean IBI (in msec) for 2 sec. Note how the shape of the response depends upon initial (pre) response level.

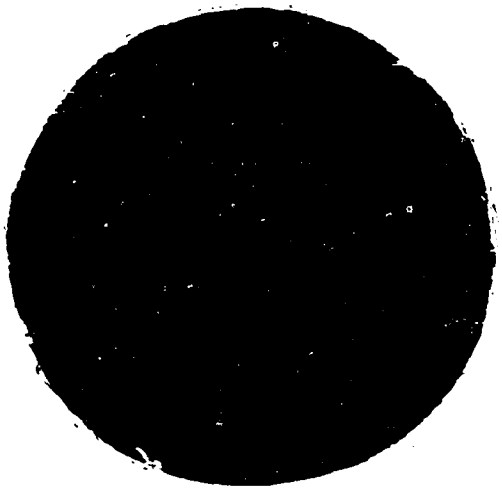


Fig. 3

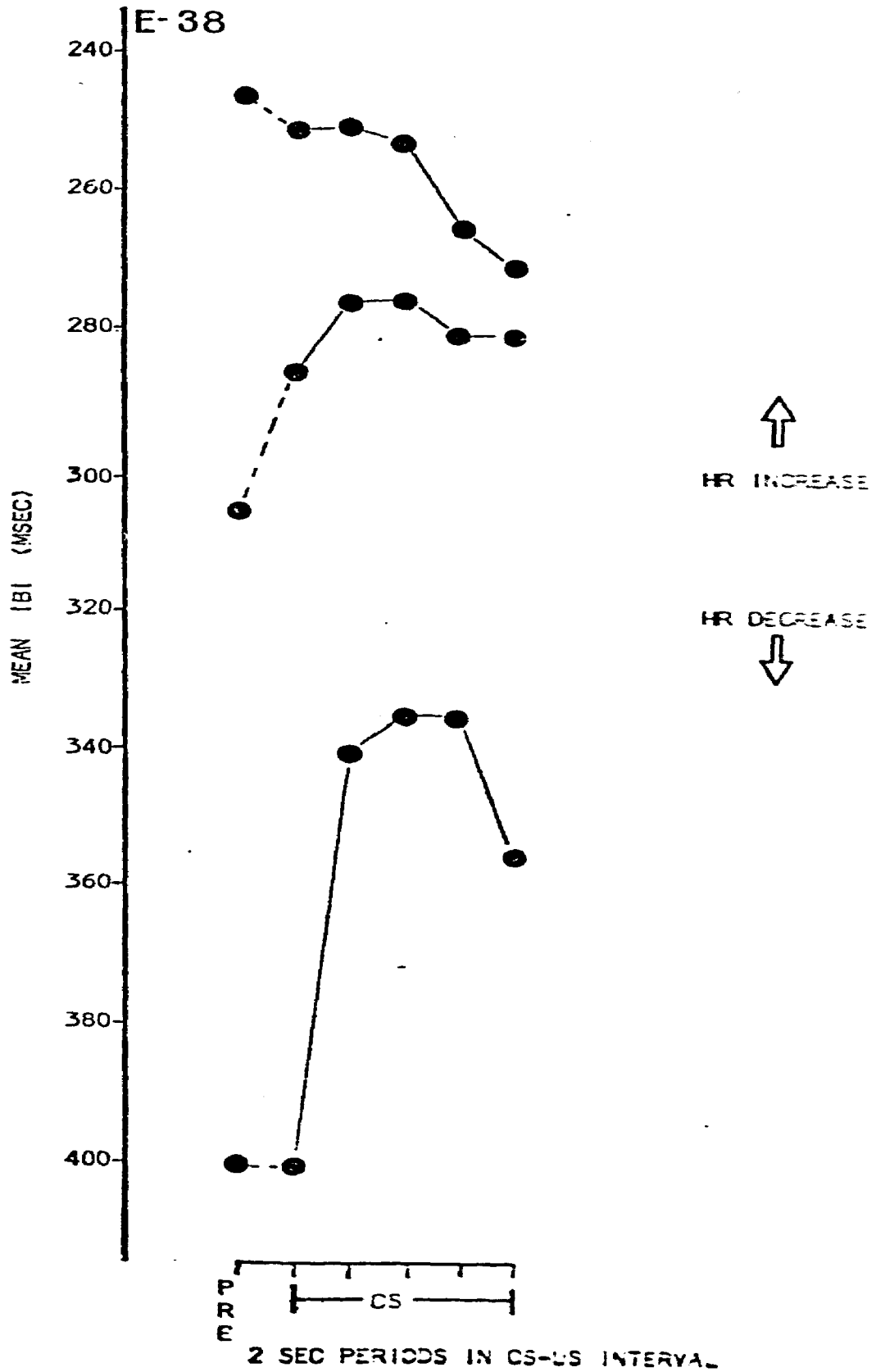
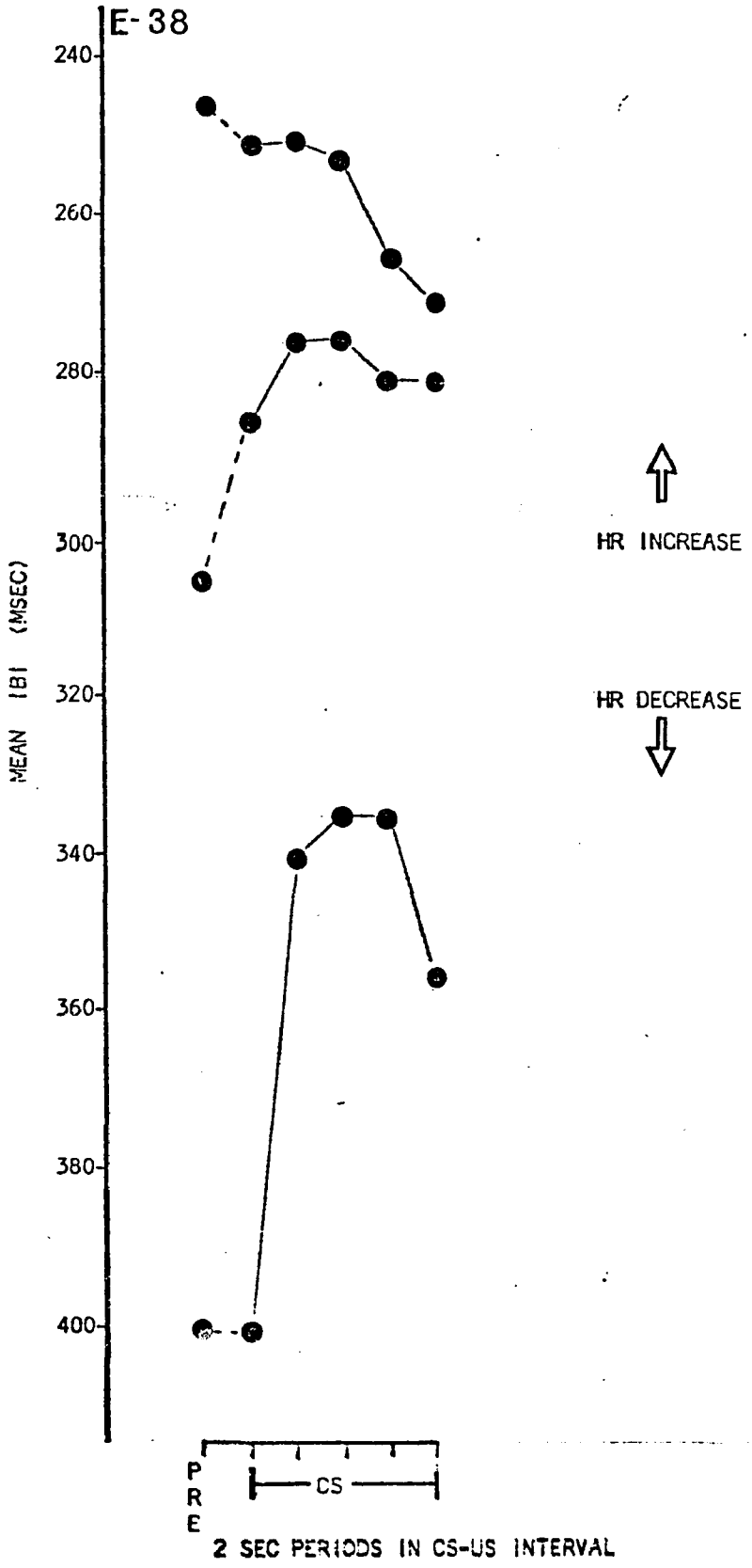

E-38
240
260
280
300
320
340
360
380
400
MEAN IBI (MSEC)
HR INCREASE
HR DECREASE
PRE
CS
2 SEC PERIODS IN CS-US INTERVAL

Figure 3. Three cardiac CRs during the same session (10 sec CS-US) for subject E-38. Each point represents mean IBI (in msec) for 2 sec. Note how the shape of the response depends upon initial (pre) response level.


E-38
240
260
280
300
320
340
360
380
400
MEAN IBI (MSEC)
HR INCREASE
HR DECREASE
PRE
CS
2 SEC PERIODS IN CS-US INTERVAL

and open circles denote the same conditions as in Figures 10-15.

Figures 4-9 indicate that at the 10 sec CS-US interval, where CS fills the duration of the interval, all subjects show a heart rate pattern of acceleration followed by deceleration. For the majority of subjects, heart rate reaches a peak during the first half of the interval. Note evidence of the LIV in the smaller magnitude CRs at IBIs smaller than 330 msec: these subjects show peak HR closer to the midpoint of the CS-US interval (4-6 sec after CS onset). Lowest heart rate after the peak occurs for most subjects during the final 2 seconds of the interval.

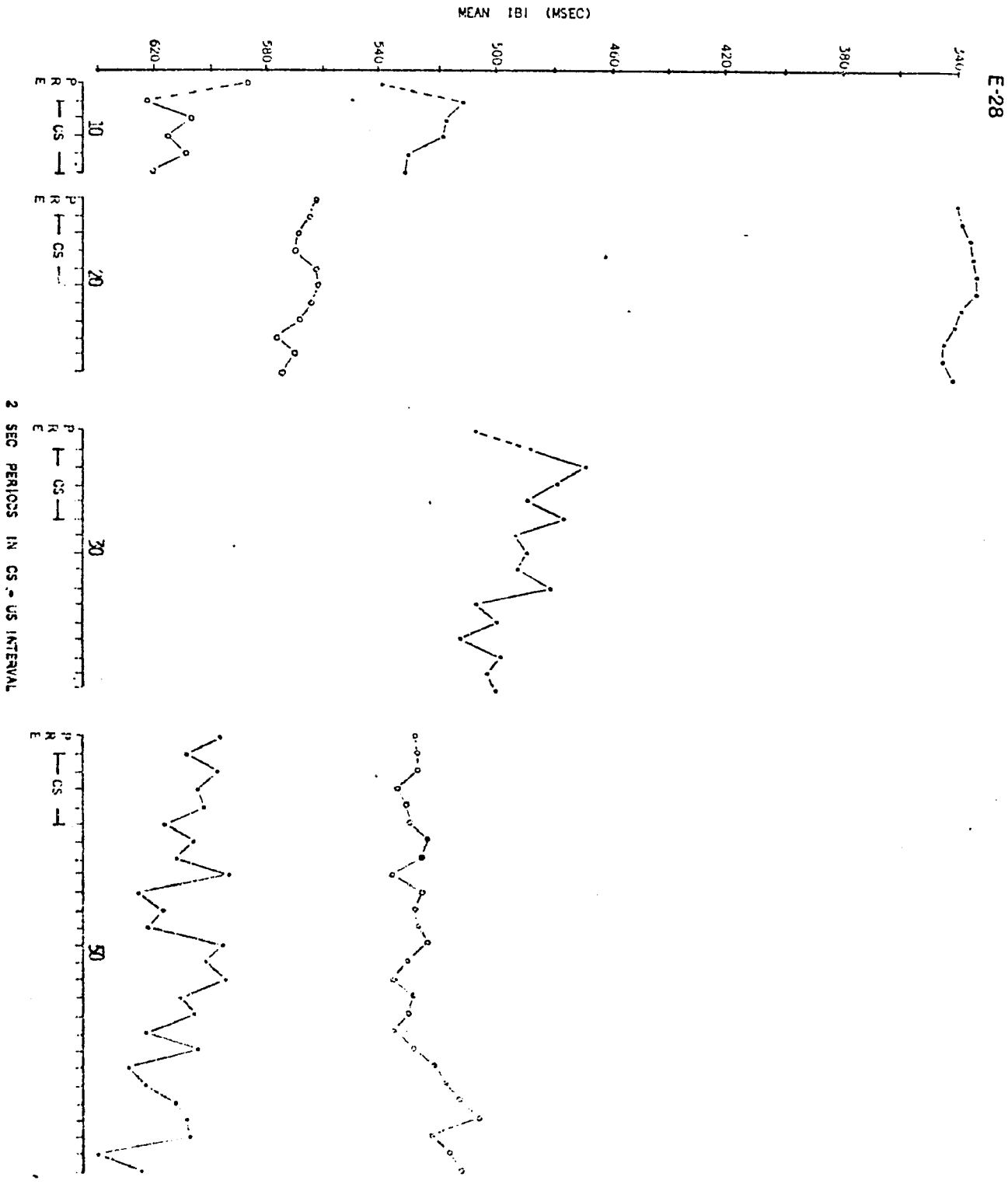
At 20 sec CS-US interval where a trace period of equal duration to CS (10 sec) is introduced, the biphasic (rate acceleration followed by deceleration) response pattern is mostly maintained, but with increased variability of form, as evidenced by two or three additional small accelerations followed by deceleration, each biphasic cycle lasting approximately 4-6 sec. Note E-34 (Fig. 5) who clearly shows two large biphasic HR patterns during the CS-US interval: one during CS and the second during the trace interval, initiated at CS offset.

At the 20 sec interval, the majority of subjects show a later HR peak in the CS-US interval. For most subjects, the lowest heart rate after the peak again occurs close to US (approximately 2-4 sec before). Once again, note evidence of the LIV in the functions of E-28, E-34, and E-18 as seen in the small accelerations to CS onset at IBIs less than 340 msec.

The 30 sec CS-US interval is marked by an increasing irregularity of the biphasic cardiac CR with additional small phasic accelerations and decelerations throughout the CS-US interval. Some consistencies do,

Figures 4-9. Individual-subject mean cardiac CRs for CS-US intervals of 10-50 sec, original exposure (filled circles) and re-exposure (open circles). Each data point represents mean IBI (in msec) for 2 sec, averaged over all criterion trials for that CS-US interval. "PRE" indicates mean IBI (in msec) 2 sec prior to CS onset.

Fig. 4


MEAN IBI (MSEC)
620
580
540
500
460
420
380
340
E-28
PRE
CS
10
20
30
2 SEC PERIODS IN CS - US INTERVAL

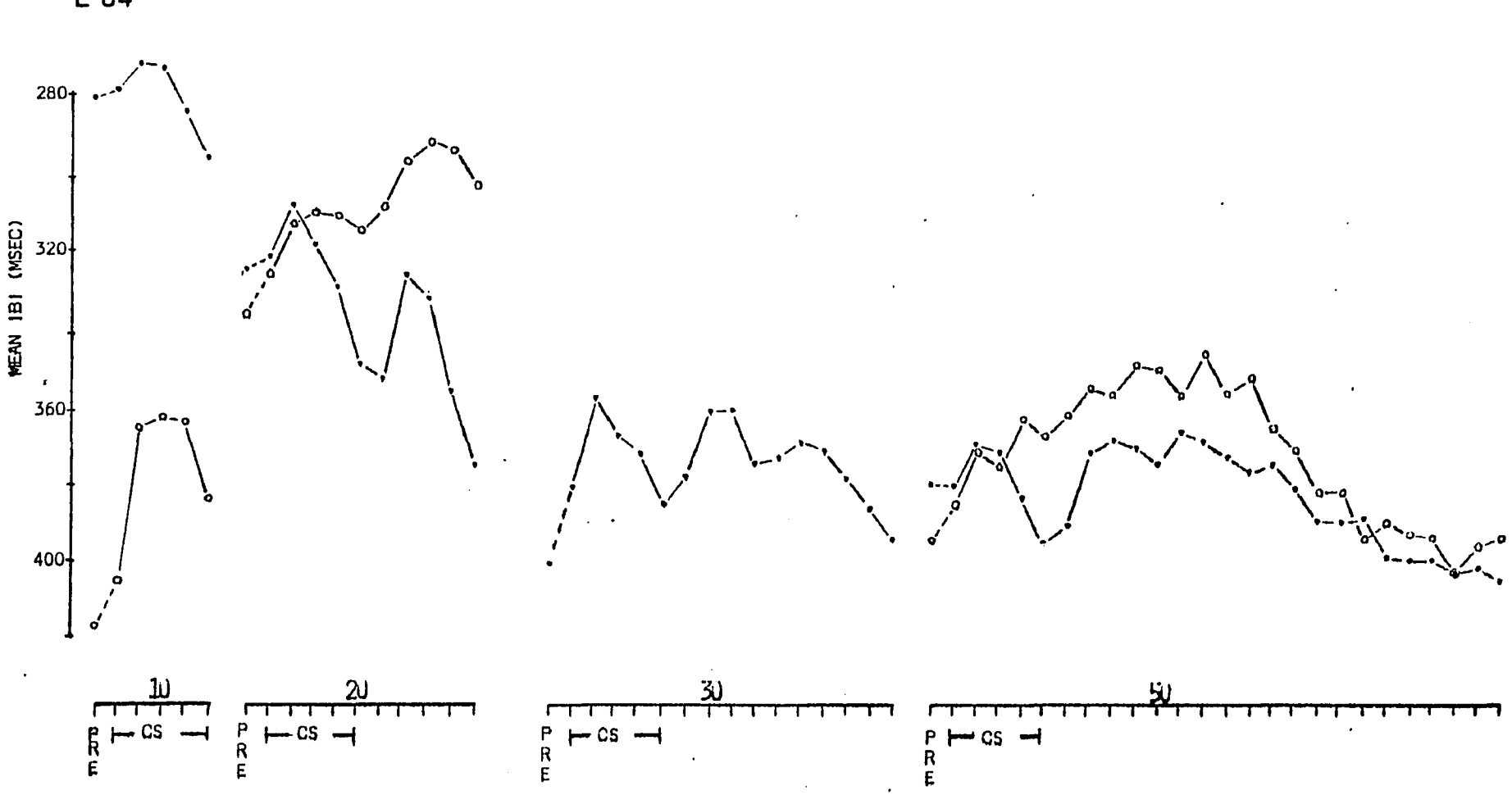

E-34
MEAN IBI (MSEC)
280
320
360
400
10
20
30
50
PRE
CS
2 SEC PERIODS IN CS - US INTERVAL

Fig. 5

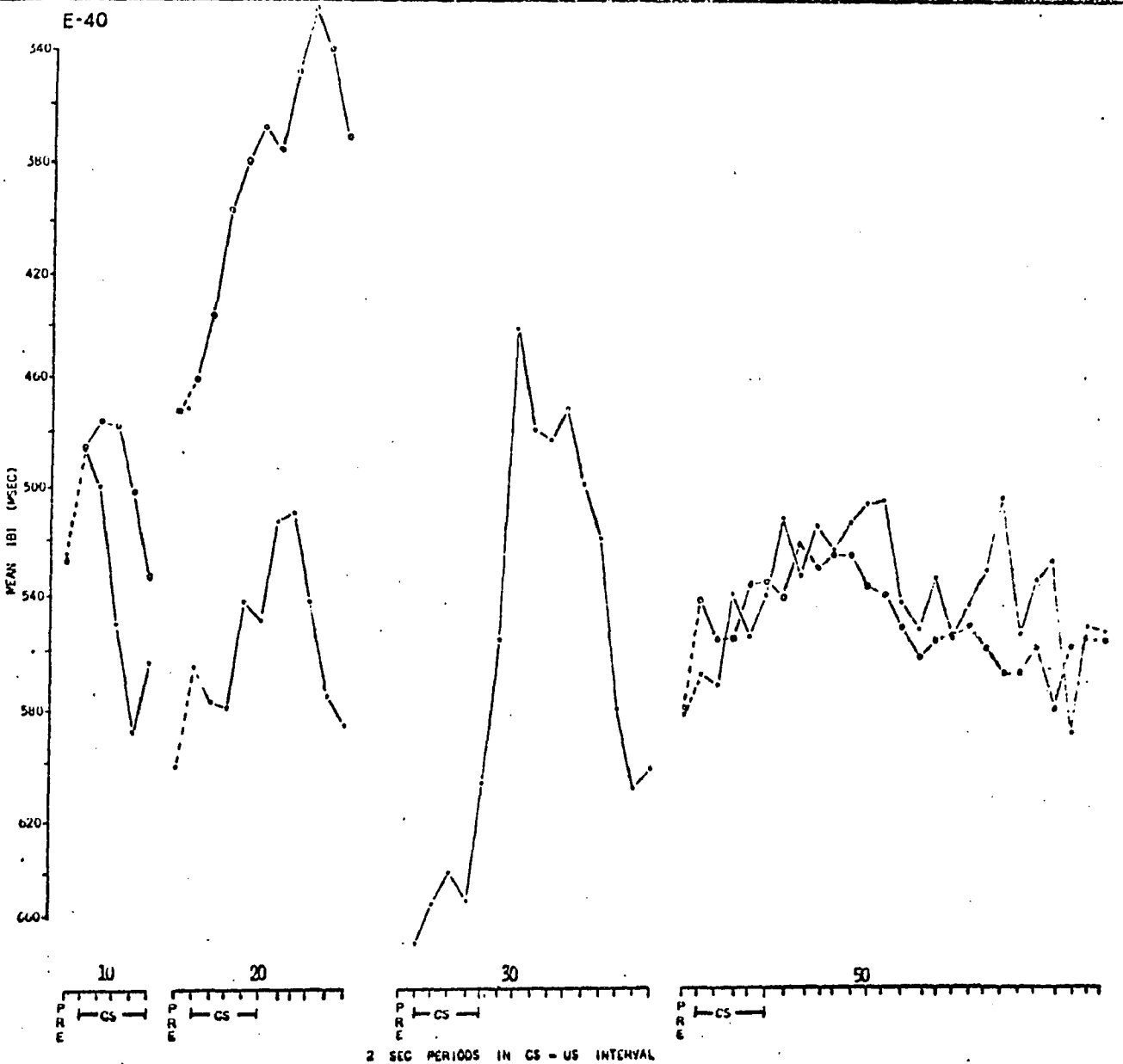

E-40
340
380
420
460
500
540
580
620
660
MEAN IBI (MSEC)
10
20
30
50
PRE
CS
2 SEC PERIODS IN CS - US INTERVAL

Fig. 6

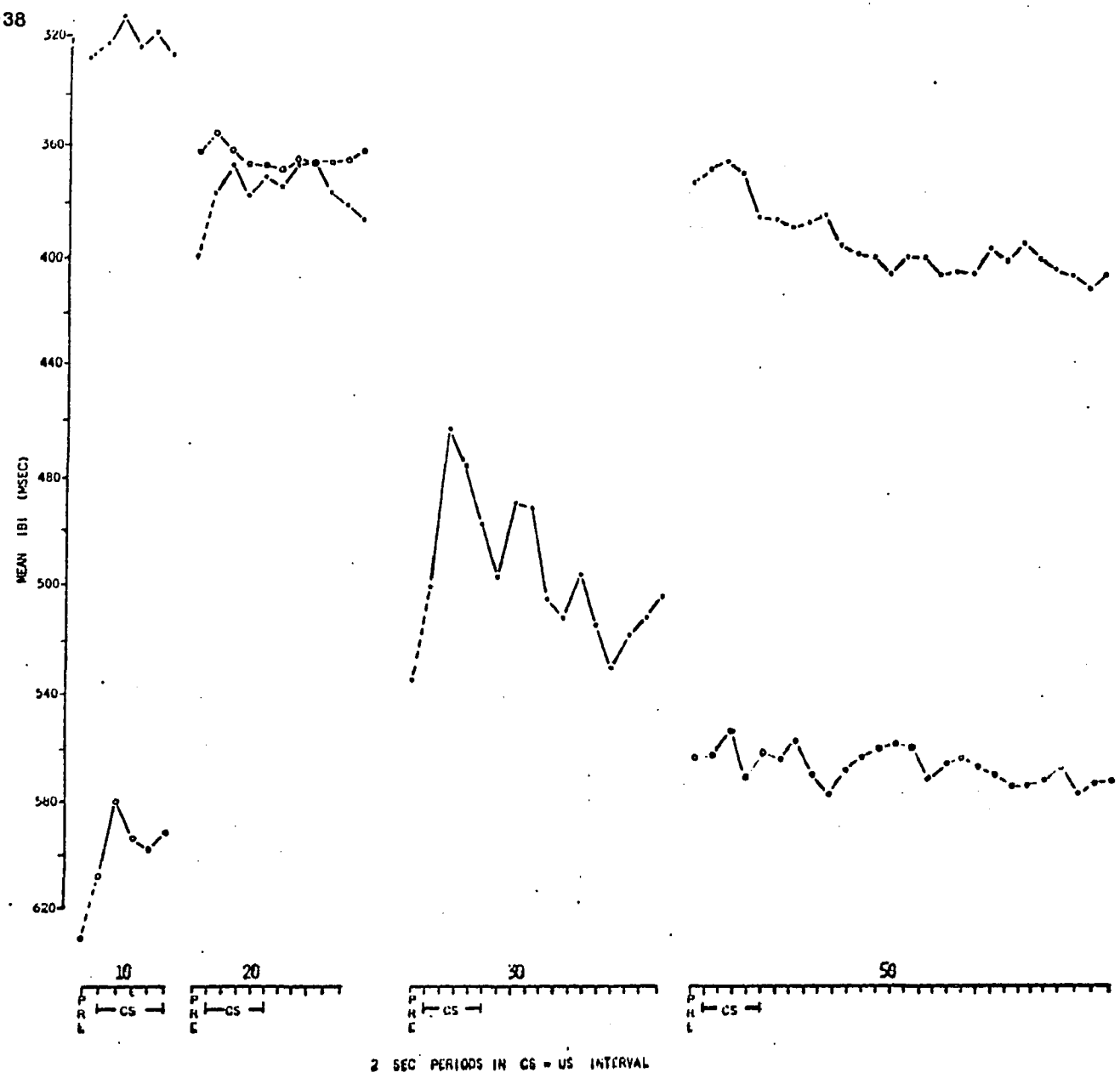

E-38
320
360
400
440
480
500
540
580
620
MEAN IBI (MSEC)
10
20
30
50
PRE
CS
2 SEC PERIODS IN CS - US INTERVAL

Fig. 7

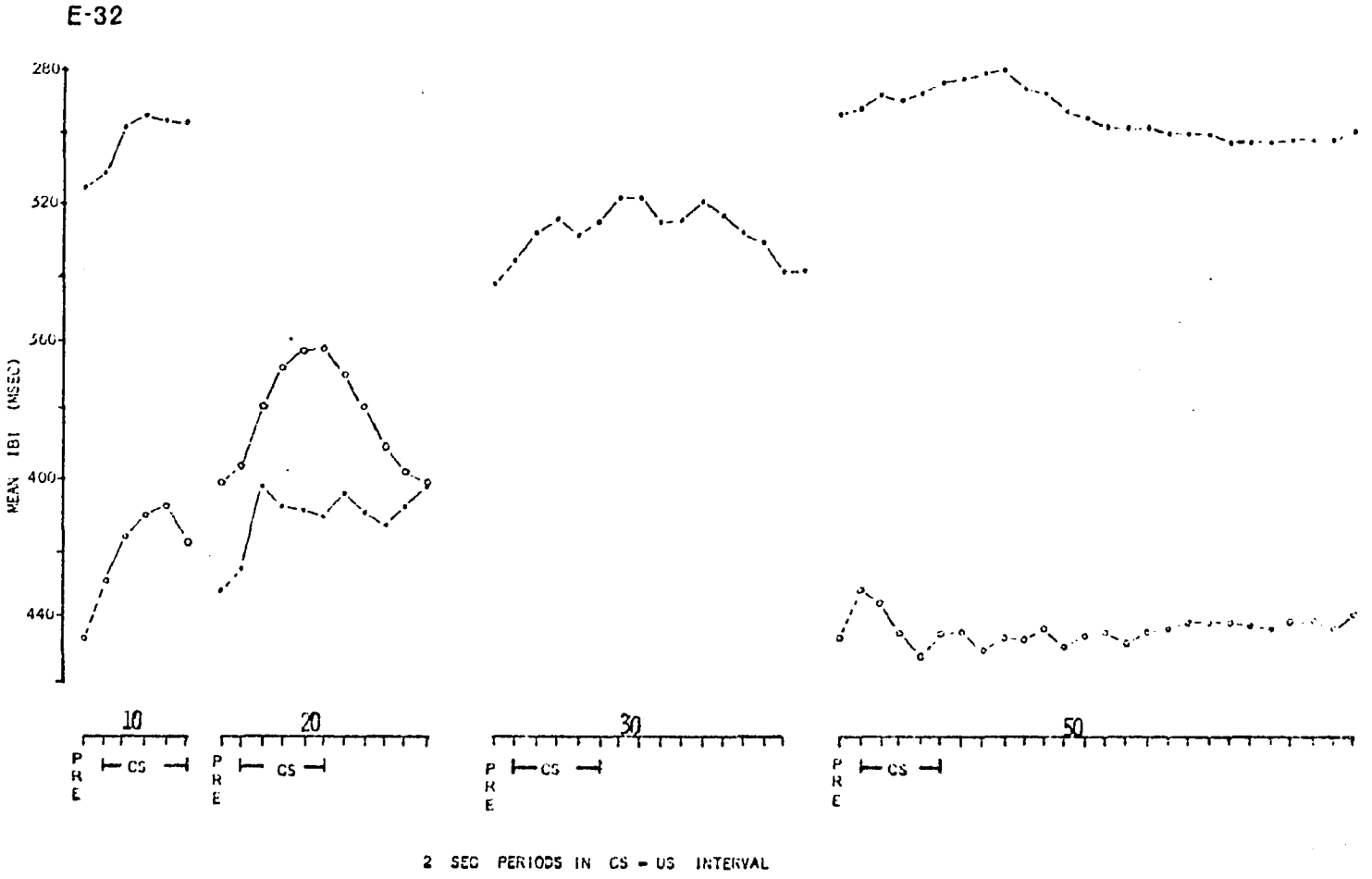
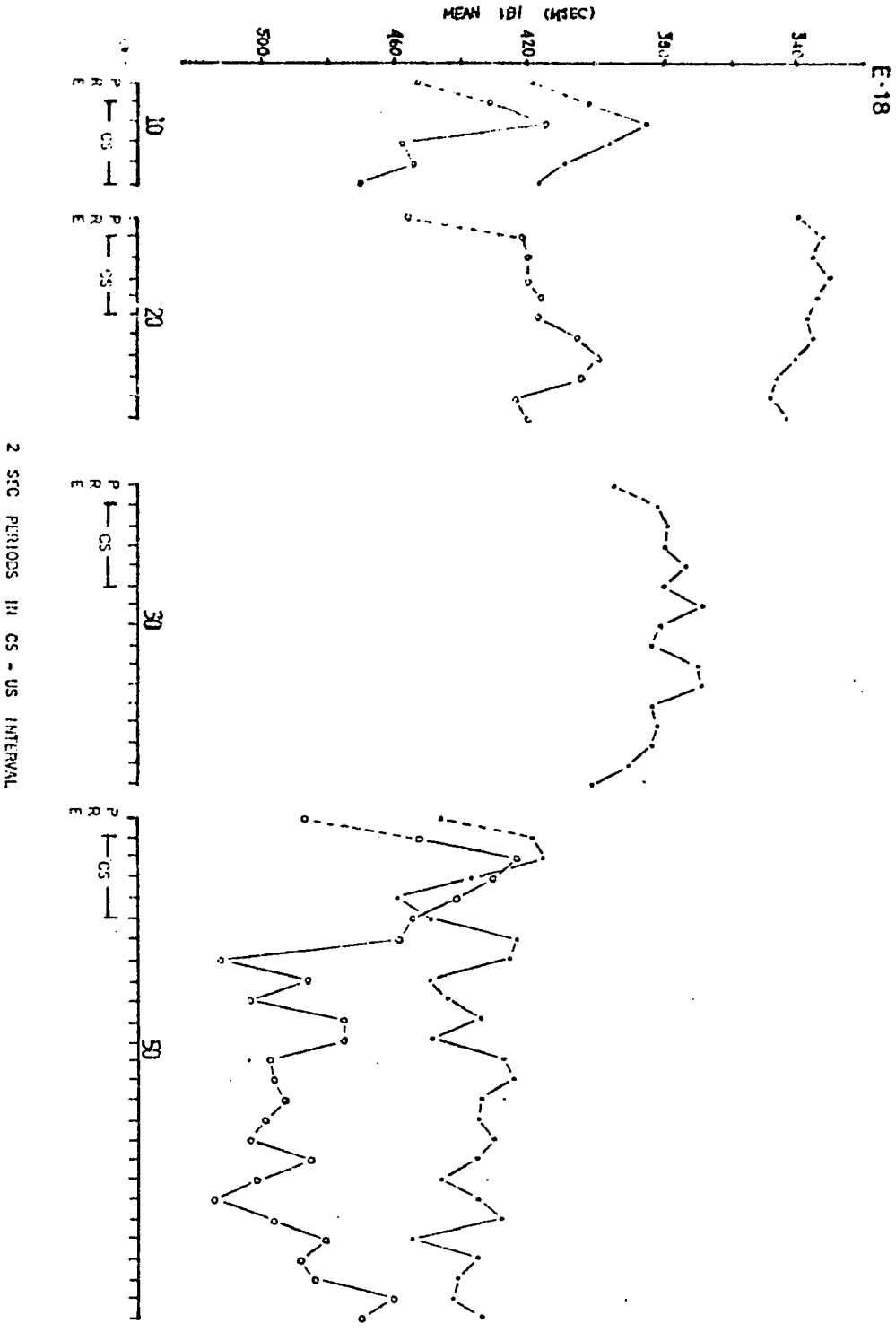

E-32
280
320
360
400
440
MEAN IBI (MSEC)
10
20
30
50
PRE
CS
2 SEC PERIODS IN CS - US INTERVAL

Fig. 8

Fig. 9


MEAN IBI (MSEC)
500
460
420
E-18
PRE
CS
10
20
30
50
2 SEC PERIODS IN CS - US INTERVAL

however, remain. An overall acceleration-deceleration sequence is still evident: as Figures 4-9 show, heart rate begins accelerating at CS onset and remains above pre-CS level until approximately 10-12 sec before US. Four subjects then steadily decelerate and reach their lowest heart rate after the peak at 2-4 sec before US. E-28 and E-38 do not clearly display this steady deceleration, but are consistent with each other: both reach an early peak (2 sec after CS onset) and reach lowest heart rate after the peak at 8 sec before US.

Again, E-34 is worth noting: for each additional 10 sec added to the CS-US interval, he "attaches" another biphasic component. This effect is also somewhat evident in E-38 (Fig. 7) at the 30 sec interval where he shows a large biphasic component during CS, a second, smaller component initiated at CS offset, and yet a third smaller biphasic component during the final 14 sec of the CS-US interval. E-32 (Fig. 8) also shows three clearly definable acceleratory-deceleratory phases, although the termination of each phase is not as clearly controlled by the end of each prior 10 sec extension to the CS-US interval. Of the six subjects, only E-40's CR is not highly variable.

In summary, a biphasic CR form of acceleration followed by deceleration at the initial 10 sec CS-US interval became more variable, as evidenced by additional phasic changes in heart rate, as the CS-US interval was lengthened. An overall acceleratory-deceleratory pattern during the CS-US interval was, however, maintained. The peak of acceleration occurred closer to US with increasing CS-US intervals; the location of lowest heart rate after the peak did not change as much, although some subjects did show a movement away from US of the location of maximum

deceleration.

Although the functions of 2 sec averaging periods (Figures 4-9) reveal short-duration heart rate changes, such as the biphasic CR form at the 10 sec CS-US interval, and, more clearly pinpoint the locations of peak acceleration and deceleration, increasing variability in the CR at longer CS-US intervals obscures some overall trends. These trends are more easily seen in the individual and group functions composed of IBIs in 10 sec averaging periods (Figures 10-18), and will be described next for the 30 sec CS-US interval.

Temporal patterning of mean interbeat intervals for individual subjects when CS began 30 sec prior to US can be found in the leftmost panels of Figures 10-15. The figures show that the majority of subjects accelerate at CS onset and continue to accelerate during the initial 20 seconds of the interval. This duration of initial acceleration at 30 sec CS-US is unlike that of the previous 20 sec CS-US interval (Figures 10-15 leftmost columns) where subjects generally reversed to deceleration within 10 sec after CS onset; also, it can be clearly seen in the group function (Figure 16, second left panel from the top).

At the 50 sec interval, as first seen from Figures 4-9, only three subjects (E-40, E-32, and E-34) have retained the overall biphasic CR form. These subjects show a later peak of acceleration than at the previous three intervals. The group function for CS onset 50 sec prior to US (Fig. 16, fourth left panel from the top), as at the 30 sec CS-US interval, shows an acceleratory component of 20 sec duration, with a longer duration of deceleration of 30 seconds.

Figure 16 (bottom left panel) shows the group function for CS onset at 80 sec pre-US and indicates, similar to changes in CR form as expressed

Figures 10-15. Individual-subject functions of successive mean inter-beat intervals over the course of the US-US interval, at each temporal location of CS (left of each double-column) and subsequent two sessions where CS was omitted (right of each double-column). Each data point represents mean IBI (in msec) for 10 sec, averaged over all criterion trials for each condition.

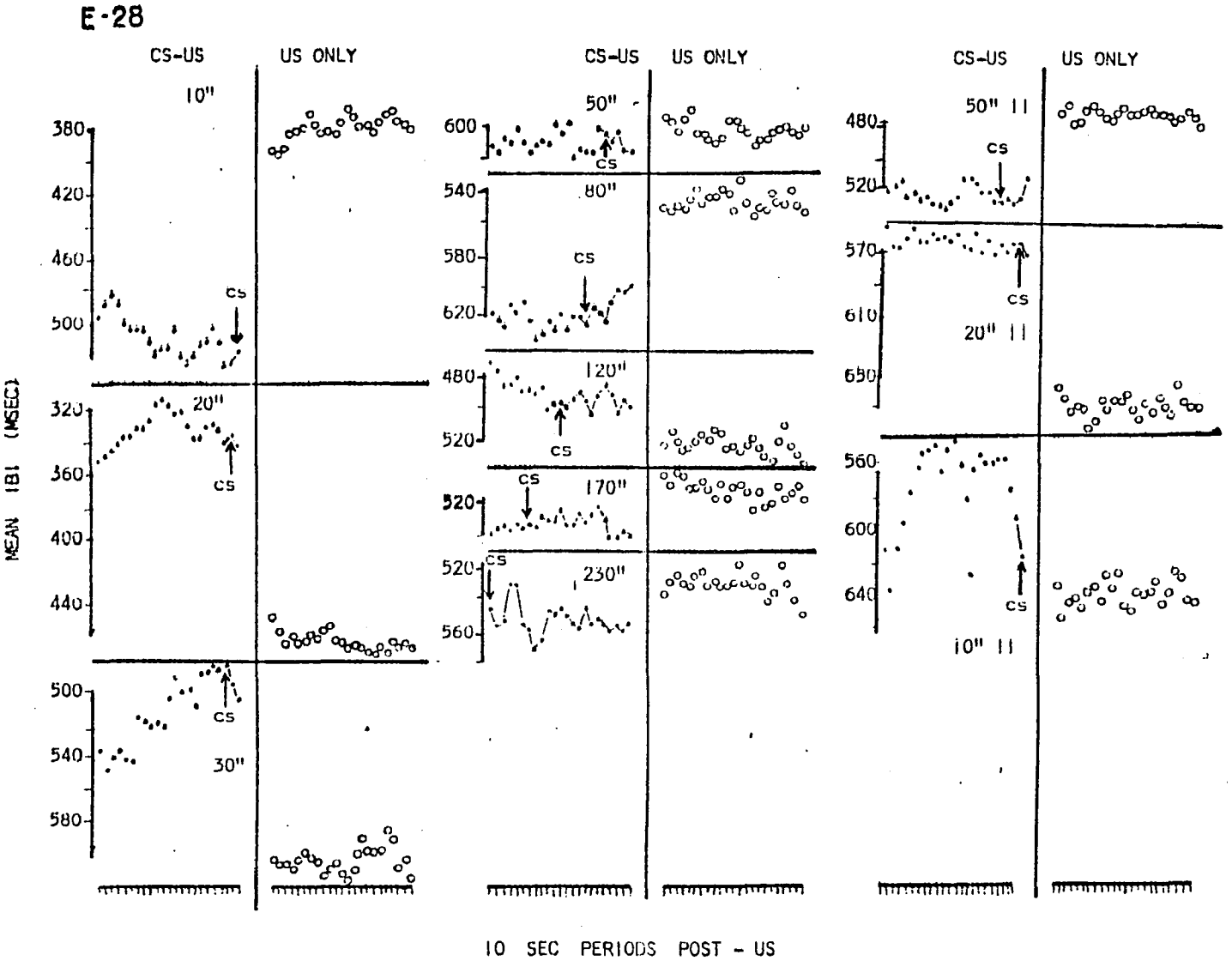
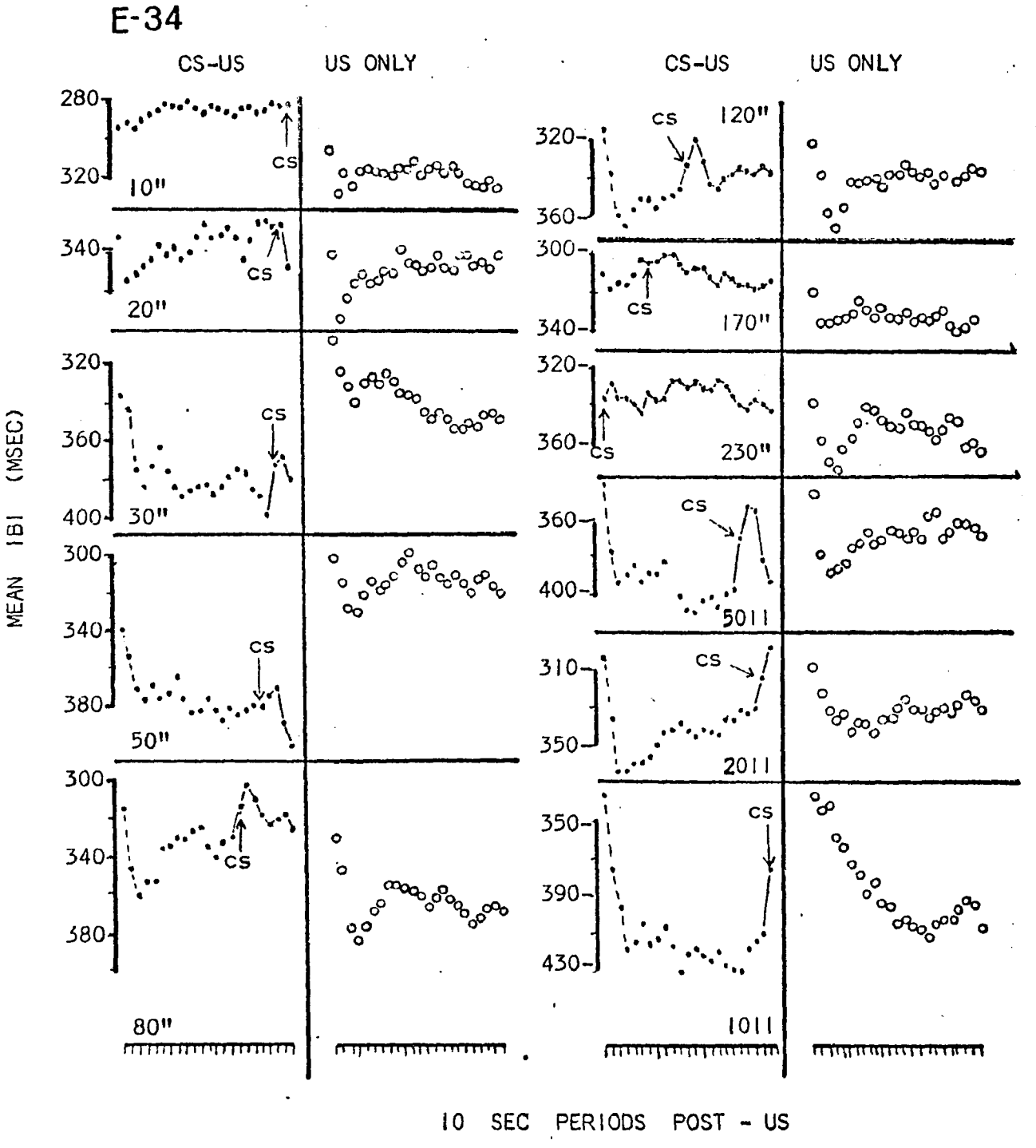

E-28
CS-US
US ONLY
10"
20"
30"
50"
80"
120"
170"
230"
50" II
20" II
10" II
CS
MEAN IBI (MSEC)
10 SEC PERIODS POST - US

Fig. 10

Fig. 11


E-34
CS-US
US ONLY
CS-US
US ONLY
MEAN IBI (MSEC)
280
320
10"
CS
320
360
120"
CS
340
20"
CS
300
340
170"
CS
320
360
400
30"
CS
320
360
230"
CS
CS
300
340
380
50"
CS
360
400
5011
CS
310
350
2011
CS
300
340
380
80"
CS
350
390
430
1011
CS
10 SEC PERIODS POST - US

E-40

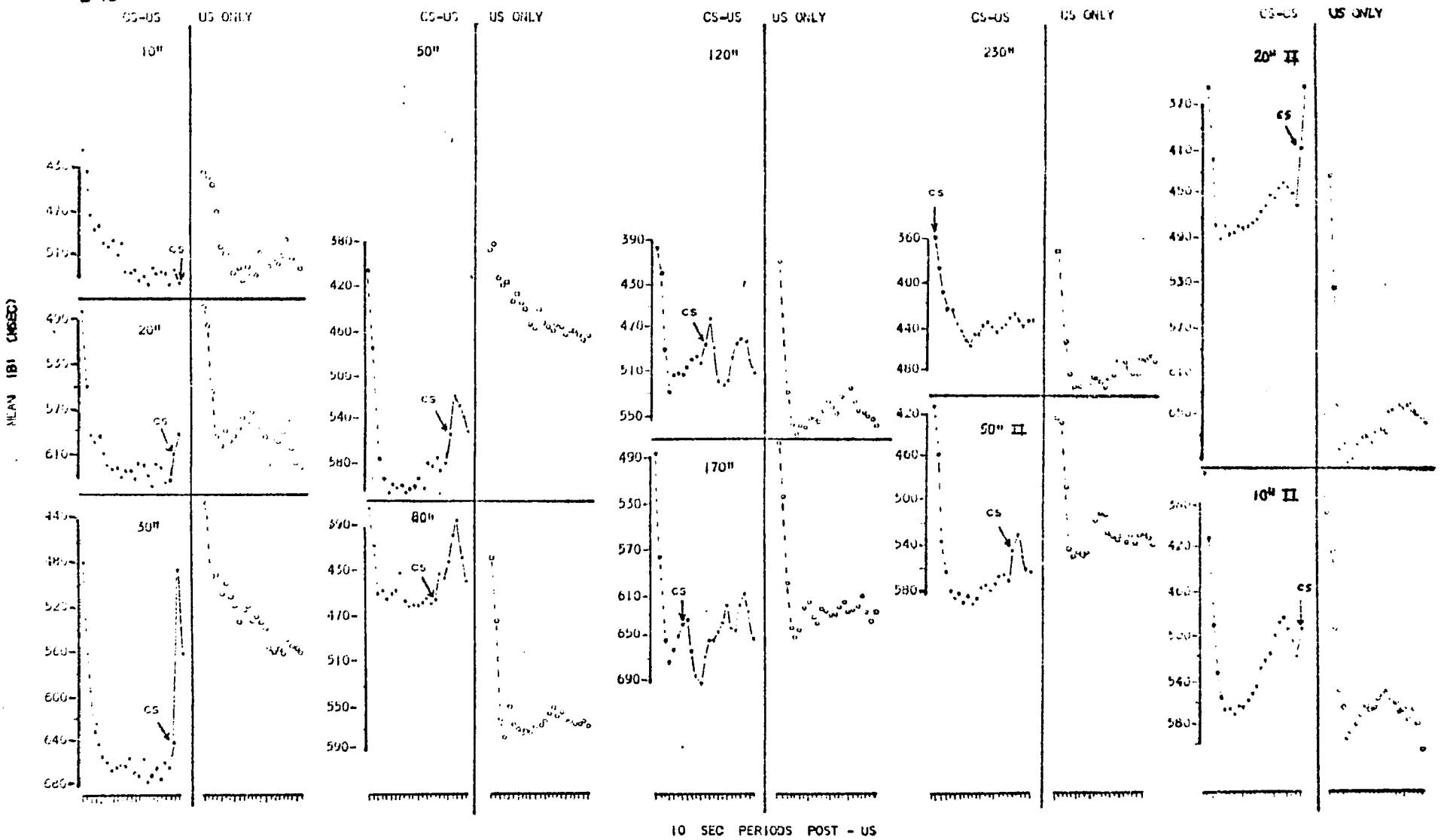

CS-US
US ONLY
10"
20"
50"
80"
120"
170"
230"
50" II
20" II
10" II
CS
MEAN IBI (MSEC)
10 SEC PERIODS POST - US

Fig. 12

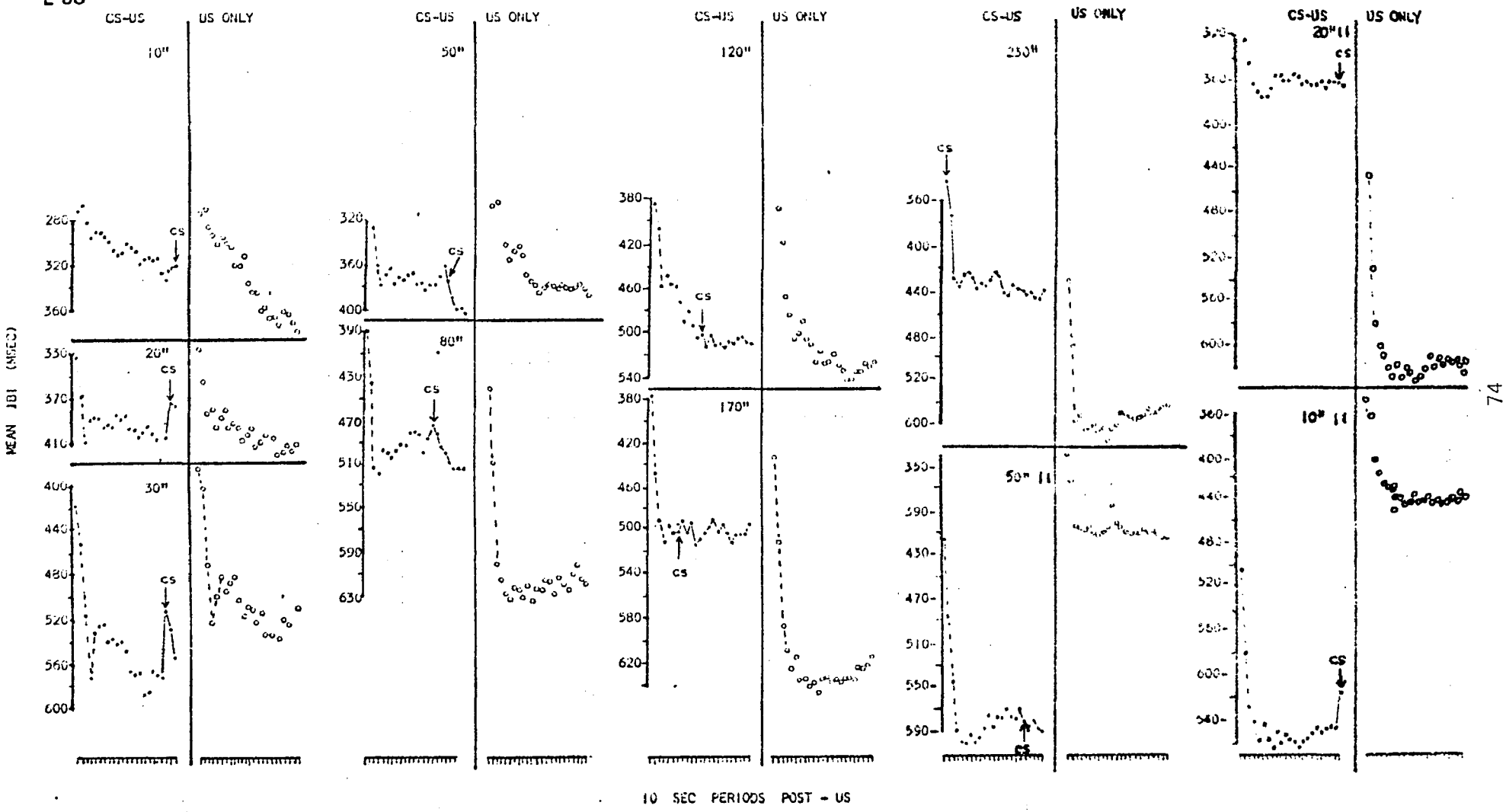

CS-US
US ONLY
10"
20"
30"
50"
80"
120"
170"
250"
20" II
10" II
50" II
CS
MEAN IBI (MSEC)
10 SEC PERIODS POST - US

Fig. 13

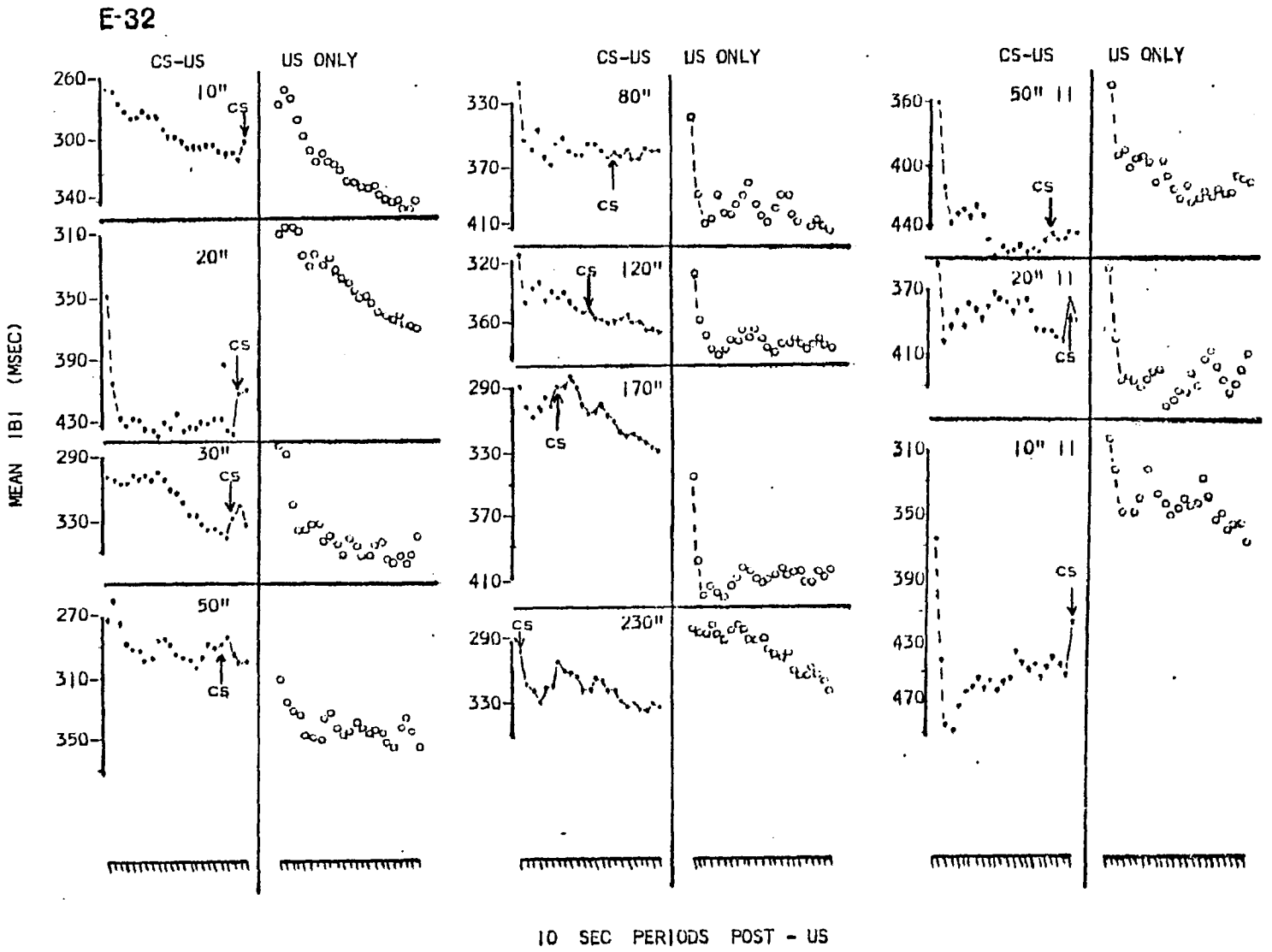

E-32
CS-US
US ONLY
10"
20"
30"
50"
80"
120"
170"
230"
50" II
20" II
10" II
CS
MEAN IBI (MSEC)
10 SEC PERIODS POST - US

Fig. 14

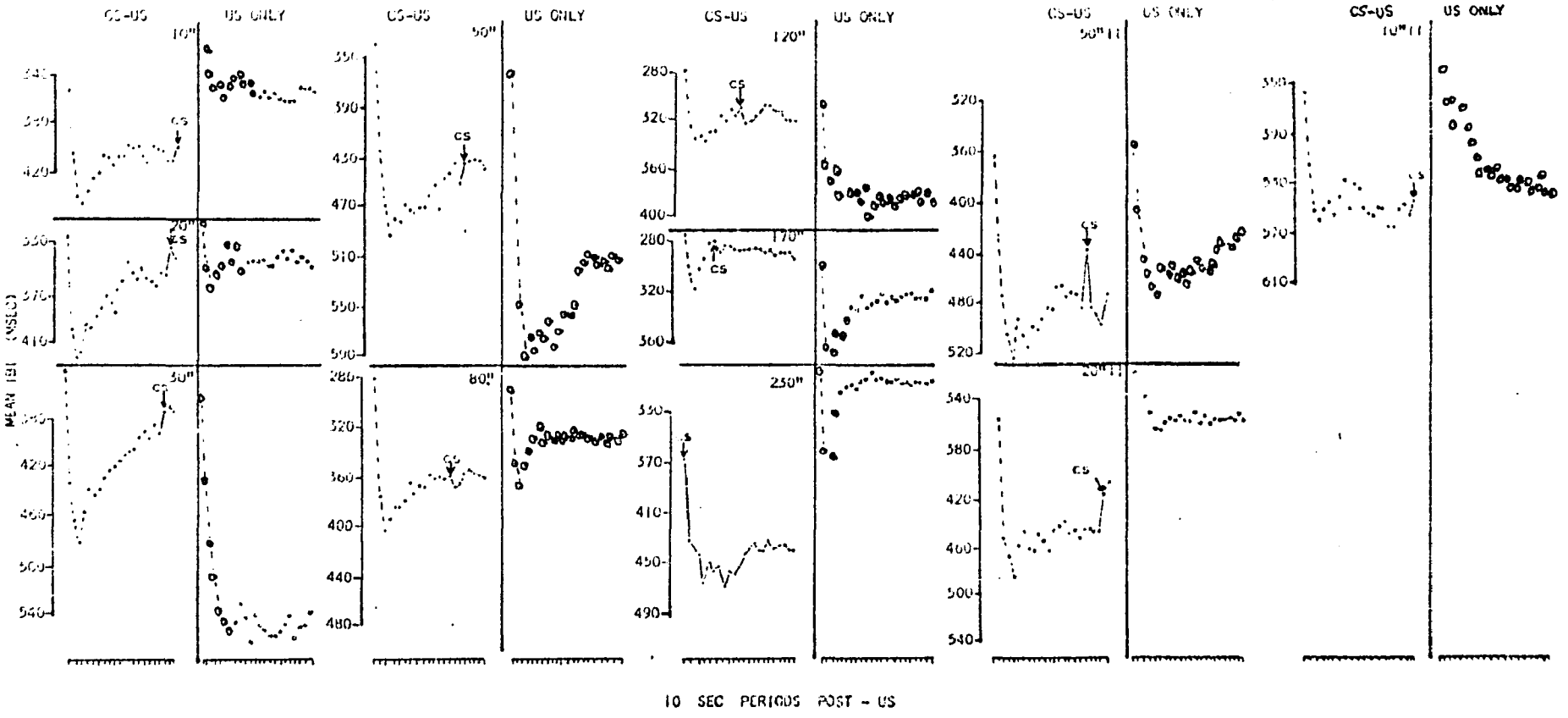

CS-US
US ONLY
10"
30"
50"
80"
120"
170"
250"
50"
20"
10"
CS
MEAN ISI (MSEC)
10 SEC PERIODS POST - US

Fig. 15

Figures 16-18. Group functions of successive mean interbeat intervals over the course of the US-US interval at each temporal location of CS (left column) and subsequent sessions where CS was omitted (right column). Each data point represents mean IBI (in msec) for 10 sec, averaged over all criterion trials for each condition, averaged over six subjects.

Fig. 16

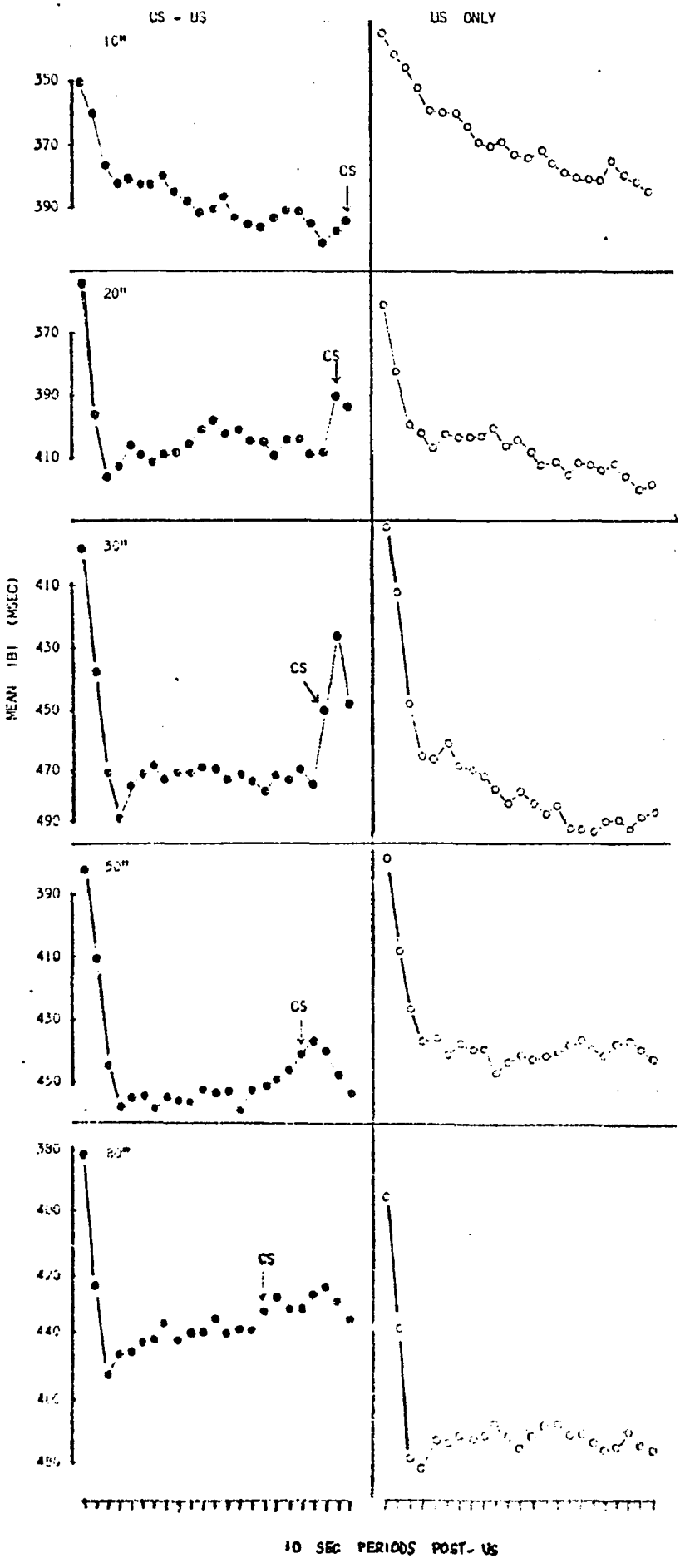

CS - US
US ONLY
10"
20"
30"
50"
CS
MEAN IBI (MSEC)
350
370
390
410
430
450
470
490
10 SEC PERIODS POST-US

Fig. 17

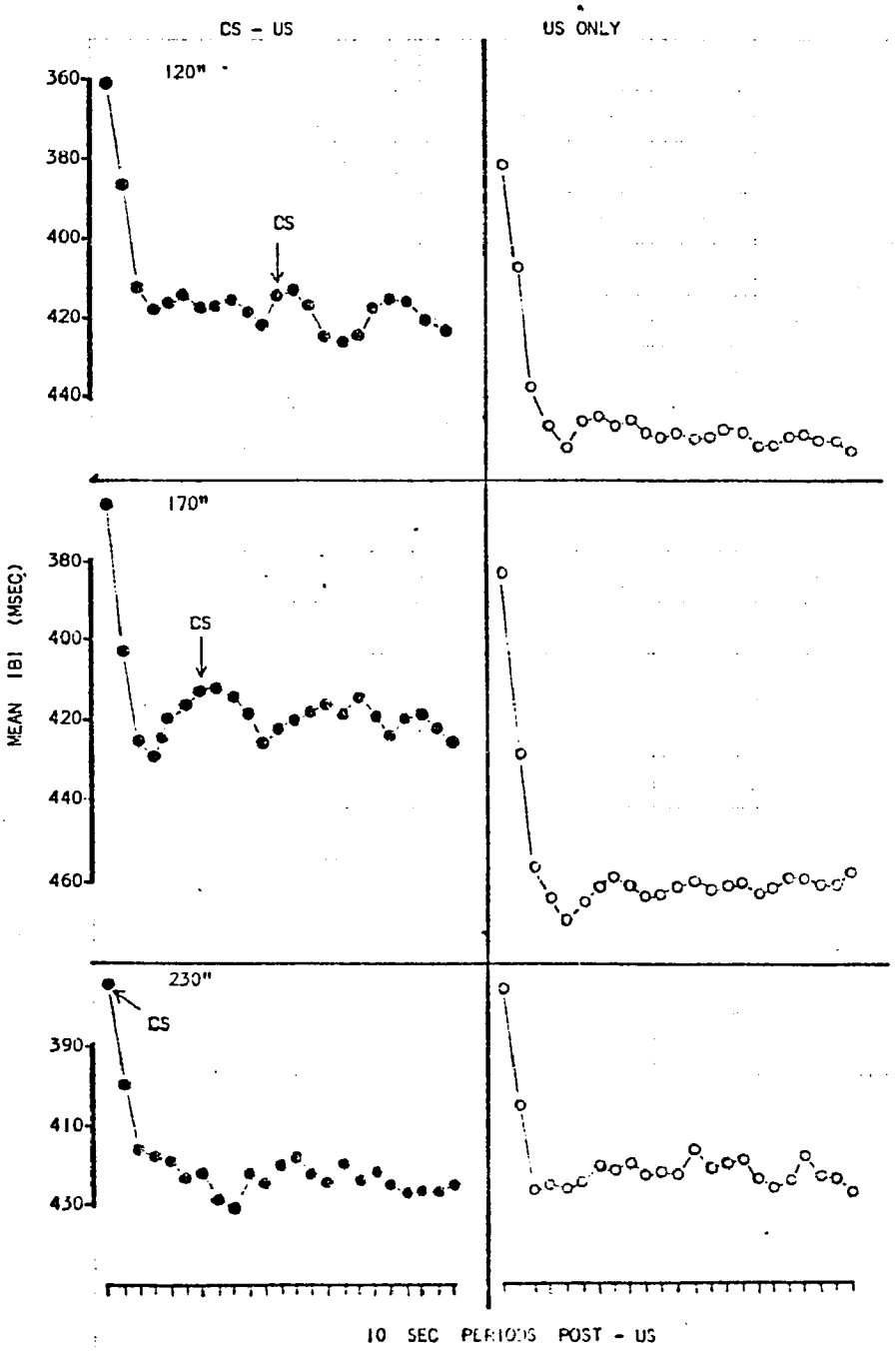
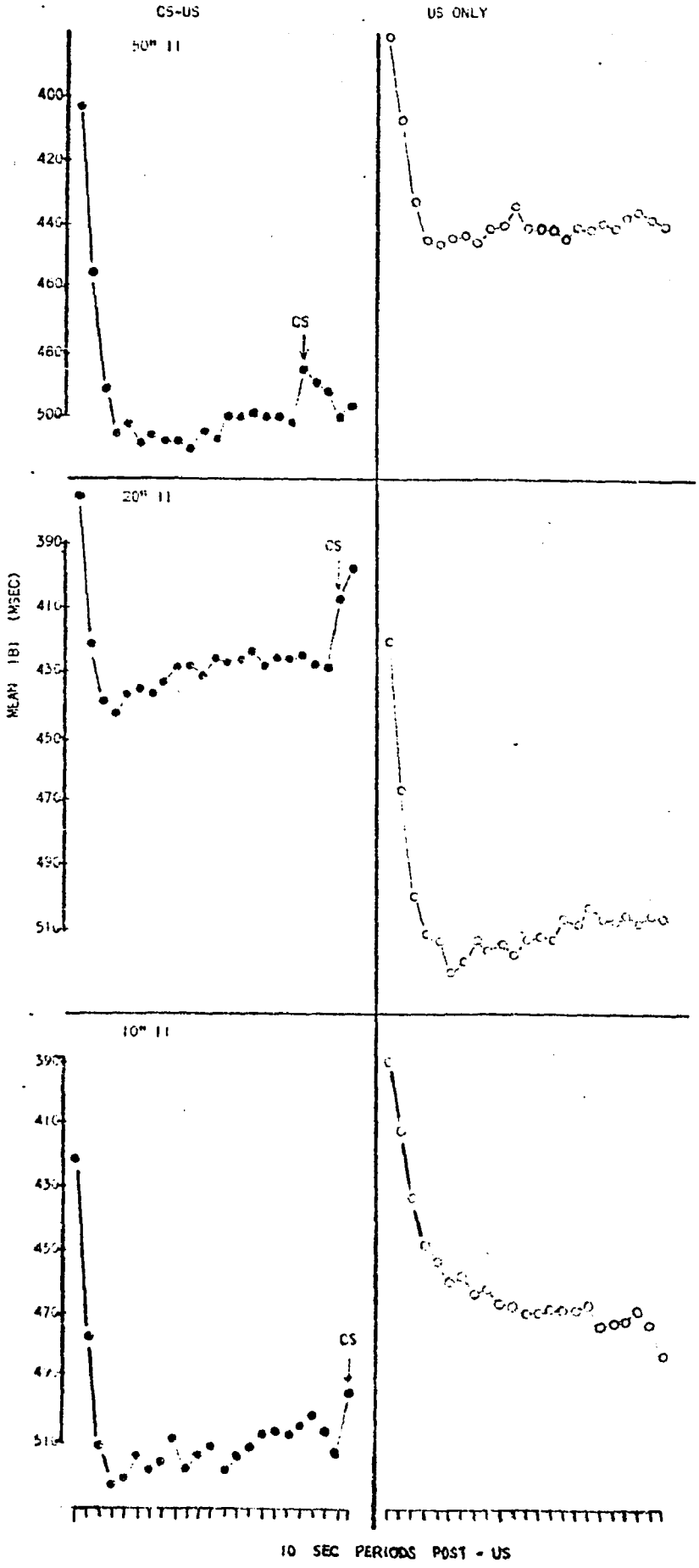

CS - US
US ONLY
120"
170"
230"
CS
CS
CS
360
380
400
420
440
380
400
420
440
460
390
410
430
MEAN IBI (MSEC)
10 SEC PERIODS POST - US

Fig. 18


CS-US
US ONLY
50th II
20th II
10th II
CS
MEAN IBI (MSEC)
400
420
440
460
480
500
390
410
430
450
470
490
510
10 SEC PERIODS POST - US

in 2 sec averaging periods at the shorter intervals, a fractionation of the overall biphasic form into smaller phasic cycles. At the 80 sec CS-US interval, the CR is subdivided into two long-duration biphasic heart rate cycles. As at the 30 and 50 sec CS-US intervals, CS onset results in HR acceleration for 20 sec followed by deceleration: acceleration is re-initiated approximately 40 sec after CS onset, again, with subsequent deceleration. The second biphasic cycle occupies the latter 40 sec of the CS-US interval. Figures 10-15, the individual-subject functions, show that the majority of subjects conform to this two-component CR pattern.

These two long-duration biphasic components of the CR are again evident at 120 sec CS-US, as seen both in the group function (Fig. 17, upper left panel), and, in the individual functions of four subjects (E-18, E-34, E-40, and E-28). This partitioning of the CR is most dramatic in E-40 (Fig. 12).

At 170 sec CS-US, there seems little consistency of heart rate trends in the CS-US interval among the subjects, apart from HR acceleration at CS onset, and lowest heart rates in the interval generally occurring within 30 sec prior to US. Additional cycles are again evident, as in E-40 (Fig. 12) who now clearly shows three long-duration cycles of acceleration followed by deceleration.

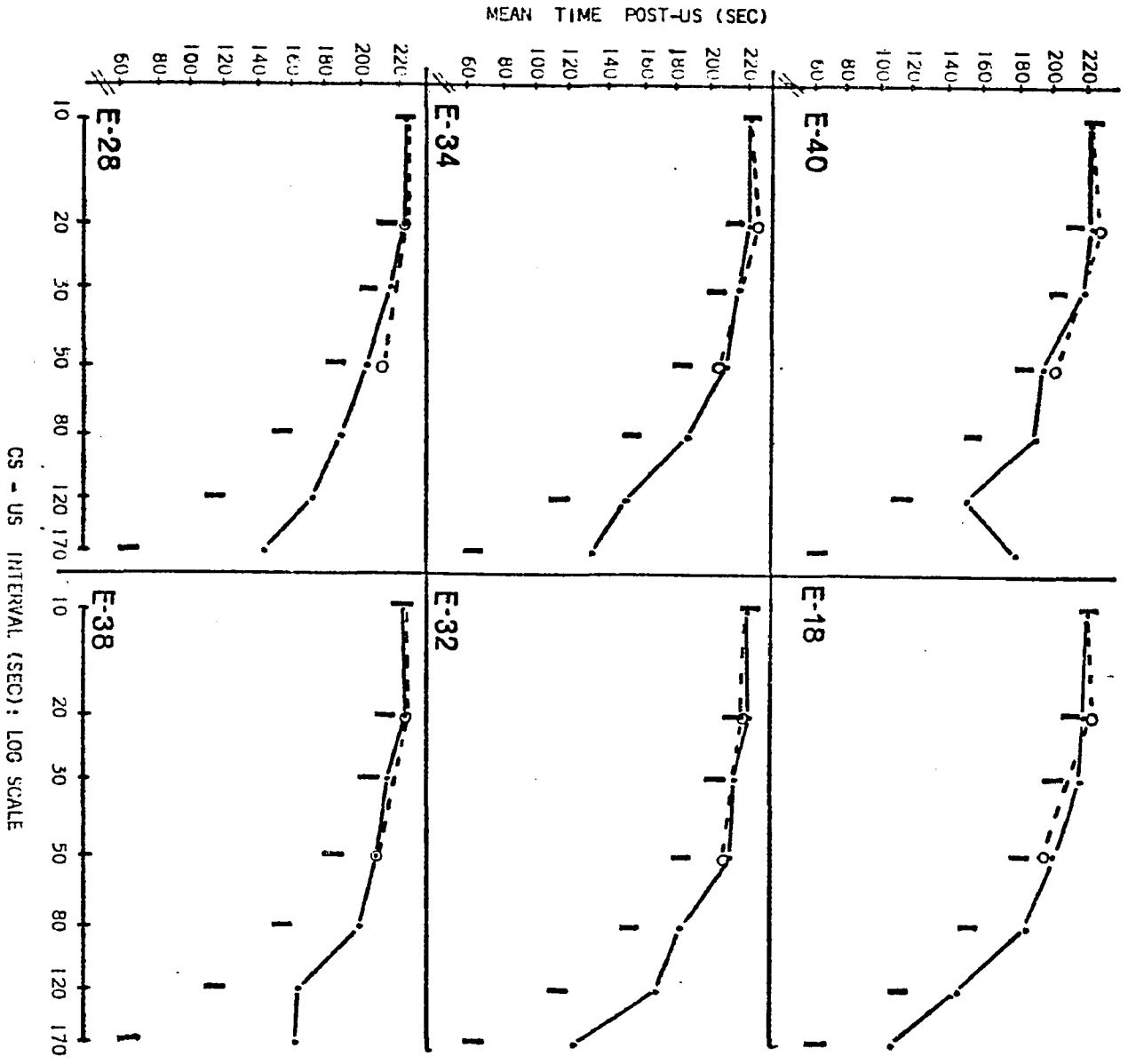
The 230 sec CS-US interval was not discussed previously with regard to CR magnitude, since the UR coincided with the CR, leading to difficulties in comparing CR magnitudes of this "backward conditioning" case with those of other CS-US intervals. Similar difficulties also arise in comparing CR form at the 230 sec interval with the shorter

intervals, since the CR cannot be distinguished from the UR. Thus, results of heart rate patterning at this interval will be reserved for the discussions of the UR and temporal patterning of heart rate during the entire US-US interval.

Over CS-US intervals from 10-170 sec, systematic changes in location of peak acceleration and deceleration of heart rate in the CS-US interval were observed. The data will be presented in two ways: (1) group functions for average location of peak change in IBI during the CS-US interval (acceleration and deceleration are differentiated) at CS-US intervals from 10-50 sec original exposure, and 50, 20, and 10 sec re-exposure,based on 2 sec averaging periods; and, (2) individual-subject functions for location of maximum change (acceleration and deceleration are not differentiated) of mean interbeat interval in the CS-US interval (10-170 sec) based on 10 sec averaging periods, for original exposure and recovery. Calculations of the latter were directly determined from the previous CR magnitude data: the location of maximum change in IBI for each trial at each CS-US interval was assessed by counting the number of 10 sec periods from CS onset until the mean IBI was maximally different from 10 sec pre-CS. These values were averaged over all criterion trials for each subject at each interval, then converted and plotted as seconds since US onset, thereby locating the CR peak in the US-US interval. Figure 19 presents, for each subject, mean location of the CR peak in the US-US interval as a function of the temporal proximity of CS to a subsequent US. Vertical bars indicate the location of CS in the US-US interval. For the 10 sec interval, the leftmost point in each function, location of peak change could not be

Figure 19. Mean location of CR peak in the US-US interval as a function of the temporal location of CS (10-170 sec CS-US). Each point represents, for each subject, mean time since the previous US to the peak (in sec) and is an average of all criterion trials at each condition. Original exposure (closed circles) and re-exposure (open circles) are shown. Vertical bars indicate the location of CS in the US-US interval. Data are based on 10 sec averaging periods.

Fig. 19


MEAN TIME POST-US (SEC)
E-40
E-18
E-34
E-32
E-28
E-38
CS - US INTERVAL (SEC): LOG SCALE

determined since the entire CR is represented by a single 10 sec average interbeat interval; therefore, a point was plotted at the midpoint of CS, since this most closely conforms to the findings based on the 10 sec averaging periods.

Figure 19 indicates consistently that as CS occurs earlier in the US-US interval, the location of peak CR occurs earlier in that interval as well. Note that the curve for E-40 at 170 sec CS-US reverses direction in that the peak of the CR occurs much closer to US. Figure 19 also reveals that although the peak CR-US interval is lengthening, it is not lengthening as rapidly as the CS-US interval, as evidenced by the increasing distance between each vertical bar (CS) and the data point above it, with longer CS-US intervals. This time between CS onset and CR peak, actually the latency to the peak CR (also termed inhibition of delay), is shown for six subjects in Figure 20. From this figure can be clearly seen that longer CS-US intervals result in longer latencies to CR peak.

Table 4 lists, for each subject at each CS-US interval: (1) location of CR peak (seconds post-US) in the US-US interval; (2) the variability of CR peak location (in standard deviation); (3) ratio of standard deviation to the CS-US interval; and, (4) latency of CR peak (seconds post-CS). Comparison of any subject's standard deviation with his ratio of SD to CS-US interval duration across intervals indicates that variability of CR peak location increased with longer CS-US intervals, and in almost constant proportion to CS-US interval duration.

Figure 21 shows the group function for location of peak accelera-

Figure 20. Mean latency to the CR peak as a function of CS-US interval duration (10-170 sec). Each point represents, for each subject, mean time (in sec) from the previous CS to the peak, and is an average of all criterion trials at each condition. Data are based on 10 sec averaging periods. Brackets around the leftmost data point indicate latency estimated from 2 sec averaging periods.

Fig. 20

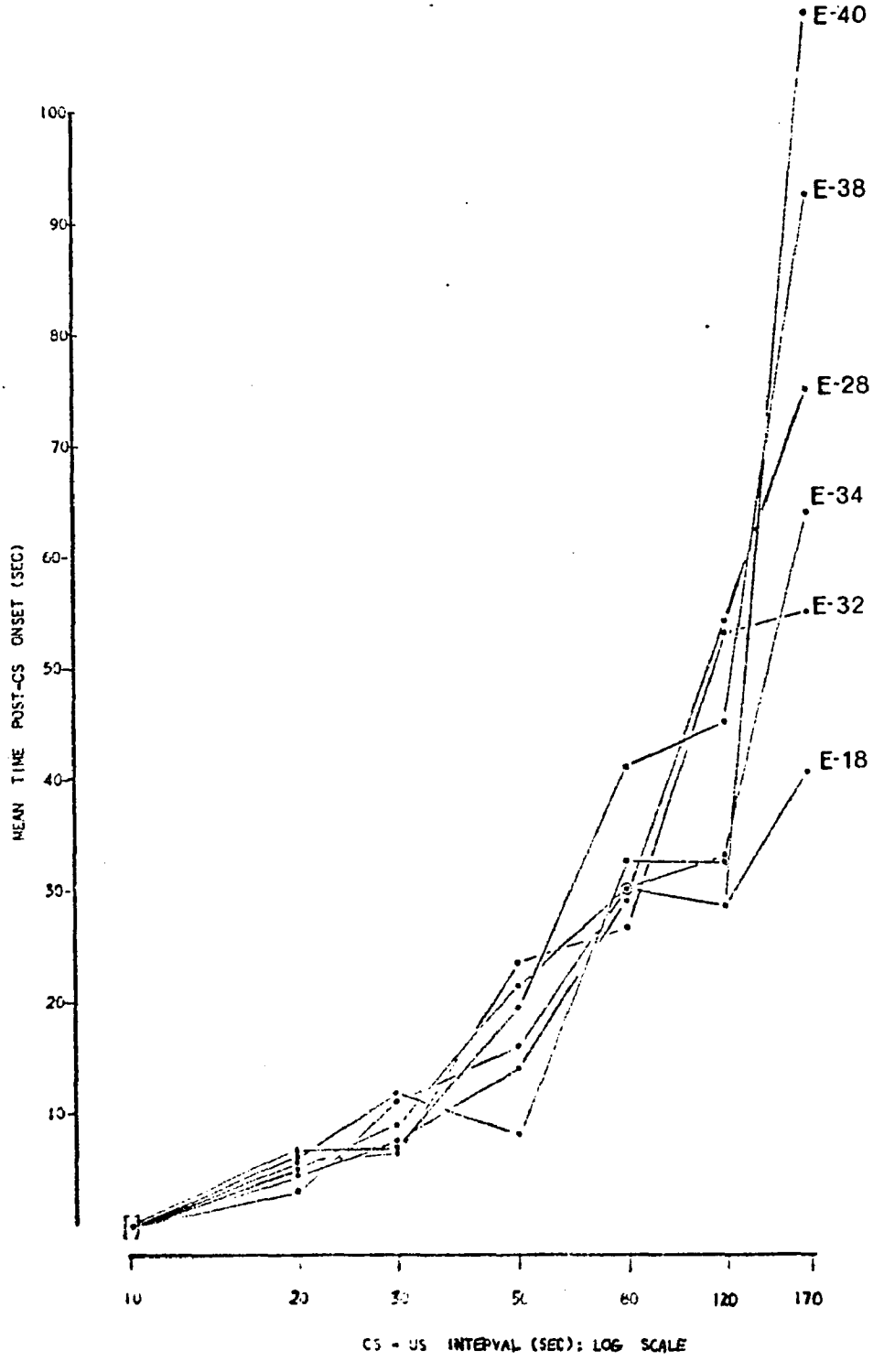

E-40
E-38
E-28
E-34
E-32
E-18
MEAN TIME POST-CS ONSET (SEC)
100
90
80
70
60
50
40
30
20
10
10
20
30
50
60
120
170
CS - US INTERVAL (SEC): LOG SCALE

Table 4

Mean location of CR peak in the US-US interval, with associated measures, as a function of CS-US interval

			CS-US Interval (Sec)							
			20	30	50	80	120	170	50 II	20 II
Subject	E-28	Location (sec post-US)	224.45	217.65	204.21	189.00	174.00	145.00	212.00	225.00
		Variability of location (SD)	5.10	9.00	13.00	20.20	37.00	44.60	15.80	5.10
		SD/CS-US interval	.26	.30	.26	.25	.30	.26	.32	.26
		Latency (sec post-CS)	4.50	7.70	14.20	29.00	54.00	75.00	22.00	5.00
	E-34		225.00	219.10	211.50	190.00	153.00	134.00	204.50	228.89
			5.10	7.70	11.80	23.30	34.70	54.70	9.90	3.20
			.26	.26	.24	.29	.29	.32	.20	.16
			5.00	9.10	21.50	30.00	33.00	64.00	14.50	8.89
	E-40		226.30	221.80	198.30	192.80	152.50	182.10	203.69	229.09
			5.00	3.90	8.40	19.30	35.50	49.50	13.80	3.00
			.25	.13	.17	.24	.29	.29	.28	.15
			6.30	11.80	8.30	32.80	32.50	112.10	13.69	9.09
	E-38		226.80	216.80	209.50	201.10	165.30	162.50	209.50	226.47
			4.80	8.20	12.10	25.60	39.30	48.30	13.90	4.90
			.24	.27	.24	.32	.32	.28	.28	.25
			6.80	6.80	19.50	41.00	45.30	92.50	19.50	6.47
	E-32		225.80	216.50	213.60	186.70	173.30	125.30	210.95	224.00
			5.10	7.50	17.50	22.90	42.20	49.10	14.50	5.00
			.26	.25	.35	.28	.35	.29	.29	.25
			5.80	6.50	23.60	26.70	53.30	55.30	20.95	4.00
	E-18		223.10	221.10	206.00	190.00	148.80	110.00	203.00	226.00
			4.90	8.30	13.10	27.20	26.30	42.80	16.30	5.00
			.25	.28	.26	.34	.22	.25	.33	.25
			3.10	11.10	16.00	30.00	28.80	40.00	13.00	6.00

Figure 21. Group functions for mean location of peak acceleration (circles) and deceleration (squares) in the US-US interval as a function of the temporal location of CS (10 - 50 sec CS-US). Each data point represents mean time (in sec) from the previous US, and is an average of all criterion trials at each condition, averaged over six subjects. Original exposure (filled data points) and re-exposure (open data points) are shown. Vertical bars indicate the location of CS in the US-US interval. Data are based on IBIs in 2 sec averaging periods.

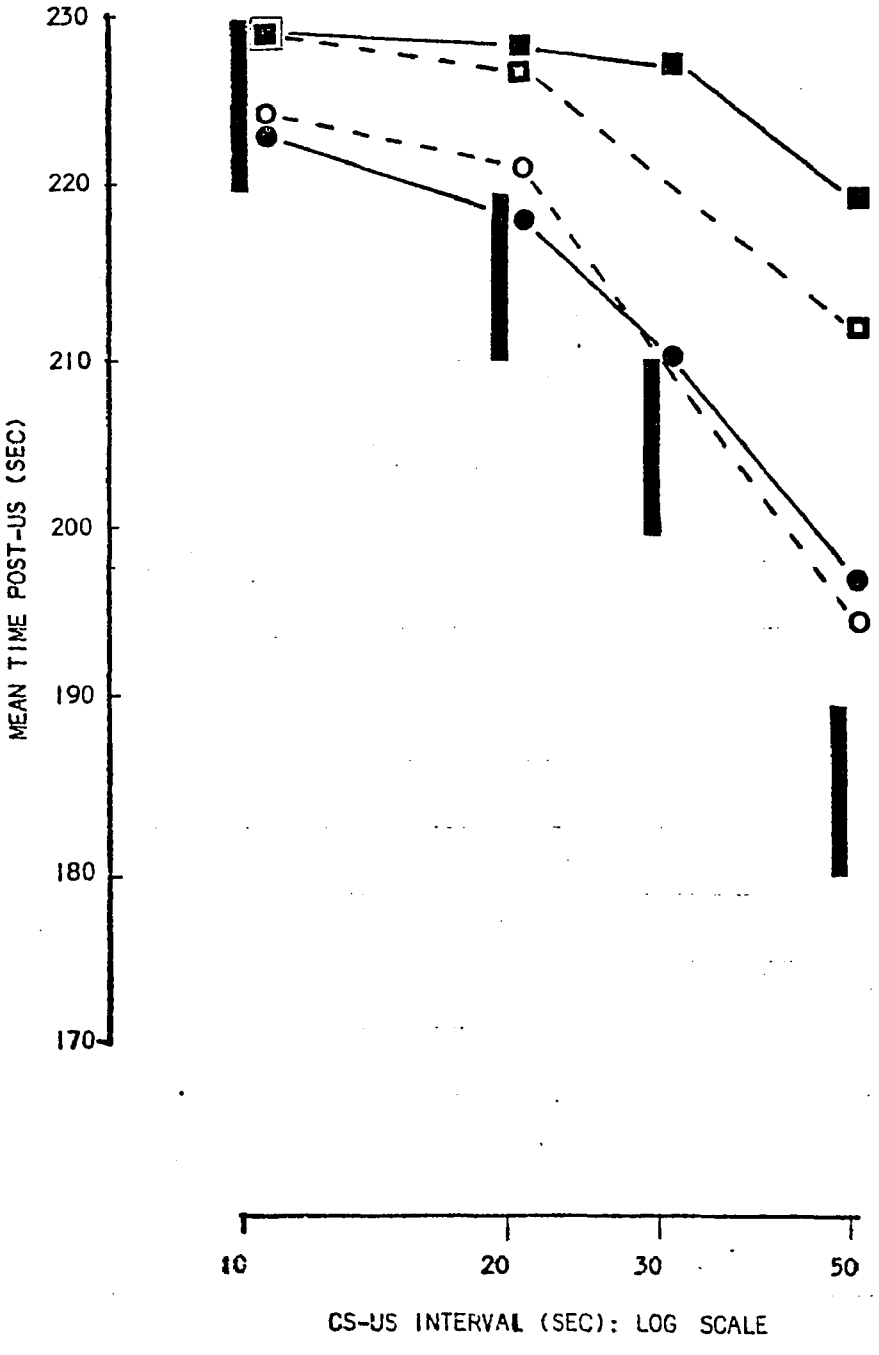
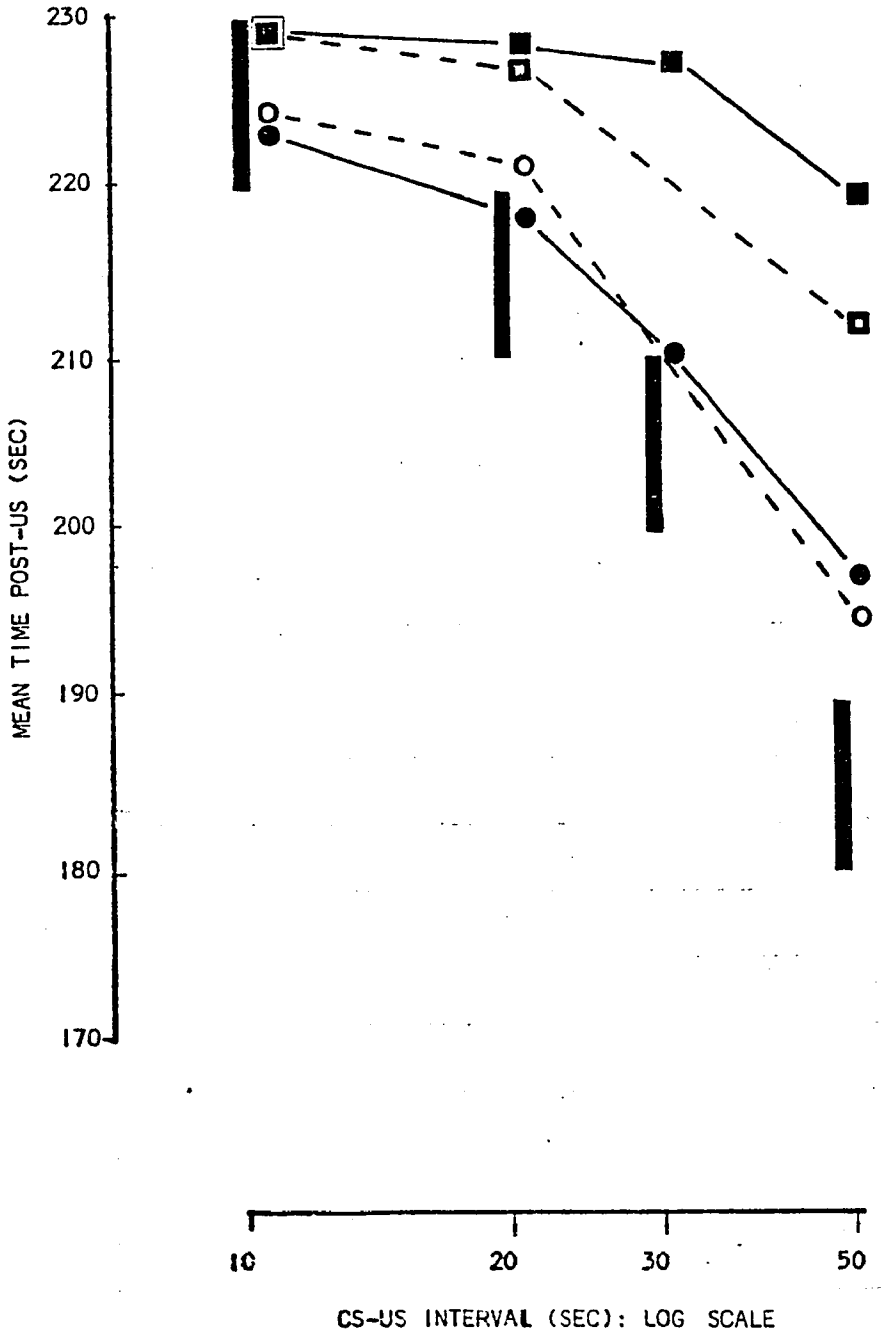

230
220
210
200
190
180
170
MEAN TIME POST-US (SEC)
10
20
30
50
CS-US INTERVAL (SEC): LOG SCALE

Fig. 21


230
220
210
200
190
180
170
MEAN TIME POST-US (SEC)
10
20
30
50
CS-US INTERVAL (SEC): LOG SCALE

tion (circles) and deceleration (squares) of the CR based on 2 sec averaging periods for original exposure of CS-US intervals from 10-50 sec (filled data points), and re-exposure of 50, 20, and 10 sec CS-US (open data points). Over the original CS-US intervals of 10-50 sec, latency to peak change in IBI, and also, the interval between peak IBI and US onset increases. Location of maximum IBI (deceleration) occurs progressively earlier in the CS-US interval over these first four intervals, though its rate of change is not as great as changes in the location of peak acceleration.

Re-exposure

After subjects experienced CS-US intervals from 10-230 sec, they were re-exposed to CS-US intervals of 50, 20, and 10 sec, in that order for all six subjects. The re-exposure intervals are designated by Roman numeral II.

At 50 sec CS-US II, Figures 4-9 (open circles) reveal that only E-40 and E-34 display CRs resembling their original forms: both subjects closely match their original acceleration and deceleration, and also display less variability (i.e., smoother curves with fewer reversals). Subject E-18 and E-32's functions at 50 sec II only resemble their original functions in the biphasic HR pattern during CS; their HR patterning during the trace interval shows irregular cycles with no obvious trends, both in original and re-exposure. E-28 and E-38 show no recovery of CR form at any segment of the 50 sec CS-US interval, nor do they show any discernible conditioned response.

The CR functions for 20 sec CS-US II in Figures 4-9 (open circles) again reveal that only E-40 and E-34 recovered their original CR form.

Two clearly defined biphasic cycles are again evident for E-34 at this interval: one cycle occurs during CS, and the other begins at CS offset. E-32's CR form at 20 sec II (Fig. 8, open circles) is less variable than the original response, with peak change in IBI better controlled by the CS-US interval; i.e., the peak change occurs in the middle of the interval. The location of maximum IBI (deceleration) occurs at the end of the CS-US interval: the mean IBI at this point equals that during 2 sec pre-CS.

In contrast with original exposure at 20 sec CS-US, the group at 20 sec II (Fig. 18) reveals a monotonic HR acceleration until US onset. This acceleratory CR is strongly evident in the individual functions (in 10 sec averaging periods) of E-34, E-40, and E-18 (Figs. 11, 12, and 15, respectively).

The 10 sec CS-US II interval again shows the most consistency of CR forms among the subjects. Five subjects show a single biphasic cycle (Figures 4-9, open circles). For four subjects, the peak IBI (acceleration) occurs closer to CS onset than at 20 sec II, as also seen in the group function (Fig. 18). Figure 21 shows that over the three re-exposure intervals, peaks (acceleration and deceleration) occur at progressively shorter latencies. Also, shorter latencies to peak heart rate at 20 sec II and 10 sec II were noted when compared with original exposure.

It appears, then, that parameters of the cardiac rate CR, such as temporal distribution of IBIs, and locations of maximum and minimum heart rate changed as a function of the temporal proximity of CS to US. With respect to the distribution of IBIs, a single biphasic waveform of acceleration followed by deceleration became increasingly irregular as

the CS-US interval lengthened: repetitive cyclic patterns emerged, first seen only in the functions expressed in 2 sec averaging periods, and then, at the longer CS-US intervals, in the 10 sec averaging periods.

Peaks of the CR (both acceleration and deceleration) occurred progressively further from both the preceding CS and the subsequent US. Also, variability in the location of maximum change in IBI during the CS-US interval increased in constant proportion to the duration of the CS-US interval.

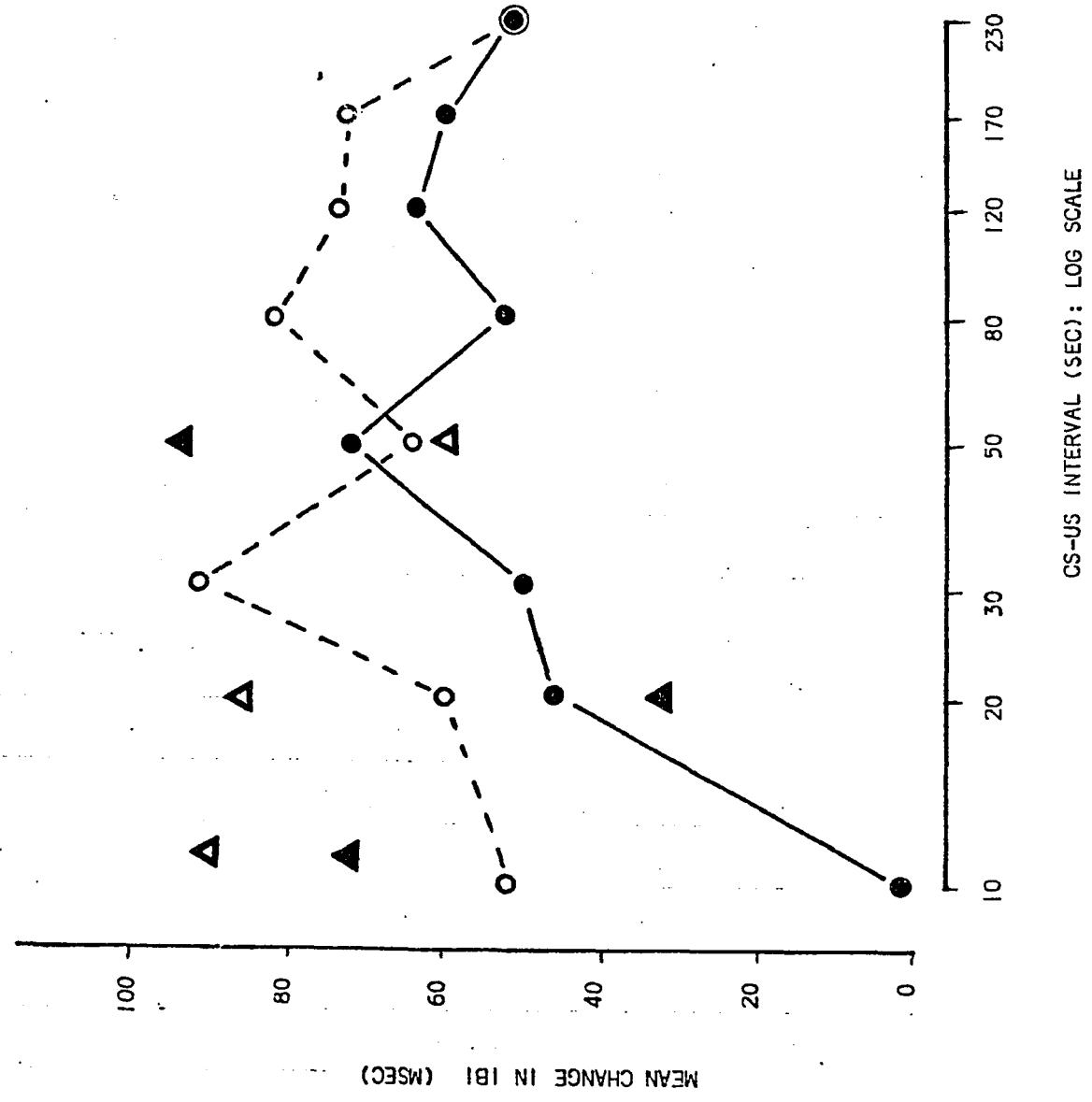
During re-exposure at 50, 20, and 10 sec CS-US intervals, recovery of original CR form was poor, and consistently evident in only two subjects. Locations of peak acceleration and deceleration were, however, systematically recovered from 50-10 sec CS-US II.

Interpolated between each set of sessions at a CS-US interval duration were two sessions in which CS was omitted, and US was delivered at periodic intervals of 230 sec. UR magnitude and patterning will now be examined in both the signalled and unsignalled conditions.

Figure 22 represents group functions for the magnitude of UR acceleration as a function of CS-US interval for sessions in which CS was presented (Filled symbols) and sessions in which CS was omitted (open symbols). Circles indicates original exposure, and triangles, re-exposure. The magnitude of acceleration was determined by subtracting mean IBI during 10 sec pre-US from the smallest mean IBI (peak of acceleration) post-US. Figure 22 indicates that in sessions where CS was presented, the magnitude of UR acceleration increased markedly until 50 sec CS-US, and then remained approximately at that level over the next four intervals. The function indicating CS omission shows that the magnitude of

Figure 22. Group functions for the mean magnitude of UR acceleration as a function of CS-US interval (10-230 sec) for sessions in which CS was presented (filled data points) and omitted (open points). Circles indicate original exposure, and triangles, re-exposure. Each data point represents a difference score and is an average of all criterion trials at each condition, averaged over six subjects. Data are based on interbeat intervals in 10 sec averaging periods. Note that for the CS-omission function, data are taken from the interpolated US-only sessions following each CS-US interval shown on the abscissa.

Fig. 22


MEAN CHANGE IN IBI (MSEC)
0
20
40
60
80
100
10
20
30
50
80
120
170
230
CS-US INTERVAL (SEC): LOG SCALE

UR acceleration increased over the first three conditions, and then was greatly decreased by the last condition (230 sec CS-US).

A comparison of the two functions in Figure 22 reveals that the magnitude of UR acceleration in the unsignalled condition generally exceeded that of the UR preceded by CS. This holds true at re-exposure of 20 and 10 sec CS-US. Re-exposure of 50, 20, and 10 sec CS-US intervals did not, however, result in consistent recovery of original values of UR magnitudes.

In the following section, anticipatory HR changes prior to CS, and in comparable measurement intervals for conditions where CS was omitted, will be examined. The pre-CS period of interest was the interval between the end of the UR (lowest point of UR deceleration after initial acceleration) and the last data point prior to CS onset. This pre-CS period was termed the post UR-CS interval. For sessions in which CS was omitted, a comparable interval was analyzed, and will be designated below as the post UR-$\overline{CS}$ interval. Thus far, each interval condition of the present study has been designated by the interval between CS onset and the subsequent US; e.g., 10 sec CS-US, 20 sec CS-US, etc. In keeping with this terminology, although HR changes during various post UR-CS (and $\overline{CS}$) intervals will be discussed below, each experimental condition will be termed, as before, by the CS-US interval. It should be clear that as CS occurs earlier in the US-US interval, thereby creating longer CS-US intervals, the post UR-CS interval becomes shorter.

Figure 23 presents the amount and direction of change in mean IBI within the post UR-CS (left side) and post UR-$\overline{CS}$ intervals (right side) as a function of the temporal location of CS, and as a function of the

Figure 23. Mean change in interbeat interval in the post UR-CS interval (left) and post UR-$\overline{CS}$ interval (right) as a function of the temporal location of CS (left, 10-170 sec CS-US). Dashed lines indicate re-exposure. Each point represents mean change in IBI (in msec) in the interval between the end of the UR and the subsequent CS (or $\overline{CS}$) onset, averaged over all criterion trials, averaged over six subjects. Negative values indicate cardiac deceleration.

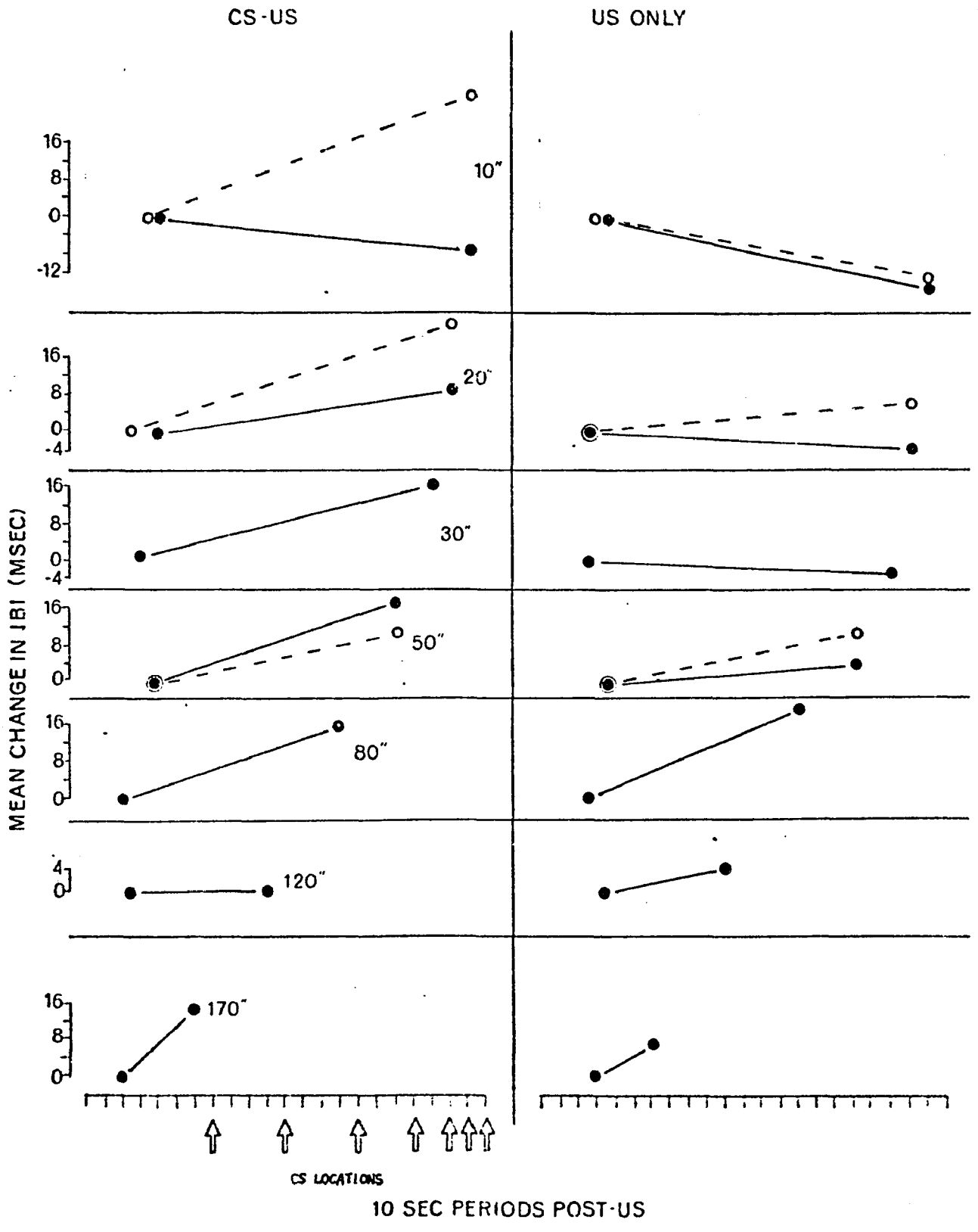

CS-US
US ONLY
MEAN CHANGE IN IBI (MSEC)
10"
20"
30"
50"
80"
120"
170"
CS LOCATIONS
10 SEC PERIODS POST-US

Fig. 23

preceding sessions at a particular temporal location of CS, when CS was omitted. Dashed lines indicate re-exposure. A comparison of the signalled and unsignalled conditions reveals the following: with CS present, change in pre-CS IBI reversed from a deceleratory trend at the 10 sec CS-US condition to an acceleratory trend over the 20-170 sec CS-US interval conditions, with the exception of 120 sec CS-US (mostly attributable to the strong deceleratory response of E-38 at this interval, evident in Fig. 13). With CS absent (Fig. 23, right side), heart rate in comparable measurement intervals did not show an acceleratory trend until later sessions (those following 50 sec CS-US). Acceleratory HR trends were noted for subsequent post UR-$\overline{CS}$ intervals.

Heart rate trends in the post UR-CS interval for re-exposure to 50, 20, and 10 sec CS-US were increasingly acceleratory for conditions where CS was presented (Fig. 23, left dashed lines, reading from the middle of the figure and moving up). By contrast, heart rate during the post UR-$\overline{CS}$ interval (Fig. 23, right side) reversed from an acceleratory trend at 50 and 20 sec ll, to a recovery of the deceleration noted in early sessions (those immediately following 10 sec CS-US 1).

Again, difficulties arise with respect to examining the post UR-CS interval at the 230 sec CS-US condition. Since the interval between US onset and the subsequent CS was 1.3 sec, during which no data were recorded, discussion of pre-CS anticipatory heart rate is impossible. However, the entire US-US function at 230 sec CS-US can be compared with that of other intervals for conditions where CS was presented and omitted.

Figure 17 (left bottom panel) shows the temporal patterning of

IBIs at 230 sec CS-US interval duration for an average of all six subjects. At this interval, heart rate after US decelerated for 80 sec (with a slight reversal at 70 sec). Comparison with all other CS-US interval functions (Figures 16-18) reveals that the longest duration of deceleration after US occurred at the 230 sec CS-US interval condition. A comparison of 230 sec CS-US, with and without CS (Fig. 17) shows clearly that post-US deceleration lasted only 30 sec when CS was omitted (right panel), as opposed to a duration of 60 sec deceleration in the previous sessions (left panel) in which CS was presented, and immediately followed US.

Pharmacological manipulations

Changes in baseline heart rate, as well as in CR and UR form and magnitude were evident as a result of ganglionic blockade by chlorisondamine, sympathetic blockade by propranolol, and parasympathetic blockade by atropine. Figures 24-27 present pre and post-drug functions consisting of successive mean IBIs (in 2 sec averaging periods) over the course of the CS-US interval for each subject at each re-determined CS-US interval. Each drug function is an average of four recorded trials (trials 3,4,7, and 8) of CS-US pairings administered after drug injections; the large quantities of data involved eliminated the possibility of recording data on every post-drug trial. The pre-drug functions are an average of the non-drug conditioning trials at each re-determined interval.

It was stated previously that atropine and propranolol were given eight trials apart within the same session, with the order reversed in

Figures 24-27. Mean pre and post-drug cardiac CRs as a function of CS-US interval (50, 20, and 10 sec ll). Each point in drug functions represents, for each subject, mean IBI (in msec) for 2 sec, averaged over four trials. Each point in the pre-drug functions represents, for each subject, mean IBI (in msec) for 2 sec, averaged over the number of pre-drug trials administered at each condition.

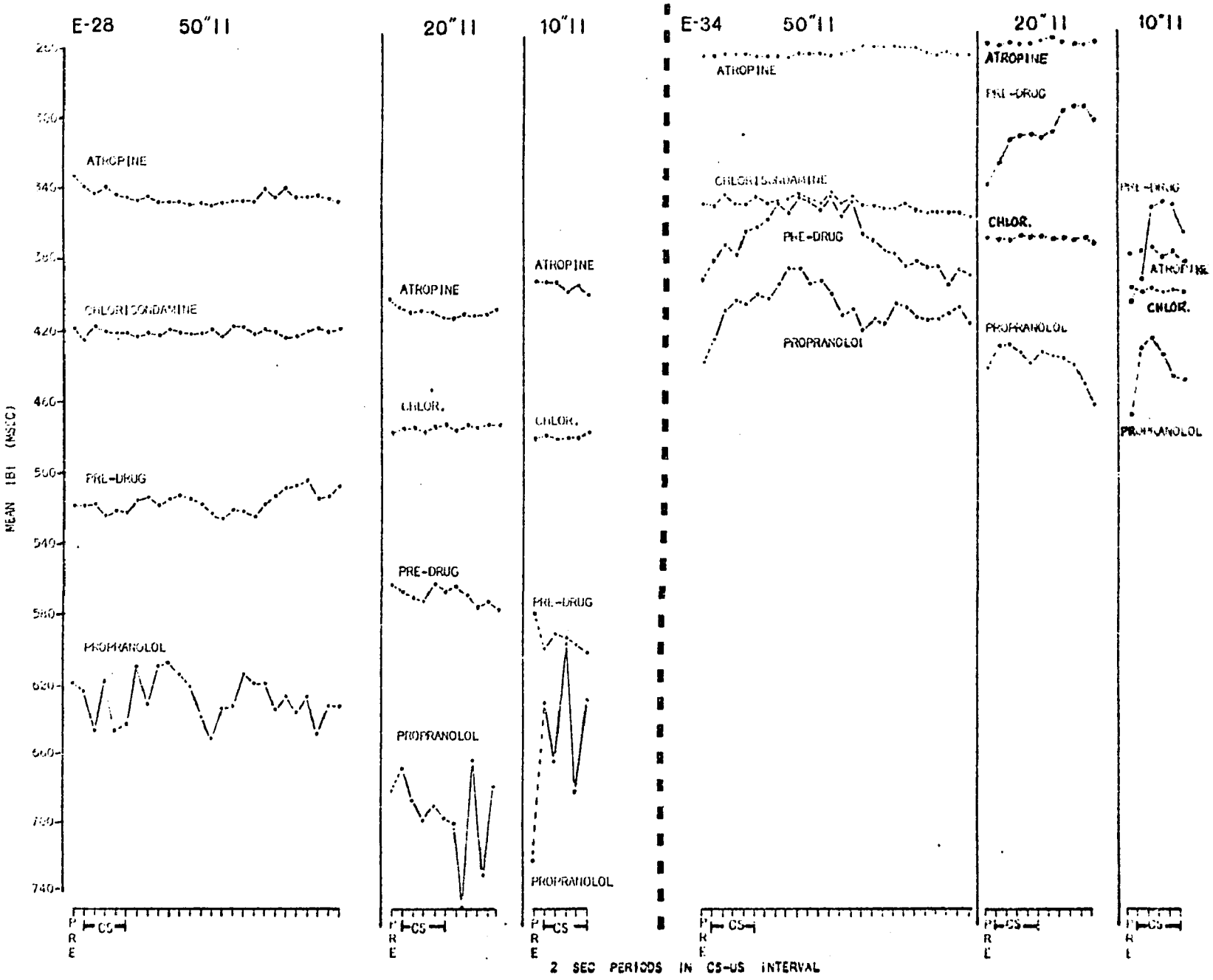

E-28
50"11
20"11
10"11
E-34
50"11
20"11
10"11
ATROPINE
CHLORISONDAMINE
PRE-DRUG
PROPRANOLOL
CHLOR.
MEAN IBI (MSEC)
340
420
460
500
540
580
620
660
700
740
PRE
CS
2 SEC PERIODS IN CS-US INTERVAL

Fig. 24

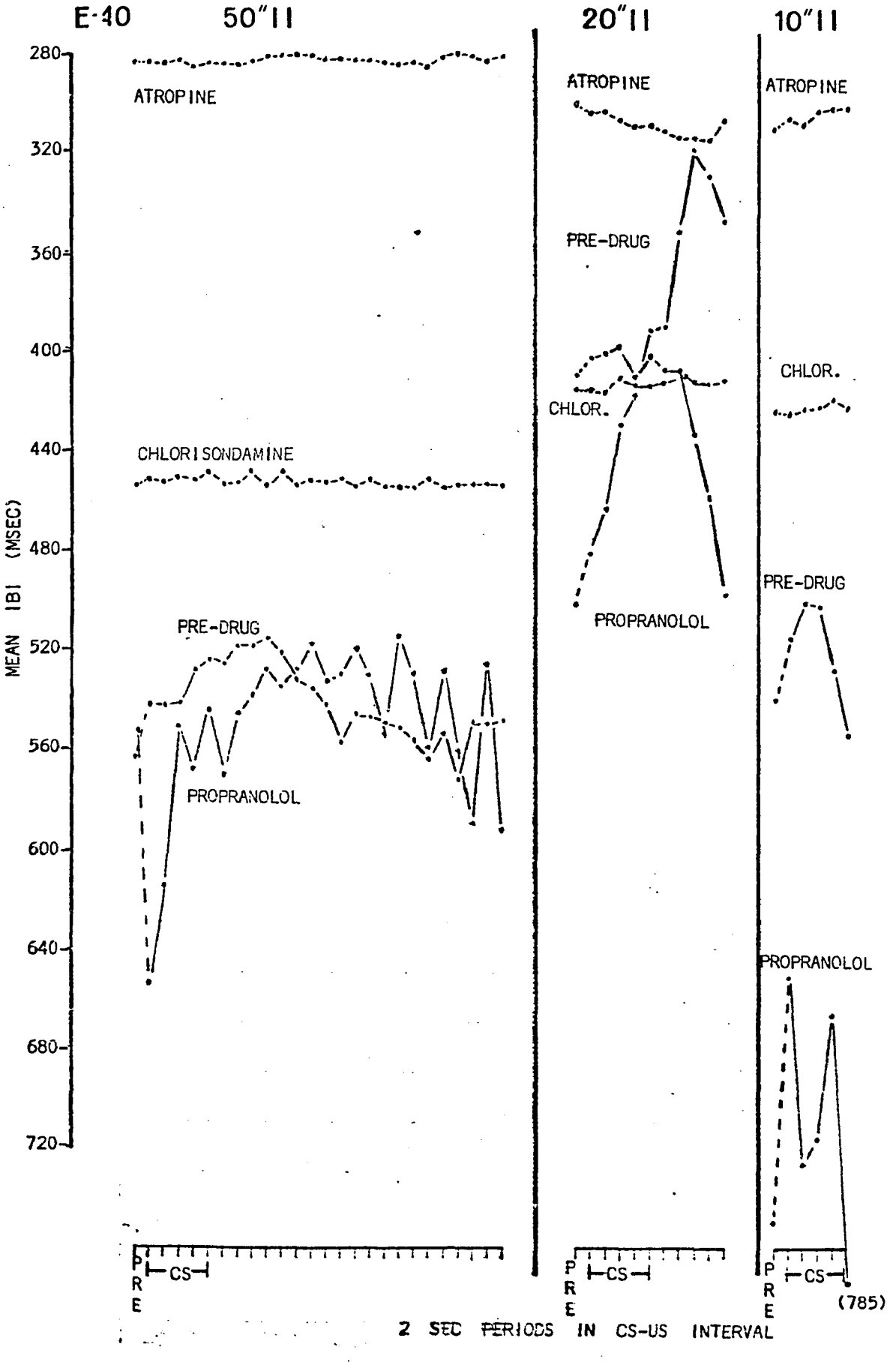
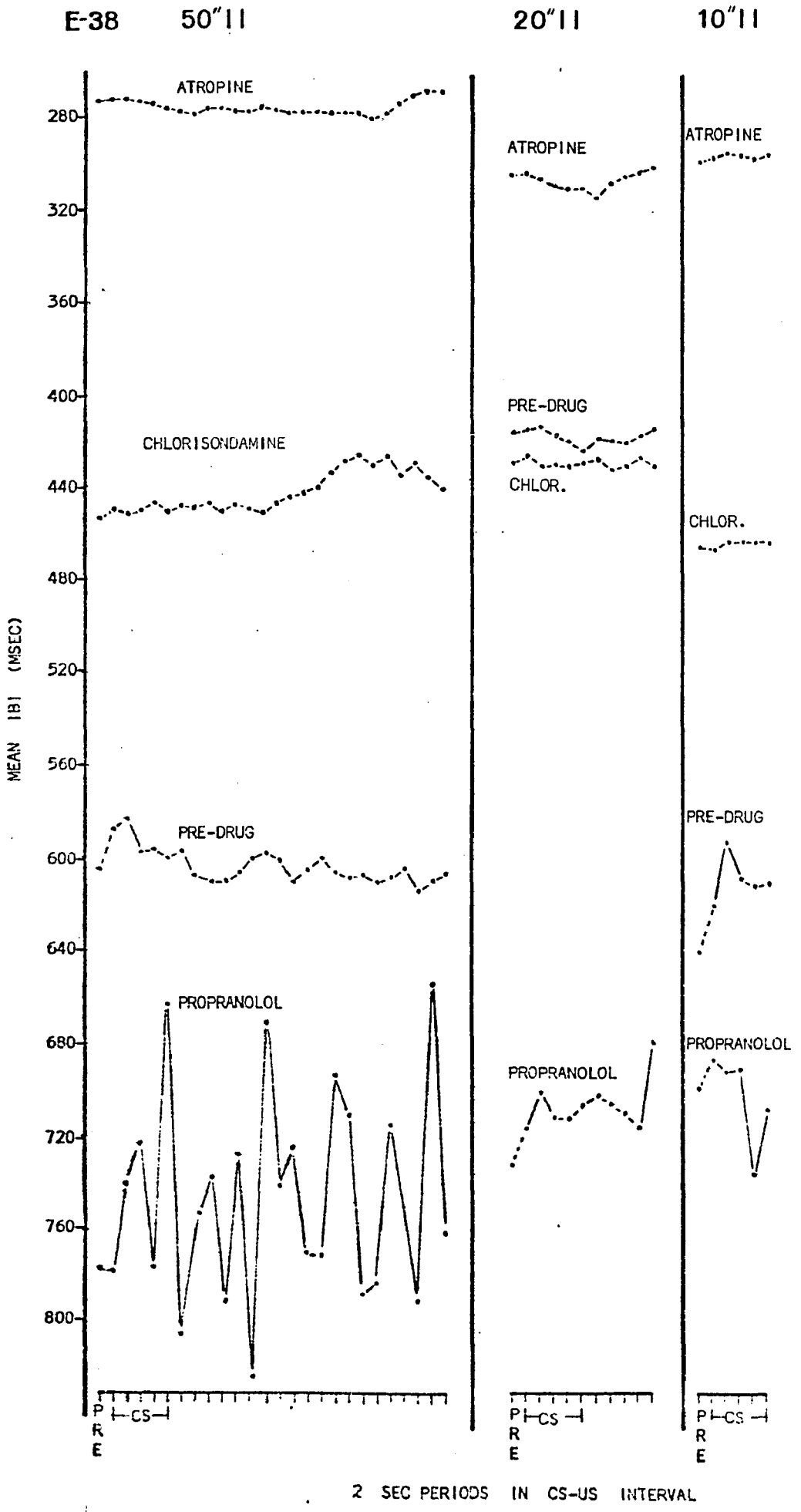

E-40
50"II
20"II
10"II
280
320
360
400
440
480
520
560
600
640
680
720
MEAN IBI (MSEC)
ATROPINE
CHLORISONDAMINE
PRE-DRUG
PROPRANOLOL
ATROPINE
PRE-DRUG
CHLOR.
PROPRANOLOL
ATROPINE
CHLOR.
PRE-DRUG
PROPRANOLOL
PRE
CS
PRE
CS
PRE
CS
(785)
2 SEC PERIODS IN CS-US INTERVAL

Fig. 26


E-38
50"II
20"II
10"II
ATROPINE
CHLORISONDAMINE
PRE-DRUG
PROPRANOLOL
CHLOR.
MEAN IBI (MSEC)
280
320
360
400
440
480
520
560
600
640
680
720
760
800
PRE
CS
2 SEC PERIODS IN CS-US INTERVAL

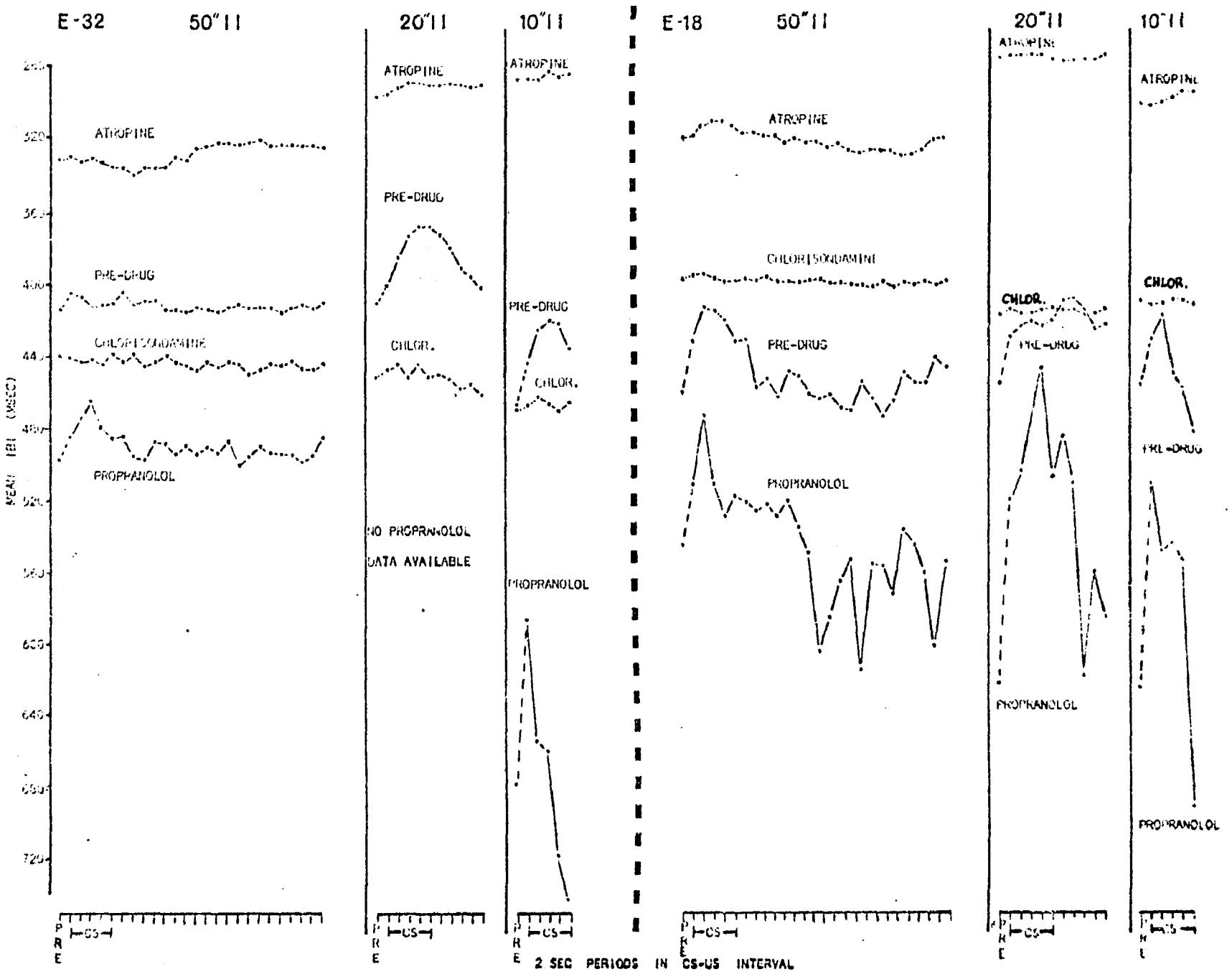

E-32
50"11
20"11
10"11
E-18
50"11
20"11
10"11
ATROPINE
PRE-DRUG
CHLOR.
PROPRANOLOL
CHLORISOQUAMINE
MEAN IBI (MSEC)
NO PROPRANOLOL
DATA AVAILABLE
PRE
CS
2 SEC PERIODS IN CS-US INTERVAL

Fig. 27

the subsequent drug session, in order to investigate the effects of adding a parasympathetic blocking agent to a sympathetic blocking agent already in the system, and vice-versa. However, because results from the second injection of each drug provided no additional information, results will be presented only from the first injection of each drug.

Effects of sympathetic, parasympathetic, and ganglionic blockade on baseline heart rate and CR form are evident from Figures 24-27. Atropine clearly raised baseline heart rate for all subjects relative to their pre-drug rates. Propranolol lowered baseline heart rate relative to pre-drug sessions in all cases but one. Chlorisondamine, in the majority of cases, raised baseline heart rate relative to both pre-drug and propranolol baseline rates, but not to the heart rate levels seen under atropine.

Figures 24-27 show that propranolol, of all drugs administered, had least effect on overall CR form. E-34 (Fig. 24) best exemplifies this result: at all re-determined intervals, the propranolol function, although occurring at lower heart rates, replicated the form of the pre-drug functions. Also, after propranolol injection, at all three re-determined CS-US intervals for this subject, peak heart rate occurred earlier in the CS-US interval than during pre-drug trials. This earlier CR peak under propranolol is most evident at the 10 sec condition where it is exhibited in all six subjects.

Although propranolol, in many cases, resulted in a CR form similar to pre-drug, increased variability was noted in some cases, as exemplified by E-40 and E-38 at 50 sec CS-US II (Figs. 25 and 26, leftmost panels). In contrast, chlorisondamine and atropine reduced pre-drug variability and also reduced the sustained acceleration and deceleration

seen in the pre-drug functions (CR functions under atropine and chlorisondamine were almost entirely flat).

Statistical adjustment of scores was suggested earlier to correct for regression of post-stimulation response levels on pre-stimulation response levels. Group covariance analysis was performed, comparing group means of peak IBI level in the CS-US interval. In this case as well, statistical adjustment of data in the comparison of CR magnitudes became necessary because the drugs also produced changes in baseline heart rate. For example, it is clear that response magnitudes under chlorisondamine and atropine are greatly reduced relative to pre-drug CR magnitudes (Figures 24-27), whereas large changes in heart rate appear under propranolol. Since these results could have been predicted from post-drug HR levels by the law of initial value, one could conclude that observed changes in CR mangitude under the drugs were due only to induced changes in HR level. On the other hand, it is also possible that these changes in CR magnitude resulted from the drugs' blocking of that portion of the autonomic nervous system which mediates the CR. In order to determine the extent of the LIV in the present data, pre-drug correlation and regression coefficients were computed relating mean minimum IBI (peak of acceleration) during the CS-US interval to both mean pre-CS IBI (during 2 sec pre-CS), and to mean maximum IBI (peak of deceleration) after the minimum, for each subject at each re-determined interval. These coefficients are presented in Table 5. In almost all cases the regression and correlation coefficients are significantly large at the .05 level. The law of initial value is clearly evident in these data. The statistical question took the following form: based

Table 5

Pre-drug regression (b) and correlation coefficients (r) of:

1) maximum CR acceleration (Y) on pre-CS mean IBI (X)= ACC

2) maximum CR deceleration (Y) on preceding maximum acceleration (X)= DEC

			CS-US Interval (Sec)					
			50 11		20 11		10 11	
			r	b	r	b	r	b
Subject	E-28	ACC	.83	.79	.91	.72	.93	.82
		DEC	.70	.92	.70	1.29	.73	1.06
			(28)[a]		(28)		(28)	
	E-34		.82	.87	.75	.37	.85	.66
			.74	1.14	.89	1.02	.92	.97
			(28)		(25)		(28)	
	E-40		.57	.24	-.13	-.07	.70	.40
			.47	1.06	.82	1.32	.67	1.18
			(24)		(18)		(28)	
	E-38		.78	.65	.99	1.00	.37	.31
			.75	.80	.99	1.03	.61	.73
			(28)		(25)		(28)	
	E-32		.96	.90	.55	.67	.60	.49
			.95	1.11	.68	.65	.84	1.12
			(28)		(24)		(28)	
	E-18		.92	.76	.86	.42	.82	.47
			.84	1.30	.91	1.63	.79	1.48
			(30)		(27)		(26)	

[a] Numbers in parentheses indicate the number of pre-drug conditioning trials on which the coefficients are based

on the regression of post on pre-stimulation response levels pre-drug, could one have expected CR levels as changed after drug injections as those observed by taking baseline HR levels into account?

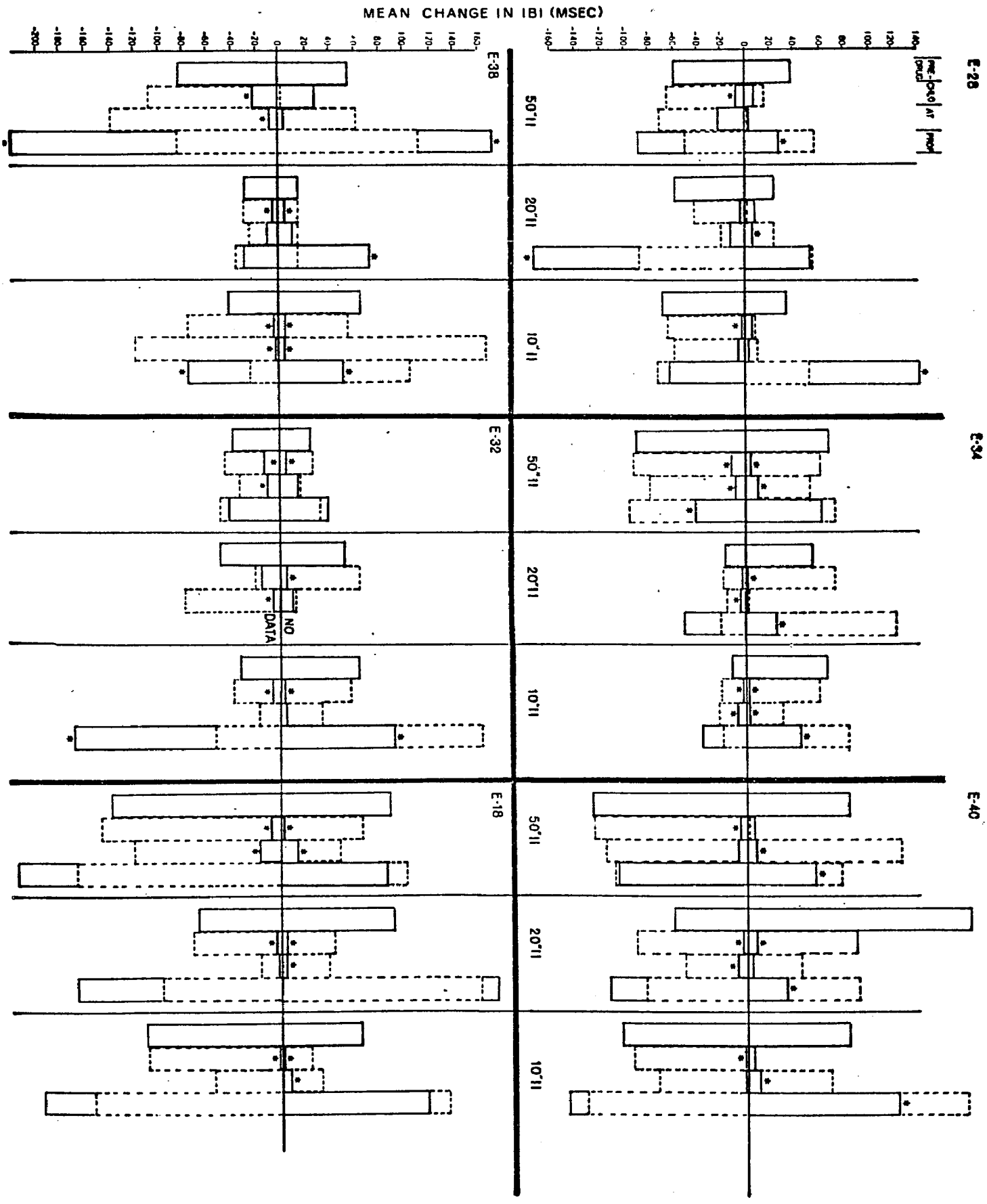
As a possible answer, regression techniques were again employed. Predictions of CR magnitudes (based on the pre-drug CR) were computed for post-drug pre-CS heart rate and compared with CR magnitudes actually obtained after each drug injection. Analysis of covariance was not performed in this case in favor of a regression technique that does not require homogeneity of regression (equality of slopes) between the pre-drug and post-drug conditions, as this assumption was violated (see Pigache, Graham, & Freedman, 1976, for a detailed description). The present regression technique differs from the analysis of covariance performed previously in five ways: (1) individual-subject rather than group data were statistically treated; (2) both components (acceleratory and deceleratory) of the biphasic CR were analyzed separately; (3) the analysis was based on mean IBIs from 2 sec averaging periods to differentiate the two components of the cardiac rate CR at the shorter CS-US intervals; (4) scores were not adjusted: predicted scores were compared against obtained scores; and, (5) pre and post-drug regression lines were not pooled since homogeneity of regression was violated.

The regression analysis was performed in the following manner: for each subject at each re-determined interval, a regression line was computed for acceleratory and deceleratory components of the mean cardiac CR from his pre-drug conditioning trials. Post-drug CR IBI levels were predicted from each regression line by standard prediction technique

(Snedecor & Cochran, 1967). Based on the difference between predicted and obtained values, and the variance associated with each, it was determined by t-tests (formula in Appendix B) if the obtained post-drug values fell outside the confidence belts established around each pre-drug regression line. For each obtained post-drug mean that fell outside, it was concluded that the drug significantly changed the peak IBI level at that particular portion of the cardiac CR being evaluated (acceleratory or deceleratory). If the value fell inside the confidence belt, it could not be determined whether the observed change in post-drug peak IBI level was attributable to altered baseline heart rate, or to the selective blocking effect of the drug on that portion of the CR.

Figure 28 shows, for each subject at each re-determined interval, magnitude of acceleratory and deceleratory components of the CR before and after drug injection. Pre-drug magnitudes are shown as the leftmost bar within each CS-US interval panel: bars rising above the zero line indicate the mean magnitude of the acceleratory component, and bars descending directly below indicate the mean magnitude of the deceleratory component. Obtained mean magnitudes of each CR component are depicted by solid bars for chlorisondamine, second bar in each set, atropine, third bar, and, lastly, propranolol, fourth bar. Although statistical analysis was performed on IBI levels, Figure 28 depicts difference scores, since these latter are perhaps more easily conceptualized as representing response magnitudes. It will be recalled that regression analysis yields identical results in tests of significance regardless of whether dependent measures are expressed as levels or difference scores (Benjamin, 1963; Myers & Honig, 1969). Also shown in Figure 28

Figure 28. Mean magnitude (in difference scores) of acceleratory and decelerator components of the CR before and after drug injection, for CS-US intervals of 50, 20, and 10 sec. Bars in each set of four represent the following, from left to right: CR magnitude for pre-drug, chlorisondamine, atropine, and propranolol. Bars above the zero line indicate magnitude of acceleration; bars below indicate magnitude of deceleration. Predicted values are depicted by dashed lines, obtained values by solid lines. Asterisks indicate statistically significant differences ($p < .05$) between predicted and obtained values. Data are based on IBIs (in msec) in 2 sec averaging periods.


MEAN CHANGE IN IBI (MSEC)
E-38
E-28
50'11
20'11
10'11
E-32
E-34
NO DATA
E-18
E-40

are CR magnitudes (dashed lines) predicted by the pre-drug regression lines from the pre-CS HR level obtained under each drug condition. Asterisks indicate a significant difference between predicted and obtained values for the .05 level of probability.

Statistical significance was not reached in many cases, possibly owing both to the very few recorded trials after each drug injection (four), and, to the need for an extremely strong drug effect to reach significance when pre-CS values after drug injection were never reached pre-drug, resulting in wide confidence belts at that portion of the regression line (Myers & Honig, 1969).

Figure 28 shows that chlorisondamine and atropine attenuated the magnitudes of both acceleratory and deceleratory components of the CR relative to predicted magnitudes in every case but two (for E-40 and E-38 at 50 sec II, facilitation of the acceleratory component was found under chlorisondamine). In some cases, although they did not reach significance, nevertheless the differences between predicted and obtained CR magnitudes were large: e.g., note the strong atropine effect for E-28's deceleratory component at 50 sec II and 10 sec II, and the atropine effect on the acceleratory component for E-38 at 50 sec II.

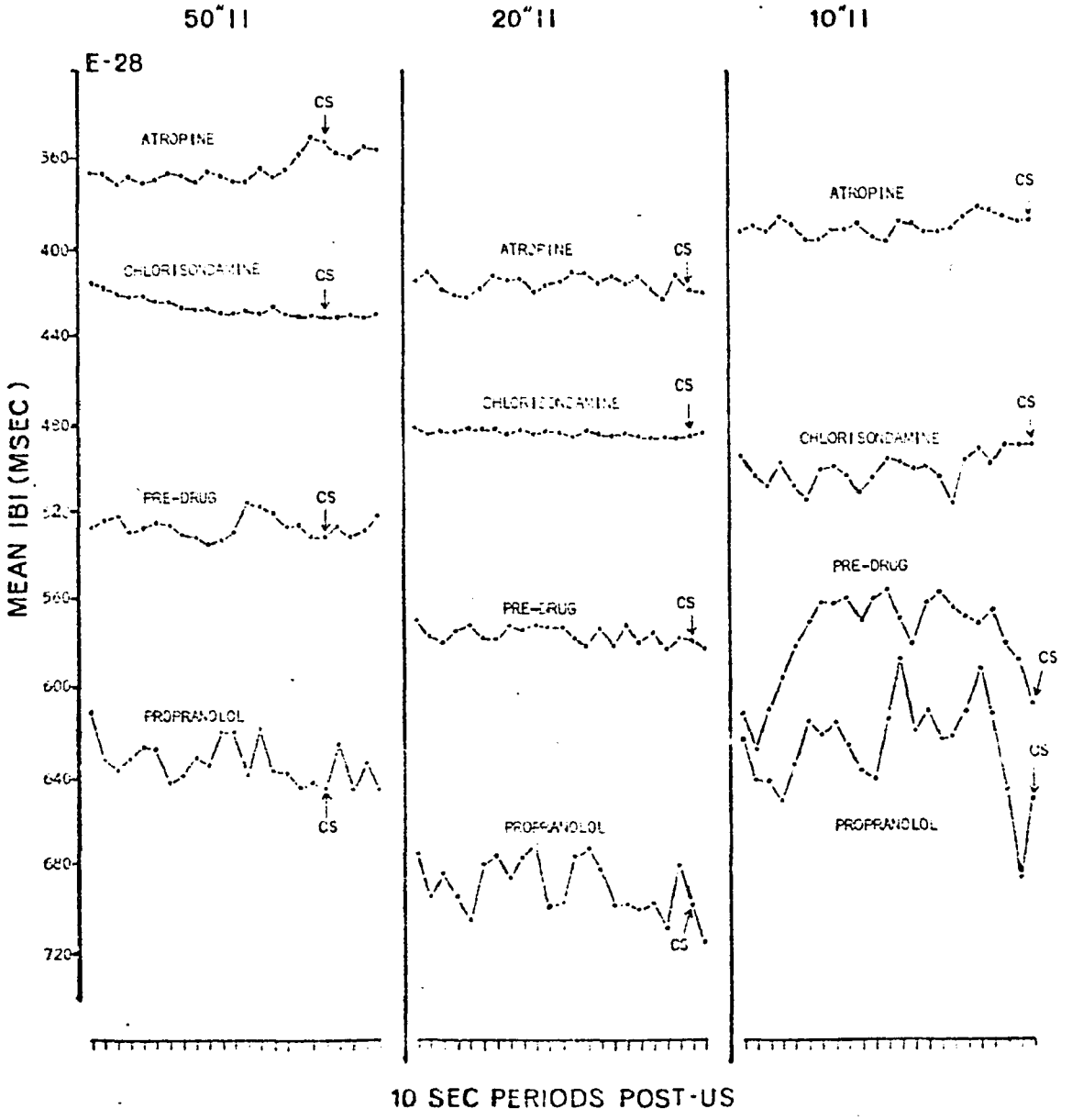
With regard to propranolol, although Figure 28 shows instances of both attenuation and facilitation of the initial acceleratory component, propranolol more often attenuated the acceleratory component, as evidenced by twelve cases of attenuation as opposed to five of facilitation. For the deceleratory component of the CR, instances of facilitation above predicted magnitudes under propranolol far outnumber attenuation (thirteen cases to four).

Because of an insufficient number of X,Y pairs available for each subject, a regression analysis could not be performed for drug effects on the UR. Results will be discussed with reference to Figures 29-33. These figures present pre and post-drug functions consisting of successive mean IBIs over the course of the US-US interval (in 10 sec averaging periods) for each subject at each re-determined CS-US interval.

Chlorisondamine, with few exceptions, eliminated the UR almost entirely, similar to its effects on the CR. Atropine, unlike its effects on CR acceleration, appears to have left some acceleration at US onset in many cases. However, overall rate trends during the US-US interval for both chlorisondamine and atropine tended generally to a slow deceleration.

Propranolol reduced the magnitude of acceleration of the UR in many cases, similar to its effects on the magnitude of the acceleratory component of the CR. This finding is, in many instances, directly evident from Figures 29-33; however, some speculation with regard to the law of initial value seems necessary in the light of instances where the UR under propranolol is larger than the pre-drug UR. For example, E-38 at 20 sec II (Fig. 32, middle panel) shows a larger acceleration of the UR post-propranolol than during pre-drug. However, one would have expected an even greater magnitude of the acceleratory component considering that the post-propranolol UR for E-38 began at a mean IBI level as low as 702 msec. One could, therefore, paradoxically conclude that propranolol attenuated the UR after taking LIV-predicted magnitudes under account. These speculations regarding the UR would have been strengthened by statistical tests had they been possible, as was done

Figures 29-33. Mean pre and post-drug functions of successive mean IBIs over the course of the US-US interval at each temporal location of CS. Each point represents mean IBI (in msec) for 10 sec, averaged over the same trials as in Figures 24-27.


50"11
20"11
10"11
E-28
ATROPINE
CHLORISONDAMINE
PRE-DRUG
PROPRANOLOL
CS
MEAN IBI (MSEC)
360
400
440
480
520
560
600
640
680
720
10 SEC PERIODS POST-US

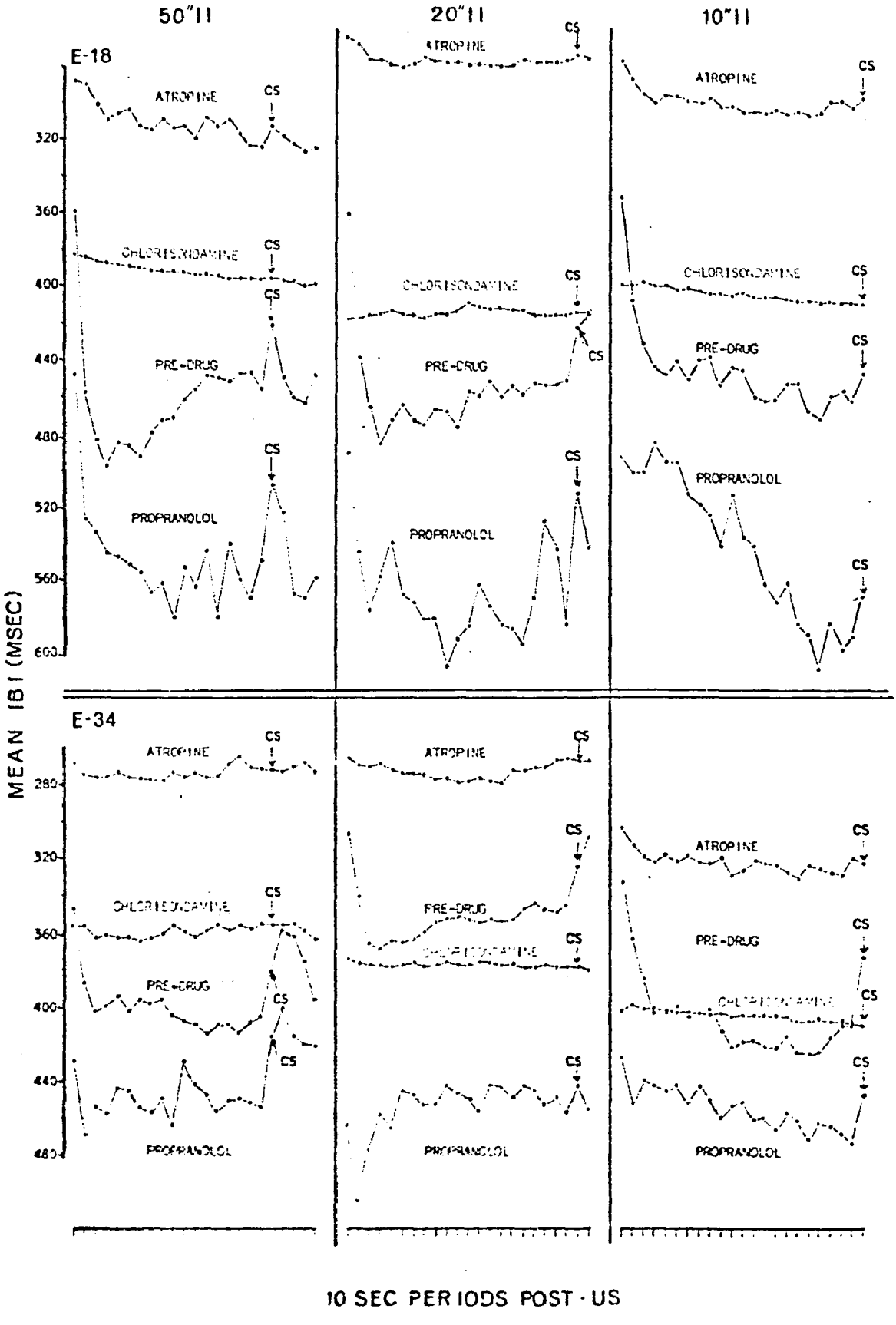

50"11
20"11
10"11
E-18
ATROPINE
CS
CHLORISONDAMINE
PRE-DRUG
PROPRANOLOL
320
360
400
440
480
520
560
600
E-34
280
MEAN IBI (MSEC)
10 SEC PERIODS POST-US

Fig. 30

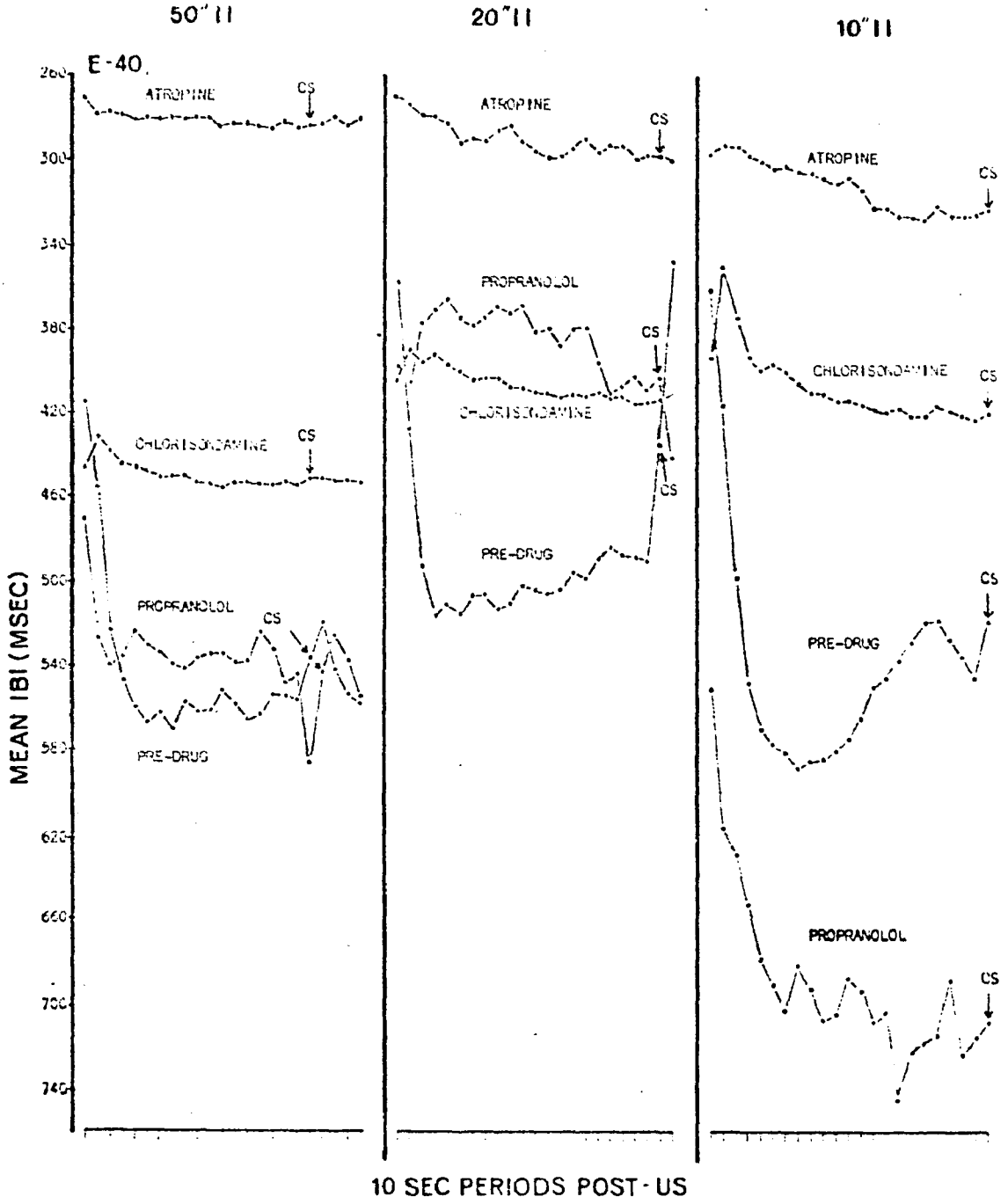

50"11
20"11
10"11
E-40
ATROPINE
CS
CHLORISONDAMINE
PROPRANOLOL
PRE-DRUG
MEAN IBI (MSEC)
260
300
340
380
420
460
500
540
580
620
660
700
740
10 SEC PERIODS POST-US

Fig. 31

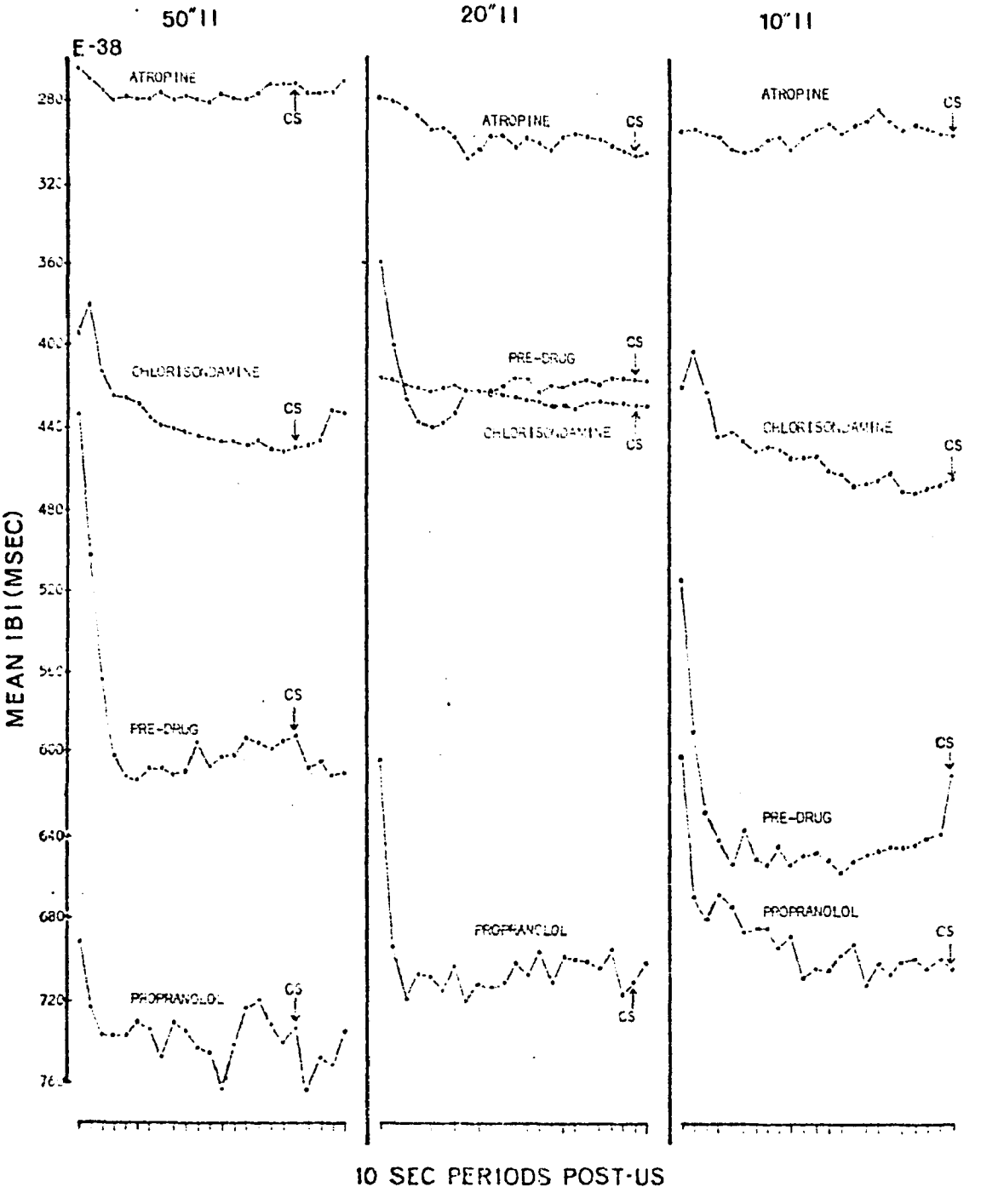

50"11
20"11
10"11
E-38
ATROPINE
CS
CHLORISONDAMINE
PRE-DRUG
PROPRANOLOL
MEAN IBI (MSEC)
280
320
360
400
440
480
520
560
600
640
680
720
760
10 SEC PERIODS POST-US

Fig. 32

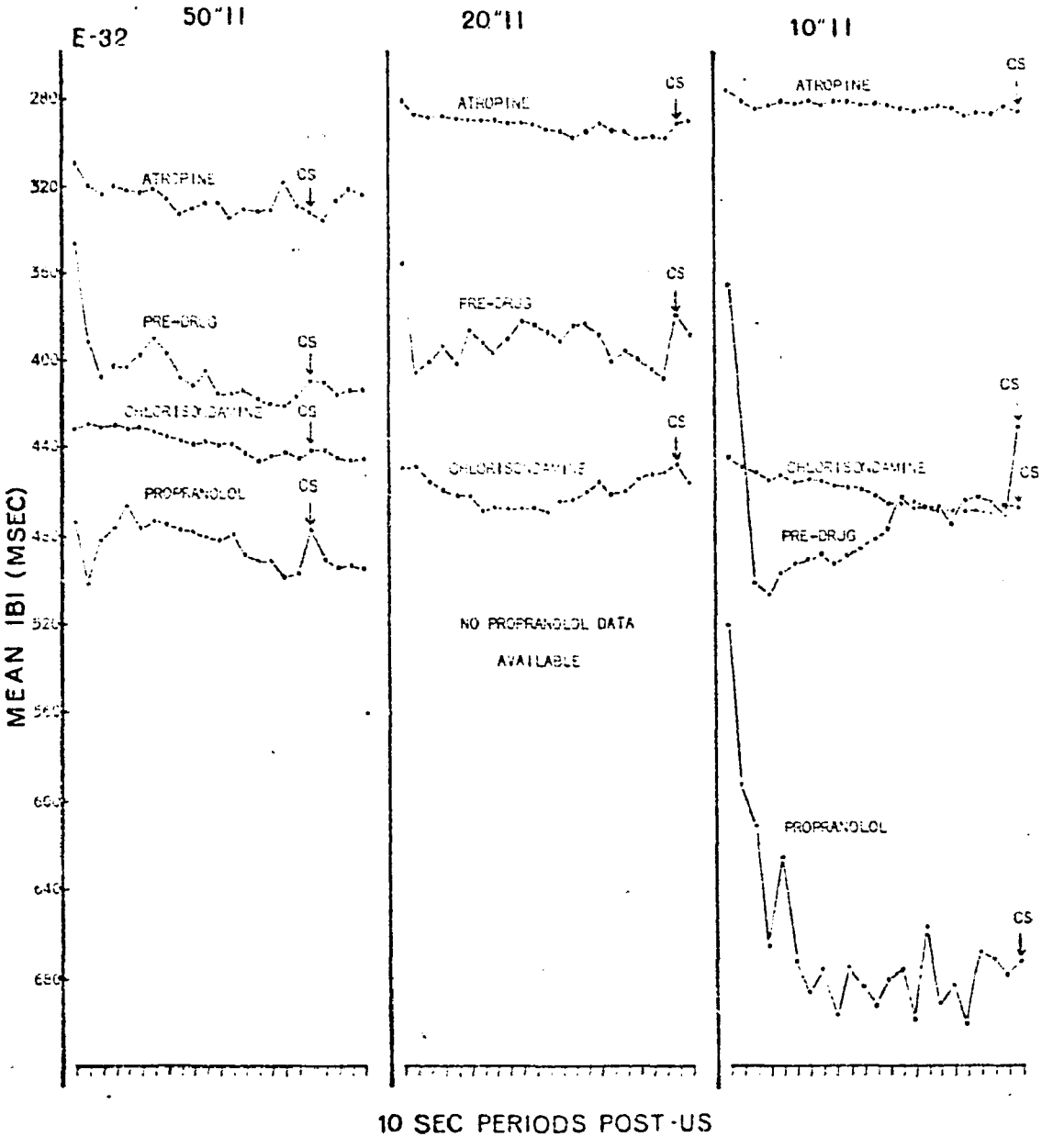

E-32
50"H
20"H
10"H
ATROPINE
CS
PRE-DRUG
CHLORISOXAMINE
PROPRANOLOL
NO PROPRANOLOL DATA
AVAILABLE
MEAN IBI (MSEC)
10 SEC PERIODS POST-US

Fig. 33

for the CR, above.

With regard to changes in rate over the course of the US-US interval after propranolol, there are large fluctuations and no clear trends, unlike chlorisondamine and atropine.

In summary, chlorisondamine and atropine raised baseline heart rate above pre-drug levels, with atropine raising it more so than chlorisondamine. Both acceleratory and deceleratory components of the CR were reduced under these two drugs. With regard to the UR, ganglionic block by chlorisondamine attenuated cardiac acceleration after shock more completely than parasympathetic block by atropine. Post-atropine and chlorisondamine functions were less variable than pre-drug functions.

Propranolol generally lowered baseline heart rate, with greater fluctuations in rate evident relative to pre-drug, chlorisondamine, and atropine functions. For both the CR and the UR, propranolol generally reduced cardiac acceleration, with the deceleratory component of the CR often enhanced. No clear trends were evident for HR deceleration after shock under propranolol.

Discussion

The intruded stimulus design of the present study draws together, in a generalized paradigm of stimulus delivery, a number of procedures that have hitherto been considered to produce qualitatively different behavioral changes. Derived from a set of experiments conducted by Farmer & Schoenfeld (1966a,b), the present procedure departs from theirs by use of response-independent delivery of both the conditioned and reinforcing stimuli. The earlier intruded stimulus experiments, as well as the present study, found behavioral changes preceding, accompanying, and following the intrusion of CS over a wide range of temporal placements in the US-US interval.

The present findings make contact with several areas of interest to behavior theory, such as, (a) the specification of basic response units for non-instantaneous dependent measures; (b) the importance of external cues for the formation of temporal discriminations; (c) the effects of CS as determined by the temporal proximity of CS to US; and, based on findings from pharmacological blocking agents, (d) the underlying neural contributions to the elaboration of HR accelerations and decelerations in the CS-US interval.

Cardiac changes resulting from experimental manipulations of stimuli have been described in varying ways by previous investigators. In some cases, authors have described the observed HR changes in their studies in terminologies other than that of conditioning. For instance, Dronsejko (1972), Hastings & Obrist (1967), and Hein (1969) speak of the

cardiac rate changes in the CS-US interval as "anticipatory adjustments". Other authors have asserted that HR changes observed in their experiments are "orienting" or "sensitized" responses, and are not true conditioned responses (e.g., Geer, 1964).

Those investigators who do consider their observed cardiac changes to be conditioned differ in their criteria for the identification of cardiac CRs, or, in many instances, do not appear to employ any criteria for response-identification. Gantt (1960) defined the cardiac CR as any regularly occurring acceleration or deceleration of heart rate during the CS resulting from the juxtaposition of CS and US. Those employing particular quantitative criteria include, for example, VanDercar & Schneiderman (1967), who specified that only HR changes during CS test trials exceeding 5% of baseline would be counted as CRs; and, Church & Black (1958) who accepted the occurrence of a cardiac CR only when the median post-CS rate exceeded the maximum pre-CS rate.

Occasionally, the totality of HR changes in the CS-US interval is segmented in the belief that each segment reflects a different underlying behavioral process, and is assigned a name as such. For example, changes in heart rate early in the CS-US interval are sometimes considered as the by-product of respiratory changes at the onset of CS (e.g., Kosupkin & Olmsted, 1943; Levy, DeGeest, & Zieske, 1966), while HR changes later in the interval, such as the deceleratory component of a biphasic CR, are occasionally thought to be the conditioned or "true" HR changes in the CS-US interval (e.g., Deane, 1965; Wood & Obrist, 1964).

The problem of specifying the occurrence of a conditioned cardiac response derives, in part, from observations that an ensemble of cardiac

measures change with manipulations of independent variables. Thus, cardiac waveforms have been seen to differ markedly in magnitude, patterning, and direction when subjects have received different values of CS-US intervals (e.g., Fitzgerald & Martin, 1971; Hastings & Obrist, 1967). It would seem that any single response criterion (for example, a specified minimum change in magnitude) ignores changes in another measure (for example, response patterning) as the more reliable indicator of conditioned cardiac changes.

Those studies reporting polyphasic changes in heart rate during long interstimulus intervals are especially responsible for the development of a rational definition of the cardiac CR. Lockhart (1966) in particular, has addressed the problem of "multiple [autonomic] response phenomena" in long interstimulus interval conditioning and has emphasized the danger of pre-judging the origin of such multiple response forms, often reflected in the assignment of different names to each distinguishable waveform in the CS-US interval (such as "true" or "orienting" responses).

Thus far, in the present study, the totality of HR changes in the CS-US interval have been treated as one conditioned response. Given observed multiple, phasic changes in heart rate throughout the entire CS-US interval, the designation of one CR seems forced. Also, it appears that conditioned changes occurred throughout the entire US-US interval, since not only were changes in HR measures observed in the CS-US interval upon manipulation of CS location, but systematic changes in heart rate were observed in the interval between US offset and the subsequent CS (the post UR-CS interval).

Schoenfeld (1976) has suggested that the conceptualization of response units in cardiac conditioning might be made to conform to that in the operant system by treating each heart cycle (EKG) as a response. Systematic changes in the rate at which these cycles occur can be thought of simply as changes in response rate, regardless of whether accelerative, decelerative, biphasic, or polyphasic waveforms are observed upon analysis of the entire US-US interval. This approach renders questions as to which segments of these changes are conditioned, orienting, or unconditioned responses irrelevant, and unnecessarily complicating.

HR changes in the CS-US interval

The present paradigm, by beginning with CS offset contiguous with US, and then moving CS location back in the US-US interval, affords an observation of delay and trace procedures in cardiac conditioning. The first CS-US interval employed (10") was a delay procedure: at this interval, subjects were most consistent in the cardiac changes they exhibited. In both original and re-determined CS-US intervals, HR uniformly accelerated and then decelerated in the CS-US interval. After merging from this delay interval into trace conditioning, i.e., after CS was moved back in the inter-US interval and longer and longer trace periods were introduced, HR changes in the CS-US interval were often characterized by a biphasic form during CS, with another biphasic form initiated at CS offset, filling the trace interval. Although Schneiderman (1972) has suggested that the introduction of a trace period in the CS-US interval disrupts the organism's "timing" of CRs initiated at the onset of CS, another interpretation may be that the offset of CS is a cue

for cardiac changes (**cf.**, Black, 1965; Black et al., 1962).

Heart rate became increasingly polyphasic and variable as CS location was moved back in the inter-US interval. This result is unlike the findings of a related experiment conducted in this laboratory (Washton, dissertation in progress): employing the same experimental chambers, species, mode and intensity of CS and US, and comparable CS-US intervals, but with a delay procedure, this latter study obtained highly uniform HR waveforms of initial acceleration followed by deceleration with rhesus subjects, even at CS durations of 2 min. The importance for organisms of cues from external stimuli is well known. For example, Ferster & Skinner (1957) demonstrated impressive stimulus control over fixed-interval responding in pigeons when different exteroceptive cues were correlated with the passage of time in the interval. It is not clear, however, in the comparison of trace and delay procedures, why a CS that remains unchanged during long CS-US intervals (delay) results in less variable HR changes than the onset of a CS followed by a "gap" (trace)(also found by Pavlov, 1927). One source of phasic HR changes in the present study was the onset and offset of CS. Also, each additional extension to the CS-US interval resulted in additional waveforms.

Pavlov (1927) attributed poor control over responding during long trace intervals to the animals' being easily distracted. In the present context, it also seems possible that CS, because of pairings with US, results in less distraction and activity when it fills the duration of the CS-US interval upon its presentation in a darkened chamber, as compared with long periods where no stimulus is present.

Although variability of CR waveforms increased with the longer

trace intervals in the present study, functions relating the temporal location of maximum change in heart rate in the CS-US interval to the duration of that interval were, by contrast, monotonic and regular. They showed that as CS was intruded further back in the inter-US interval, the location of maximum heart rate change after CS tracked CS location to a certain extent. Latencies of peak heart rate changes, however, were not constant as CS intrusion point was manipulated. It was rather the case that latency increased while a constant proportion of the duration of the interval was maintained.

These findings demonstrate that cardiac measures such as latency to peak heart rate change, and the variability of the peak location, all bear a lawful relation to overall HR changes in the CS-US interval, regardless of the variability of HR waveforms within that interval.

In addition to changes in CR waveform, latency, and variability measures, the magnitude of HR changes in the CS-US interval was also affected by the movement of CS back in the inter-US interval. CR magnitudes increased over the first three interval conditions (10-30 sec), decreased for the next two CS-US intervals (50 and 80 sec), and then increased once more over the succeeding two intervals (120-170 sec). A study conducted by Dronsejko (1972) is the only one which manipulated CS-US intervals within-subjects, and also began with shorter, proceeding to longer intervals, as in the present design. She presented nine CS-US intervals ranging from 4-12 sec to human subjects by order of increasing durations. Dronsejko found that cardiac response magnitudes, as measured from the deceleratory component of biphasic responses which emerged at 8 sec CS-US, were largest at 10 sec CS-US. Her study differs

in important ways from the present design, however, in that (a) all CS-US intervals were presented within one experimental session; (b) a delay procedure was employed; and, (c) almost all the CS-US intervals used were shorter than the durations used in the present study.

Again, exact precedents for the present design are lacking; however, the overall findings in the literature have been that long CS-US intervals result in small cardiac CR magnitudes when trace procedures are employed (e.g., Black et al., 1962; Fitzgerald & Martin, 1971). The present findings are not in agreement with the above over part of the range of intervals employed, and, it seems possible that starting at shorter intervals in a within-subjects design may account for them. Pavlov (1927) stated that long-trace reflexes "are always formed slowly and with difficulty" (p. 115) and often began long-trace conditioning by simultaneously presenting CS and US, with subsequent lengthening of the CS-US interval.

Difficulties of interpretation arise from the present findings after the observation that CR magnitudes increased, then decreased, and then increased again as the CS temporal location was moved back in the inter-US interval. Since the course of the CR was not truncated at the shortest (10 sec) interval (i.e., a full biphasic form was evident) the argument that longer intervals allow time for the peak of the CR to occur (e.g., Brown & Peters, 1967; Dronsejko, 1972; Schneiderman, 1972) does not seem applicable here. The biphasic waveform simply stretched out in time over the first three intervals, with peak HR occurring later in the CS-US interval. In the fourth and fifth CS-US intervals employed (50 and 80 sec), CR magnitudes were small; at these intervals, CS was

occurring 2.5 - 3 minutes after the previous US, and approximately 1 - 1.5 minutes before the subsequent US. These would seem to be long time intervals, in both directions, for subjects to continue associating CS strongly with US. What is a "long time" for rhesus monkeys? Dmitriev & Kochigina (1959) suggest that 1 - 2 min. US-US intervals are the outside limit for the formation of time reflex in rhesus monkeys; it is possible that this also applies to CS-US intervals. There are several studies which have successfully demonstrated cardiac CRs with 1 min. CS-US intervals in rhesus subjects, but always with a delay procedure, contrasting with the present trace procedure (e.g., Randall, Brady, & Martin, 1975; Randall, Kaye, Randall, & Brady, 1973; Randall & Smith, 1974; Snapper, Pomerleau, & Schoenfeld, 1969).

When the CS-US interval was lengthened further, as at 120 sec CS-US, CR magnitudes increased significantly once again: this was the first CS-US interval where CS occurred temporally closer to the previous, rather than the subsequent US (110 sec US-CS; 120 sec CS-US). So, as CS occurred earlier in the US-US interval, the shorter time periods between CS and the previous US resulted in increased CR magnitudes, thereby possibly refuting the many experimenters who have regarded backward conditioning as impossible or weak (Fitzgerald & Walloch, 1966; Kimble, 1961; Pavlov, 1927; Spooner & Kellogg, 1947). Some investigators have found CS to maintain "excitatory" properties in backward conditioning procedures (e.g., Champion & Jones, 1961; Wolfle, 1932) and, other authors have suggested, similar to the present argument, that backward and forward conditioning are not qualitatively different, but are on a continuum of temporal contiguity to US (Hull, 1943; Jones, 1962).

A problem remains: if temporal proximity of CS to US were the sole determiner of CR magnitude, then the increasing CR magnitudes over the first three intervals seem a contradiction to this hypothesis. It appears that there is an "optimal" CS-US interval at shorter CS-US intervals, at least in the present design, at which subjects exhibit their largest possible CRs. After this interval, which is 30 sec, CR magnitude declines as CS occurs temporally remote from either the preceding or following US.

HR changes in the US-CS interval

The magnitude of acceleration immediately following an unsignalled US exceeded post-US acceleration when US was preceded by CS. This finding has been observed for HR, skin conductance, and GSR, and has been termed the "preception effect" by several authors (Coles, Herzberger, Sperber, & Goetz, 1975; Lykken, 1962; Lykken, Macindoe & Tellegen, 1972). Preception is the hypothetical interpretation of warning signals (CSs) as "produc[ing] an afferent 'set' which serves to attenuate selectively the sensory representation of the noxious stimulus [US] when it occurs" (Lykken, 1962). A more likely interpretation may be that the preception effect is a manifestation of the law of initial value. CS produced higher HR levels in the CS-US interval than during a pre-CS period in the present study: in other studies claiming preception, the effect of CS on raising response levels in the CS-US interval is evident from their figures. Thus, when US occurred, HR levels were already high; i.e., the CR was already in progress, thereby resulting in attenuated UR magnitudes when compared with URs not preceded by CRs. Lykken et al. (1972) reject

the notion that their results are an effect of unequal baseline levels, and state that their findings were not "caused" by the LIV, although they do not state why. It should be made clear that the LIV does not "cause" anything; it is simply a name assigned to an observed empirical relationship, i.e., that higher pre-stimulation response levels result in smaller post-stimulation response magnitudes.

CS was found to exert its effects both prior, and subsequent to its occurrence in the inter-US interval. This is similar to findings from the "intruded stimulus" experiments where the temporal locus of CS determined whether substantial, or no changes in response rate occurred around its intrusion point (Farmer & Schoenfeld, 1966 a,b; Snapper, Kadden, Shimoff, & Schoenfeld, 1975). A common feature of the intruded stimulus studies, some temporal conditioning procedures, and of the present procedure is the regular presentation of CS and US. Gantt et al. (1951) interpreted regular increases in dogs' heart rates prior to a CS, when both CS and US were presented periodically, as evidence for temporal conditioning. Farmer & Schoenfeld classed such increases in response rate prior to CS (in their case, the response was key pecking rate of pigeons) with the conventional evidence for the secondary reinforcing properties of CS (cf., also Kelleher & Fry 1962; Segal, 1962). They pointed out that CS was in the temporal position to become a conditioned positive reinforcer through pairings with the primary reinforcer (food), and ascribed to that fact the maintenance of a "scalloped" response rate pattern prior to CS occurrence, and a post-reinforcement pause-like drop in responding briefly after CS. The present data show, as in the findings of Farmer & Schoenfeld, and Gantt et al., approximately

monotonic heart rate accelerations prior to CS, but only for the CS-US intervals over 10 sec duration. At the 10 sec interval, HR decelerated in the period prior to CS. In the sessions where US was unsignalled, HR trends in comparable measurement periods did not reverse from deceleration to acceleration until the unsignalled-US sessions interpolated between the 50 and 80 sec CS-US onditions. It might be said from this finding that CS exerted control over HR increases immediately preceding its occurrence early in training since, when CS was absent, no such increases were observed. As training progressed, however, with CS moving back in the US-US interval, these increases began to appear even in the absence of CS.

However, CS does not necessarily exert "backward" control: it was emphasized previously that US-CS pairings may have accounted for larger CR magnitudes when US became temporally closer to the following CS. Other authors have also found it more profitable to consider the temporally forward rather than backward effects of US-CS pairings (e.g., Moscovitch & LoLordo, 1968). The conceptualization of the "forward" effects of regular stimulus pairings may weaken the belief that temporal conditioning is a special case of Pavlovian conditioning, or is evidenced by changes only in a particular segment of a "trial"; i.e., by lawful increases in pre-CS heart rate. Again, lawful changes in the temporal patterning of heart rate were observed throughout the entire inter-US interval. To invoke a whole set of terms for HR changes in this interval, such as the UR, succeeded by the temporal reflex, succeeded by the CR is unnecessary.

As indicated up to this point, the intruded stimulus design subsumes a number of stimulus scheduling procedures, including trace, delay,

forward, backward, and temporal conditioning. It also seems to cover procedures which Rescorla and collaborators (Moscovitch & LoLordo, 1968; Rescorla, 1969 a,b; Rescorla & Solomon, 1967; Solomon & Corbit, 1974) have termed "warning-signal" and "safety-signal" training. These authors have suggested that a CS acquires "warning-signal" functions when it occurs in close proximity to US (in a forward direction) as reflected in larger magnitude responses, and acquires "safety-signal" functions at long intervals between CS and US, as reflected in small magnitude responses early in the CS-US interval. The present findings of increased CR magnitudes from 10-30 sec CS-US durations are at odds with these formulations, since CS' acting as a warning signal should have produced the largest response magnitudes at the shortest (10 sec) interval.

One aspect of the present findings does conform to some predictions of Solomon & Corbit (1974). These authors, along with Moscovitch & LoLordo (1968) state that CS acquires inhibitory properties when it not only immediately follows US, but also precedes a long shock-free interval. The inhibitory effects of CS on heart rate are presumably demonstrated, according to Solomon & Corbit, by longer durations of UR cardiac decelerations. In the present study it was found that the longest duration of UR deceleration did occur at the "backward" conditioning procedure, where CS occurred immediately after US, and also preceded the longest shock-free interval. Since a gradual increase in UR deceleration as CS occurred temporally closer to the previous US might be a criterion for safety-signal effects of CS, the finding that there were no such gradual increases in the present study do not further confirm the safety-signal hypothesis.

One difficulty in inferring the "warning" or "safety" effects of

CS from HR changes is that HR accelerations or decelerations cannot be reliably predicted from our notions concerning the relative "aversiveness" of differing experimental procedures. For instance, if HR increases are supposed to reflect "fear" (e.g., Black et al., 1962; Church, LoLordo, Overmier, Solomon, & Turner, 1966; Rescorla & Solomon, 1967), those experiments demonstrating HR acceleration to a CS preceding food delivery must be explained (e.g., Gantt, 1960; Moore & Marcuse, 1945; Randall, Brady, & Martin, 1975; Schoenfeld, Matos, & Snapper, 1967). Conversely, if HR decelerations are supposed to reflect relaxation or relief (e.g., Solomon & Corbit, 1974), experiments demonstrating deceleratory CRs prior to shock must be explained (e.g., Fitzgerald & Teyler, 1970; Flynn, 1960; Zeaman & Smith, 1965). As Schoenfeld & Cole (1972) have pointed out, the "positive" or "negative" characteristics of stimuli as well as of responses, are determined by the choice of organism, scheduling and stimulus parameters. The intruded stimulus design employed here allowed investigation of the stimulus control of behavior by an unambiguous and "primitive" (Farmer & Schoenfeld, 1966 a,b) procedure of stimulus intrusion unencumbered by (a) inferences from the experiences of experimental subjects; or, (b) by inferring different underlying behavioral processes to procedures which may be parametrically related.

Autonomic innervations of the cardiac CR and UR

Some evidence concerning the nature of autonomic contributions to experimentally-produced changes in heart rate was provided by the present data with regard to : (a) the assessment of which branch of the autonomic nervous system controls resting heart rate of rhesus subjects during experimental sessions; (b) the possible role of hormonal influences (epinephrine and norepinephrine) on the cardiac CR; and, (c) the possible source of control over the cardiac CR and UR as assessed by pharmaco-

logical blockade of both branches of the ANS.

Attempted denervation of the heart by ganglionic blockade with chlorisondamine allowed evaluation of the intrinsic rate of the rhesus heart; the intrinsic rate was approximately 140 BPM (an average of all six subjects), which is close to the intrinsic rate of 145 BPM reported by Dews & Herd (1974) for chronically restrained rhesus subjects after hexamethonium injection (another ganglionic blocking agent of less potency than chlorisondamine). A comparison of intrinsic and "control" (i.e., pre-drug resting heart rate) rates allows deductions about which branch of the ANS has the controlling influence over resting heart rate. Klose et al. (1975) found that HR levels of their restrained rhesus subjects, after pharmacological denervation (combined atropine and propranolol injection), were lower than pre-drug levels, contrary to the present findings of rates after denervation by ganglionic blockade generally higher than pre-drug. Klose et al. concluded greater sympathetic tone in their rhesus subjects: the evidence here indicates higher vagal tone exercising a restraining influence on resting rate. The present findings also contrast with Dews & Herd (1974) who found balanced sympathetic and parasympathetic control (i.e., no changes in rate were observed under ganglionic blockade) during resting periods between exercise tasks.

Ganglionic blockade by chlorisondamine showed that the vagus exerted a controlling influence over resting heart rate during pre-drug sessions. Blockade by chlorisondamine also showed that hormonal influences on the cardiac CR were non-existent by the demonstration that both acceleratory and deceleratory components of the CR were almost entirely eliminated at all re-determined CS-US intervals after administration of

chlorisondamine. These findings are in contrast to Randall, Kaye, Randall, & Brady (1973) and Bond (1943) who, after observing slow HR increases during long CS-US intervals after surgical denervation of their subjects, attributed the HR increases to the release of catecholamines.

The effect of parasympathetic blockade by atropine sulfate on baseline heart rate in the present rhesus subjects, and for various species in other investigations, was an elevation of rate above pre-injection levels (e.g., for rabbits, Downs et al., 1972; for dogs, Dykman & Gantt, 1959; for rats, Fitzgerald, Martin, & O'Brien, 1973; for humans, Obrist, Wood, & Perez-Reyes, 1965). In addition, baseline heart rate under atropine was higher than that under chlorisondamine, revealing levels of heart rate achieved under mostly sympathetic control when unopposed by the vagus.

Atropine's effect on baseline heart rate has been discussed. The drug's effect on the CR was to reduce the magnitude of both the accelleratory and decelleratory portions of the biphasic HR waveform and to flatten the response function almost entirely; i.e., phasic HR changes in the CS-US interval were absent (also reported by Obrist et al., 1965; Fitzgerald, Martin, & O'Brien, 1973; and Schneiderman et al., 1969).

Propranolol's overall effect was to lower baseline heart rate, as also reported by other investigators (e.g., Nakano & Kusakari, 1966; Powell, Goldberg, Dauth, Schneiderman, & Schneiderman, 1972; Sampson, Francis, & Schneiderman, 1974), and, with respect to its effect on the CR, it reduced the acceleratory portion (Kadden, Schoenfeld, & Bindler, 1975; Cohen & Pitts, 1968; Obrist, Howard, Lawler, Sutterer, Smithson, & Martin, 1972), and it enhanced the magnitude of the decelleratory portion.

The above findings of complete elimination of the CR's accelera-tory portion by vagal block, and partial elimination by sympathetic block imply a greater vagal contribution to HR acceleration. However, the high overall HR levels observed after vagal blockade probably masked the sympathetic contribution by severely limiting HR acceleration (LIV). Regression analysis was performed to compare CR magnitudes predicted at high heart rates (undrugged) against the obtained high rates under atropine, and, in many cases, attenuation of CR magnitude under atropine was found. However, although the differences between predicted and obtained values were often large, the majority of cases were not statis-tically significant. Consequently, one cannot conclude that HR acceler-ations were small because of the parasympathetic blocking effect of atropine; or, it may have been rather the result of overall HR levels being so high that a sympathetic component could not manifest itself. Ganglionic blockade by chlorisondamine was the only pharmacological manipulation which resulted in complete elimination of the acceleratory portion of the CR uncomplicated by considerations of the law of initial value, since baseline HR levels were not nearly so changed after adminis-tration of chlorisondamine, and most of the findings from this drug were statistically significant. A possible hypothesis here is that the initial acceleratory portion of the CR has two innervations, sympathetic and parasympathetic, as also concluded by other investigators (e.g., Cohen & Pitts, 1968; Dykman & Gantt, 1959). This hypothesis will be seen to apply to the deceleratory portion of the CR as well, and will follow below.

The evidence for dual innervation of the deceleratory portion of the cardiac CR consists of the finding that the magnitude of the decel-

eratory component of the CR was enhanced after propranolol injection, revealing vagal action when unchecked by sympathetic tone. This finding is surprising in that it is at odds with the findings of other studies. Fredericks et al. (1974) and Sampson et al. (1974), with rabbit subjects, found no effect of propranolol on deceleratory CRs; and, Kadden et al. (1975) found no change in the magnitude of the deceleratory portion of biphasic CRs in rhesus subjects after propranolol injection.

Other evidence from the present study does not so clearly argue for dual innervations of the deceleratory portion of the CR in that HR deceleration was completely eliminated by vagal blockade. Sympathetic action should have become evident in the form of HR acceleration toward the end of the CS-US interval when the vagus was blocked, had there been an original sympathetic component to the latter part of the CR. The sympathetic contribution probably consisted of checking the strong deceleratory action of the vagus, as stated above. If HR levels had been lower under vagal blockade, perhaps by the use of smaller dosages of atropine, a remaining sympathetic component in the form of HR acceleration may have been revealed.

Thus, it is suggested that ANS innervations of the cardiac CR take the following form: the acceleratory portion is probably the result of combined increase in sympathetic activity and release of vagal restraint, also suggested by Bond (1943), Cohen & Pitts (1968), Dykman & Gantt (1959), Katcher et al. (1969), and Klose et al. (1975). The present hypothesis that the CR deceleration is probably the result of an increase in vagal activity checked by sympathetic tone departs from the conclusions of most studies in the literature. Only one other study (Kazis, Milligan, &

Powell, 1973) concluded dual innervation of their deceleratory CR in rabbit subjects. They stated that the observed HR decelerations pre-drug were the combined result of increased vagal restraint and inhibition of sympathetic tone after observing that either atropine or propranolol decreased the magnitude of the response, but only combined administration eliminated it completely. Here, a facilitation of deceleration was observed after sympathetic blockade, suggesting that this deceleration was not originally mediated by an inhibition of sympathetic tone, but that active firing by the sympathetics normally checked the deceleratory action of the vagus.

Much lack of agreement has arisen among investigators about which branch of the ANS is the more important contributor to experimentally-produced HR changes (Cohen, 1974). In the present study, for both acceleratory and deceleratory portions of the CR, these questions must remain unresolved, since 1 mg/kg atropine-block of the vagus cannot be reliably compared against 1 mg/kg propranolol-block of the sympathetic nervous system. Also, it is not even certain if these dosages resulted in total blockade. Differences could be seen in the degree of sympathetic and parasympathetic blockade with respect to their effect on temporal patterning of heart rate in the present study. Atropine appeared to raise HR levels to a "ceiling", as evidenced by flattened functions, more than propranolol lowered HR levels to a "floor". Perhaps 1 mg/kg propranolol was not a sufficient dosage to achieve complete sympathetic blockade; had it been, one may have observed flattened functions occurring at very low HR levels, similar to the atropine effect at high HR levels. Rather, the functions observed under propranolol were characterized by

extremely large changes in heart rate over successive averaging periods and were highly irregular. These irregular functions under propranolol are puzzling, considering that propranolol is used as an anti-arrhythmic drug (Goth, 1974). A visual inspection of individual polygraph records reveals that interbeat intervals were very arrhythmic under propranolol.

Kelleher, Morse, & Herd (1972) found episodic changes in heart rate of squirrel monkeys almost completely eliminated only after 3 mg/kg injection of propranolol, and Klose et al. (1975), in rhesus subjects, established total sympathetic blockade at 3 mg/kg administration of propranolol after testing lower dosages. Many investigators tested the amount of beta-blockade by propranolol by infusing isoproterenol, a beta-agonist drug which stimulates the heart and induces tachycardia; if heart rate does not increase after isoproterenol injection, it is concluded that the dosage of propranolol employed was sufficient to block beta-receptors in the heart. Although Robinson, Epstein, Beiser, & Braunwald (1966) found .25 mg/kg propranolol sufficient to challenge the infusion of isoproterenol in human subjects, it is possible that even 1 mg/kg of propranolol, as used in the present study with rhesus subjects was insufficient to achieve total blockade.

Results from pharmacological blockade of the unconditioned response in the present study differed only in one respect from those found for the conditioned response: it was found that some UR acceleration remained after vagal block by atropine. This finding suggests a greater sympathetic role in shock-induced HR changes, i.e., in the UR An inspection of data from Klose et al. (1975; their Table 4) also reveals that UR acceleration was larger than CR acceleration after parasympathe-

tic blockade in their rhesus subjects, although the difference does not appear large and was not tested statistically. Washton (dissertation in progress) also obtained larger magnitudes for the UR as compared with the CR after parasympathetic blockade. Perhaps, in the present case, the sympathetic nervous system was more mobilized by higher stimulus intensities (as concluded by Obrist et al., 1965, for human subjects), i.e., by the shock-US than by the light-CS, although it is admittedly risky to compare the subjective intensities of two stimuli when they differ in modality.

Summary

Findings from the present study consisted of the following:

1. Cardiac CR waveforms were most consistent among subjects at the shortest CS-US interval and became increasingly polyphasic as CS occurred earlier in the inter-US interval.

2. Latency of maximum heart rate, and variability of the location of maximum heart rate in the CS-US interval increased with, and in constant proportion to the duration of the CS-US interval.

3. As CS occurred progressively earlier in the US-US interval, maximum heart rate occurred in earlier positions as well.

4. CS offset often resulted in cardiac rate changes.

5. The magnitude of HR change in the CS-US interval increased over the first three CS-US durations (10-30 sec), decreased for the following two durations (50 and 80 sec), and then increased for the succeeding two CS-US interval durations (120-170 sec).

6. The magnitude of HR acceleration immediately following US was smaller, in most cases, when US was preceded by CS.

7. The temporal patterning of heart rate immediately prior to CS was deceleratory at 10 sec CS-US, and acceleratory for the remaining CS-US interval conditions, with the exception of 120 sec CS-US. In comparable measurement intervals when CS was omitted, heart rate patterning was deceleratory until later US-only sessions (after 50 sec CS-US), at which time acceleration began to appear.

8. The duration of HR deceleration after US was greatest at the 230 sec CS-US interval duration.

9. Resting heart rate was highest after vagal block (by atropine) and lowest after sympathetic block (by propranolol). Ganglionic block (by chlorisondamine) generally resulted in HR levels above pre-drug levels, but not as high as HR levels under atropine.

10. Vagal and ganglionic block each flattened the CR almost entirely. Sympathetic block reduced the magnitude of the acceleratory portion of the CR, and increased the magnitude of the deceleratory portion.

11. Vagal block did not reduce UR acceleration as completely as it reduced CR acceleration.

Summary of conclusions

The following conclusions were drawn from these findings:

1. The temporal proximity of CS to US was a powerful variable in determining the effects of CS on HR changes during the entire inter-US interval, as reflected in measures of magnitude, temporal patterning, latency, and variability.

2. Increased variability in HR functions during long CS-US intervals probably resulted from the absence of an external cue during such intervals.

3. Variability in cardiac waveforms at longer CS-US intervals does not necessarily affect other cardiac measures which may display lawful and monotonic relationships to the duration of the CS-US interval.

4. CS offset can become a cue for cardiac rate changes, particularly when, in earlier conditions, it was immediately followed by shock.

5. Resting heart rate of the rhesus subjects was under greater control of the vagus from evidence of higher resting heart rate after complete autonomic blockade.

6. Acceleratory and deceleratory portions of the CR are probably each innervated by both sympathetic and parasympathetic branches of the ANS.

7. Catecholamine-induced heart rate changes, potentially evidenced by slow HR increases during long CS-US intervals after complete autonomic blockade, were not detected.

Appendix: Table A

Mean IBI during 10" pre-CS (X) and at maximum change from X in the CS-US interval (Y) at CS-US interval durations of 10-170". Each datum is a mean of all criterion trials at each duration. Based on IBIs from 10" averaging periods.

	CS-US Interval (Sec)													
	10		20		30		50		80		120		170	
Subject	X	Y	X	Y	X	Y	X	Y	X	Y	X	Y	X	Y
E-28	538.78	534.78	376.38	377.19	556.50	552.44	604.32	593.68	621.40	584.80	505.20	469.20	539.40	498.10
E-34	283.26	281.63	329.10	334.50	406.10	359.55	388.40	368.85	340.88	298.63	354.56	317.67	329.07	319.50
E-40	553.36	550.29	627.26	576.11	667.24	495.88	582.17	508.25	479.78	426.78	501.00	452.58	573.46	509.62
E-38	331.90	327.50	446.68	381.84	563.56	492.89	374.72	404.39	500.32	481.05	526.07	490.67	554.63	478.26
E-32	315.26	300.47	443.72	408.22	347.95	324.53	293.36	285.27	377.93	375.87	358.20	346.20	300.94	269.31
E-18	419.10	404.45	384.57	354.29	424.50	377.33	492.15	455.50	432.70	395.00	341.33	321.33	288.00	280.71
SUM	2441.66	2399.12	2607.71	2432.15	2965.85	2602.62	2735.12	2615.94	2753.01	2562.13	2586.36	2397.65	2585.50	2355.50
MEAN	406.94	399.85	434.62	405.36	494.31	433.77	455.85	435.99	458.84	427.02	431.06	399.61	430.92	392.58

Appendix B

$\underline{t}$ - formula for testing the significance of change in peak IBI level (for CR acceleration and deceleration) after selective and total autonomic blockade

$$\underline{t} = \frac{Y_{pred} - Y_{obt}}{\sqrt{\frac{s^2_{y.x\ pre\text{-}drug}}{N_{pre\text{-}drug}} + \frac{s^2_{y.x\ post\text{-}drug}}{N_{post\text{-}drug}} + \frac{(s^2_{y.x\ pre\text{-}drug})(\overline{X}_{pre} - \overline{X}_{post})^2}{\Sigma (X - \overline{X})^2_{pre\text{-}drug}}}}$$

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