THE PERIPHERAL EFFECTS OF DRUGS ON SKIN CONDUCTANCE

THE PERIPHERAL EFFECTS OF CHOLINERGIC AND ADRENERGIC DRUGS ON PALMAR SKIN CONDUCTANCE IN HUMANS

By

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SCOPE AND CONTENTS:

The pharmacology of autonomic innervation to the peripheral skin conductance (SC) effector was studied. The drugs used included atropine, bretylium, acetylcholine (ACh), epinephrine (EPI), and amphetamine. Drugs were administered by iontophoresis (IPS) and by local subcutaneous injection. Although several IPS procedures were used, all proved to be inefficient and unreliable. Subsequent experiments using atropine and ACh supported the theory that innervation to the peripheral SC effector was mainly cholinergic. However, results obtained using EPI suggest that an adrenergic component might also be involved. It was concluded though that this component probably had little physiological significance. Experiments using amphetamine and bretylium were inconclusive. A comparison of behavioral and drug induced changes in SC suggested that the psychological relevance of SC might be improved through a range-correction based on pharmacologically determined SC range scores.

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CHAPTER ONE

INTRODUCTION

Electrodermal measures (skin conductance and skin potential) have featured prominently in the psychological research literature for more than 75 years, yet even today a clear understanding of their psychological relevance and psysiological determinants remains unavailable. A partial explanation for this somewhat surprising state of affairs lies in the methodological problems involved in accurately measuring electrodermal activity. Thus, a chapter about electrodermal recording in a recent handbook on psychophysiological methods (Brown, 1967, p.50) concludes, "The number of compromises alluded to in this chapter... may be regarded as an indicant of the unfinished state of the art." Fortunately, however, most of the major methodological problems have been solved more or less satisfactorily and it is now possible to critically evaluate and/or corroborate the earlier contradictory Galvanic Skin Response (GSR) literature with some measure of confidence. Having done so, it will then be possible to build a firm theoretical orientation around which to design future experiments. In this paper, primary emphasis will be placed on a pharmacological

investigation of the physiological basis of skin conductance (SC) activity, although some pertinent data on the psychological relevance of SC minima and maxima will be noted.

PHARMACOLOGICAL STUDIES OF SC

There seems to be little doubt that, in man, acetylcholine (ACh) is the main neurohumoral transmitter to the sweat glands since either ACh, or muscarinic[1] drugs such as Mecholyl and Pilocarpine, can promptly and reliably induce profuse sweating, while muscarinic blockers such as atropine inhibit most natural sweating (Wilcott, 1966; Gordon & Maibach, 1965; Silver, Montagna, & Karacan, 1964; Haimovici, 1950). However, it has been suggested that epinephrine (EPI) is involved in neurohumoral transmission to the sweat glands because it too can cause sweating in humans (e.g. Haimovici, 1950). In this paper particular attention will be directed toward studying the extent of cholinergic[2] and adrenergic[3] involvment in neurohumoral transmission to the eccrine sweat glands in the skin (and other effectors of electrodermal activity), since the problem has considerable theoretical importance in a study of the autonomic nervous system. Of note at this point is that the skin is an extremely convenient organ in which to study drug effects and interactions on the human autonomic nervous system since it provides a readily accessible model containing

vascular, nervous and glandular components which are sensitive to drug action in very small, non-systemic doses. This makes the study of the autonomic nervous system through the use of cholinergic and adrenergic stimulating and blocking drugs readily feasible.

Although it was not until 1934 that Dale and Feldberg tentatively identified the neurohumoral transmitter at the sweat gland as acetylcholine (ACh), some relevant pharmacological research on the mechanisms underlying SC had been performed as early as 1911 (Wells and Forbes, 1911) in an attempt to differentiate between two major theories explaining the origin of the GSR. Briefly, one theory, as proposed by Féré (1888) and modified by McDowall (1933) and others, stated that the GSR was caused by variations in local blood flow in the skin. The other theory, as advanced by Tarchanoff (1890) and since modified by many others (see Darrow 1927; Edelberg, 1964) stated that electrical activity in the sweat glands was mainly responsible for the GSR. As a test of the sweat gland theory atropine was used to stop sweating. The results, unfortunately, were inconclusive. Thus Waller (1918), Marckbreiter (1919), and Aveling and McDowall (1925) found that atropine did not have any effect on the GSR, while Wells and Forbes (1911), Landis and DeWick (1929), and Richter (1926) found increased skin resistance (SR) and either a decrement in amplitude or abolition of GSRs. Unfortunately, these investigators administered the

drug in many different ways, and it seems unlikely that the local concentration of atropine achieved at the effector site was equivalent.

Later research showing that GSRs could not be elicited in Ss having a genetically based absence of sweat glands provided strong support for the sweat gland hypothesis. However, the controversy over the effects of atropine on the GSR has persisted into much more modern times. Thus, for example, Carmichael, Honeyman, Kolb & Stewart (1941, p.334) say "The response (GSR) was consistantly found to persist after atropinization of the skin area by iontophoresis.(4) There was no tendency towards a progressive decrease in the value of the response, nor was the response ever wholly abolished." Some of the discrepancy in the above results can doubtless be ascribed to variations in the method of administration of the drug, i.e. oral, intramuscular or subcutaneous injection, iontophoresis etc. However, Montagu (1958) used "the same" procedure as Carmichael et al (1941) (iontophoresis) and abolished skin resistance responses (SRRs). Since that time, Lader and Montagu (1962), Wilcott (1964), and Venables and Martin (1967a), have supported Montagu's (1958) results using iontophoresis; however, Venables and Martin used only one S, Lader and Montagu 2 Ss, and Wilcott 5 Ss, one of which continued to show GSRs after the experimental procedures. Consequently a definitive statement about the effects of atropine on SC cannot be made on

the basis of the current literature. This problem will be investigated in the present paper.

The effects of epinephrine (EPI) on SC have also been studied. These results, unfortunately, are equally, or even more confusing than those noted for atropine. Richter (1929 p.601) found that tonic SR increased after a subcutaneous injection of epinephrine in the arms of 40 Ss. As he says, "...in almost every subject a slight increase occurred, but there were marked individual differences in the magnitude of this increase." O'Leary (1932) found that a subcutaneous injection of EPI did not have any effect on a cat's SR; however, he found a rise in SR after an intravenous injection. In general agreement with the above results, Perry and Mount (1955) found an increase in SR after an intramuscular injection of EPI in humans, while Densham and Wells (1927) found a decrease in GSR amplitude after iontophoretic induction of EPI in the fingers of several Ss.

In light of the fact that Dale and Feldberg (1934) had found that the neurohumor released at the sweat glands was ACh, and that epinephrine and ACh often have antagonistic actions in the body, the above results seem reasonable. However, in 1949-1950 the phenomenon of human adrenergic sweating was discovered. Haimovici (1950) studied the effects of subdermal injection of adrenergic and cholinergic stimulating and blocking drugs on sweating at the palms of humans.

He showed that 84% of all Ss injected with EPI showed palmar sweating; however, when ACh or Mecholyl were injected all Ss showed palmar sweating. When EPI and either ACh or Mecholyl were injected simultaneously, "... in the first three minutes the intensity of the response, as a rule, appeared to be equal to the sum of the individual epinephrine and mecholyl or acetylcholine responses..." (1950, pp.516-517). Systemic administration of Dibenamine (an adrenergic blocking agent) alone was shown to halt all spontaneous sweating. Haimovici (1950, p.517) concludes "From the foregoing data it appears that in man, sweating can be inhibited by an adrenergic blocking agent and conversely that localized sweating can be elicited by adrenergic agents. These results raise the problem of the presence of an adrenergic component in the nervous mechanism of sweating in man." Wada (1950), Chalmers and Keele (1952), Rothman (1954), Hurley and Witkowski (1961), Silver, Montagna & Karacan (1964) and Dutta (1967) also have found that subcutaneous injections of epinephrine induce a localized sweating at the forearm and/or palm; however, Harrison and KcKennon (1963) and Gordon and Maibach (1965) found that a systemic injection of EPI caused a marked decrement in spontaneous palmar sweating, while Lader and Montagu (1962) were unable to affect SC with an "adrenergic" blocker. Considerable evidence indicates that non-sudorfic elements in the skin may affect SC (Edelberg, 1966); however, it is also clear that sweat gland activity is mainly responsible for SC effects. How then is it possible to reconcile

the reports that EPI both causes sweating and causes a decrease in SC?

Evidence supporting one possible explanation has been presented by Chalmers and Keele (1952), Rothman (1954), and Lader and Montagu (1962). Chalmers and Keele have shown that EPI could induce sweating, and that adrenergic inhibitors caused such sweating to cease. They then showed that atropine had no effect on adrenergically induced sweating and thus concluded that adrenalin did not work by causing the release of ACh. Finally, atropine was injected into one arm and tolazoline, an antiadrenergic agent, was injected into the other arm of several Ss. Heat was then applied to the legs. "It was at once clear that whereas the area injected with atropine was entirely free of sweat, the area injected with tolazoline sweated as profusely as the uninjected areas on both arms. Therefore the nerve supply to the thermally active sweat glands of the forearm appears to be exclusively cholinergic" (1952, p.52).

In attempting to support a sweat gland vs. vasomotor interpretation of SC phenomena, Lader & Montagu (1962) iontophoretically induced either atropine or bretylium into the palms of 8 Ss. Bretylium was used "...to paralyze the adrenergic nerve endings governing vasomotor tone..." (p.126). They concluded, "The present experiments have demonstrated that (1) atropine abolishes the psycho-galvanic

reflex without affecting vasomotor activity, and (2) bretylium abolishes vasomotor tone without affecting the psycho-galvanic reflex. It is concluded that the psycho-galvanic reflex occurs independently of vasomotor activity and that it is wholly dependent on a cholinergic mechanism." (p.133).

Rothman (1954, p.167) who reviewed the evidence on adrenergic vs. cholinergic sweating concluded that "All this suggests either that adrenergic sweating is not a physiological phenomenon or if the natural nervous sweating mechanism has an adrenergic component, that this plays an auxiliary role which is not essential." To explain this "auxiliary tole" of adrenalin, Rothman suggested that adrenalin may function by causing the myoepithelium of the sweat glands to contract. Thus injection of adrenalin subcutaneously would result in the extrusion of preformed sweat and this could be seen as sweating. In effect, Rothman would have us ignore the data on adrenergic sweating as being irrelevant to our understanding of the mechanisms underlying SC.

The evidence that adrenergic sweating is not a physiological phenomenon, however, is subject to criticism and reinterpretation. For example, in Chalmers and Keele's experiment, tolazoline was used as an adrenergic blocker; however, "(T)olazoline and phentolamine produce a moderately effective α-adrenergic blockade that is relatively transient. In addition they have important direct actions on cardiac

and smooth muscle that may be divided into three classes: (1) sympathomimetic... (2) parasympathomimetic... and (3) histamine-like." (Goodman and Gillman, 1965, p.557). In addition, apocrine sweat glands are often found in the forearm, while psychologically relevant SC activity is primarily caused by eccrine sweat glands. This would tend to reduce the relevance of Chalmers and Keele's findings. Furthermore, Kuno (1956) has calculated that in light of the total volume of sweat stored in one sweat gland tubule and considering the total number of sweat glands in a circumscribed area, adrenalin must be causing active secretion of sweat. This was demonstrated by Hurley and Witkowski (1961) who observed active excretion of eccrine sweat stained with methylene blue and reported "This observation indicates that local adrenergic eccrine sweating is not due mainly to myoepithelial expression of preformed eccrine sweat but results from active secretion of sweat as do other types of eccrine sweating." (p.652).

Lader and Montagu's paper is particularly open to criticism. As noted above, they used bretylium in order to "...paralyze the adrenergic nerve endings governing vasomotor tone..." (1962, p.126) and claimed that "...bretylium abolishes vasomotor tone without affecting the psychogalvanic reflex." (p.133). Unfortunately, this claim is the extent of their evidence since they failed to quantify and report their data on the SC effects of bretylium.

Furthermore bretylium has since been shown to be an anti-cholinergic agent having nicotinic blocking properties, and not to be a direct adrenergic blocking agent (Green & Hughes, 1966; Burn, 1968). However, how does one then explain the fact that bretylium and atropine had opposite effects on vasomotor tone in Lader & Montagu's (1962) paper? An explanation lies in an understanding of the theory of sympathetic neural innervation presented by Burn & Rand (1959).

It has long been known that cholinergic fibres exist in nerves that release adrenalin, although their function has remained obscure. Burn & Rand have hypothesized that "...all sympathetic postganglionic fibres are in fact cholinergic, liberating acetylcholine, and that the principal function of this acetylcholine is, not to act directly, but to liberate noradrenalin. This liberation of noradrenalin is unaffected by atropine, and the action of acetylcholine is therefore nicotine-like." (Burn, 1965, p.114). What is the evidence supporting such a hypothesis?

Firstly, it has been shown in "adrenergic" nerve-organ preparations that ACh, in addition to norepinephrine, is released by stimulation of the sympathetic postganglionic nerve. At high frequencies of stimulation, it has been found that none of the ACh acts directly on the target organ (since addition of atropine causes no decrement in effect at high frequencies of stimulation). However, as stimulation

frequency goes down the direct post-synaptic effect becomes larger (Burn, Rand & Wien, 1963; Wolner 1965; Gillespie & Mackenna 1961). Secondly, it has been shown that anticholinesterase increased the response amplitude of adrenergically innervated organs to sympathetic nerve stimulation when potential post-synaptic effects of ACh were blocked (Hukovic, 1966; Burn et al 1963; Armitage & Burn, 1967). Thirdly, it has been shown that hemicholinium, which prevents the synthesis of acetylcholine, blocks the responsiveness of most sympathetic postganglionic target organs (Chang & Rand 1960; Brandon & Rand 1961). Finally, it has been shown that bretylium and guanethidine, which block the nicotinic action of ACh at the neuromuscular junction (Burn, 1968; Green & Hughes, 1966), also block the effects of excitation of most postganglionic sympathetic fibers (Exley, 1957; Burn & Rand, 1960; Green & Hughes, 1966; Hukovic, 1960). All this evidence strongly suggests that ACh is involved in the release of norepinephrine and the concept has gained increasing acceptance in the years since it was first suggested (Ganong, 1967).

Now then, if as Burn & Rand would suggest, the nicotinic action of ACh is involved in releasing norepinephrine, then blocking this action with bretylium should inhibit the release of norepinephrine and cause vasodilation. This is what Lader & Montagu observed. Since atropine is a muscarinic blocker, it should have no effect on adrenergically maintained

vasomotor tone and this is what was reported. On the other hand, if EPI is involved in causing SC effects, one would have expected bretylium to cause a drop in SC and/or a decrement in SCR amplitude. However, Lader & Montagu reported that bretylium had no effect on SC. Unfortunately, as noted above, they failed to substantiate this claim with any quantitative data and only presented a two-minute section of a SR record in which "...(w)hen the treated finger was compared with the control, both the psychogalvanic reflexes and the resistance levels were found to be comparable ..." (1962, p.131). As given, however, these data are uninterpretable since a pre-drug comparison of the tonic and phasic SR levels in the two fingers is not presented. Lader & Montagu's results therefore can not be considered definitive. On the other hand, even if they took some general note of the differences in tonic and phasic SC levels of the control and experimental fingers before IPS, their failure to quantify their results precludes discovery of any small effects. This would be an important consideration if the control of sweating and hence SC was mainly cholinergic but had a small adrenergic component. As Burn (1968, p.179) has suggested, "It is conceivable that in a tissue where the amount of norepinephrine in sympathetic nerve endings is less than elsewhere the acetylcholine which is not used in liberating norepinephrine, and which is therefore free to act itself, may be greater in amount."

If the sweat glands represent a model of this type, bretylium would be expected to have a minimal effect, while atropine, on the other hand would be expected to have a large effect on sweating and SC since it would be blocking the main transmitter, ACh.

More evidence of an indirect nature supports the idea that epinephrine may be involved in synaptic transmission at the sweat glands. Thus, for example, according to a Burn & Rand type interpretation, if an adrenergic component were involved in sweat gland function, sweating should occur after the introduction of either adrenergic or cholinergic drugs into the skin. A host of experiments have shown this to be true. Introduction of both types of drugs simultaneously should have an additive effect. Haimovici (1950) has suggested that this is the case although his method for quantifying the data is open to question. Adrenergic blockers should block adrenergic sweating, but they should have no effect on cholinergic sweating. Chalmers & Keele (1955) have shown this to be true, as has Rothman (1954) although Haimovici claims that Dibenamine, an adrenergic blocker, inhibits all spontaneous sweating. The effects of cholinergic blockers must depend on whether they are muscarinic or nicotinic blockers. Muscarinic blockers should prevent all cholinergically induced sweating. Recent experiments with atropine (Lader & Montagu, 1962; Venables & Martin, 1967; Wilcott, 1964) have tended to support this

conclusion, although the earlier literature is quite contradictory. Muscarinic blockers on the other hand should not affect adrenergically induced sweating. Chalmers & Keele (1952) have observed this result. Since recent Es have found that muscarinic blockers inhibit most or all normal sweating it seems likely that if EPI is a natural mediator, an insufficient amount of EPI is probably normally released to cause adrenergic sweating, although individual differences in the degree of adrenergic innervation might be important. Therein may lay a possible explanation for the controversy over the effects of atropine, for example. Finally, nicotinic blockers should only block the release of noradrenalin at the nerve endings. Since the amount of noradrenalin released during normal sweating would have to be very small, nicotinic blockers should have small effects on sweating and SC. Lader & Montagu's results have suggested this may be the case with bretylium although their results are difficult to analyze.

In light of this proposed function of epinephrine in neurohumoral transmission to the sweat glands, it may be asked why systemic doses of epinephrine have often been found to decrease SC. It is a well known fact that homeostasis in the cardiovascular system is maintained by a wide variety of reflex mechanisms. For example, in an emergency when large quantities of blood are needed in the muscles, there is a reflex constriction of vasculature in the skin while vasodilation occurs in skeltal muscle. Injected

systemic doses of EPI would probably cause a similar effect. This would affect circulation to the sweat glands and cause changes in SC. Furthermore, reflex central inhibition of arousal through the reticular formation due to excess EPI might reduce SC in a manner analogous to the reflex vagal inhibition of heart rate in the presence of excessive stimulation by EPI. It seems likely, therefore, that an interpretation of the effects of epinephrine on SC after intravenous injections or systemic doses of epinephrine will be fraught with great difficulties. It is not surprising then that the relevant literature is contradictory. In order to clearly establish the effect of epinephrine on SC and SCRs and circumvent complicating reflex arcs it would seem necessary to investigate the effect of small doses of epinephrine administered directly under the recording SC electrodes. Such an approach has not been reported in the literature and it will be investigated in the present paper.

RANGE CORRECTION AND THE PSYCHOLOGICAL RELEVANCE OF SC SCORES.

Although SC tonic levels clearly reflect some aspect of "arousal", great difficulties are involved in evaluating raw SC scores because "(i)ndividual differences in the potential range of ED (electrodermal) activity vary across Ss to the extent that skin conductance measures accompanying a variety of behaviors from sleep to stressful performance may not display any overlap among subjects. Furthermore,

the absolute values of SC range appear to be unrelated to central psychological processes." (Miller, 1968b). In cross-sectional research, therefore, it would seem advantageous to correct for these individual differences in SC range. Lykken, Rose, Luther, & Maley (1966) have suggested a statistical transformation of raw SC scores which a variety of data suggests "...may accomplish marked reductions in error variance." (p.481). Since the absolute values of the range scores appear to be psychologically irrelevant, they may be eliminated, using the formula

$$\text{Range Corrected Score (RCS)} = \frac{SC_{ix} - SC_{i\,(min)}}{SC_{i(max)} - SC_{i(min)}}$$

Where SC_{ix} is the raw SC score for Subject i in situation x, while $SC_{i(max)}$ and $SC_{i(min)}$ are estimates of that subjects maximum and minimum SC activity, respectively.

In effect then, the range corrected SC score expresses the experimental SC score as a fraction of the entire range. As such it can be considered to be a measure of variation based upon the range. The efficacy of this transformation, of course, depends on the extent to which reasonable estimates of S's SC_{max} and SC_{min} can be obtained. Previously, estimates of SC_{max} had usually been obtained by having Ss blow up a balloon to bursting or by similar behavioral maneauvers. Estimates of SC_{min} were obtained in a rest period during which Ss were encouraged to rest and sleep. The difficulties

involved in obtaining accurate estimates of S's SC range using behavioral techniques, however, are almost obvious. For example, some nervous Ss fail to sleep during even an extended recording session while other placid Ss are hardly ruffled by blowing up a balloon to bursting. Errors in behavioral estimates of either SC minima or maxima would have considerable effects on the resultant RCS and constitute the primary stumbling block in the use of the range correction technique. This type of measurement difficulty weakens the power of range correction to reduce error variance and, indeed, in several recent studies (Miller, 1968a; Lykken, Miller, & Strahan, 1968) due to these problems range correction has not been a particularly powerful technique.

A potential solution to this problem might be accomplished if SC range estimates were obtained via pharmacological manipulation of the peripheral SC effector. Thus drugs which stimulated the peripheral effector could give one an estimate of SC_{max}, while blocking drugs would give one an estimate of SC_{min}. However, the extent to which peripheral pharmacological manipulation of SC would result in a psychologically relevant score is unknown. For example, direct stimulation of the sweat glands by ACh might cause tonic SC to go far above psychologically relevant levels. Similarly, use of a drug to block sweating might lower tonic SC below normal levels. These are

empirical problems, however, and they will be investigated in the present paper. Before this can be done though, one must know whether or not SC effects are purely cholinergic in aetiology, or whether adrenergic stimulating (and blocking) drugs would effect SC. If an adrenergic component is involved, it might then prove necessary to use a combination of cholinergic and adrenergic drugs to manipulate SC. Depending therefore on the outcome of research into the effects of atropine, ACh, EPI and bretylium on SC, it was decided to compare SC levels during sleep and "arousal" with pharmacologically induced SC levels.

CHAPTER TWO

CHOLINERGIC INVOLVEMENT IN SKIN CONDUCTANCE

EXPERIMENT 1.

The effects of atropine administered via iontophoresis on SC

As mentioned above, iontophoresis (IPS) has been the most frequently used method for administration of atropine in recent experiments on sweating and electrodermal activity. This is because "Atropinization by iontophoresis appears to afford the best method of obtaining an adequate local concentration of the drug. It seems probable that most of the electric current enters the skin through (sweat) gland ducts since these constitute low resistance pathways through the high-resistance stratum corneum. Consequently, the atropine would be preferentially delivered in high concentration at its effector sites..." (Lader & Montagu, 1962). However, it appears that the methods of IPS used heretofore have not provided an adequate basis for its general application. The most glaring problem lies in the fact that the necessary parameters for standardization of the technique across Ss

have not been given. For example, invariably only total current flow has been specified (i.e. Current x Time). However, considering the variability in finger sizes both within and across Ss and the variation in electrode techniques, the obvious parameter to control is current density, not total current, if one wants to make some kind of a generalizable dose-response statement. A second big problem with the procedure was discovered during preliminary studies of IPS of atropine. In this preliminary work, a constant current IPS system was used, and the dose of atropine administered was quantified by noting the total current flow over time in a restricted area of skin. A second site was iontophoresed with an equal constant current passing through a solution of physiological saline. This procedure is essentially the same as that used in several recent experiments in the literature. It soon became obvious, though, that when IPS current density was kept comparable to that used by other investigators, atropine was not eliminating SCRs, which was contrary to recent reports. A likely possibility was that the problem was one of dose, however.

At this point, two possibilities were considered. In order to get a higher dose of atropine into the skin, one could prolong the IPS interval. However, this would have rendered the procedure too inconvenient for general use.

Therefore, instead it was decided to use a constant voltage IPS procedure. By using this technique, it was reasoned that the total current flowing into the skin and hence the dose of atropine administered would depend upon the Ss SC level. It was assumed that Ss having low SC would probably only need a little atropine to eliminate SCRs, while Ss having high SC levels would need considerably more. In a constant voltage system the current flowing, and the dose administered would vary automatically depending on the S's SC. It seemed, therefore, that use of a constant voltage system would give a fast, convenient technique which would be efficient across Ss. The only major problem remaining involved the choice of an appropriate voltage.

With these considerations in mind, it was decided to run an experiment in which a dose-response relationship for the effects of atropine on electrodermal activity could be determined, using a constant voltage method of iontophoresis with area controlled. It was hoped that following this experiment it would be possible to rapidly move on to a study of the effects of other cholinergic and adrenergic stimulating and blocking drugs on both SC and skin potential. However, the first experiment never got off the ground, so to speak, because preliminary results showed that for intervals of iontophoresis of up to twenty-minutes at the maximum voltage Ss would accept (approximately 30-40 volts) an insufficient amount of atropine was entering the sweat

glands in order to eliminate all SCR activity. Furthermore, it was often found to be impossible to maintain a high constant IPS voltage across the skin for long intervals of time, because Ss complained of pain. As a result, the IPS voltage often had to be reduced several times during a session. During IPS the SR drops sharply, and in a constant voltage system as the resistance drops, the current flow increases, frequently to the profound discomfort of S. On the other hand, in a constant current IPS system, as the resistance of the skin goes down, the only effect is a decrement in the voltage dropped across the skin, and perhaps a drop in the painfulness of the IPS current. Tursky & Watson's (1964) work on subjective magnitude estimations of shock induced pain using a constant voltage or a constant current system supports the above interpretation.

In addition, after IPS, tonic SC increased dramatically to a level which appeared unrelated to normal SC. In a constant voltage IPS system, the current flow (and hence the drug dose administered) is a function of SC. Since post-IPS SC levels did not seem to be related to pre-IPS SC levels, it appeared that the dose of atropine administered was also not a function of normal SC. As a result of these problems, use of a constant voltage system was abandoned. Instead, in the first experiment, a constant current was passed through the experimental finger during IPS. In this way, the dose of atropine administered would be made uniform.

However, IPS current and voltage effects were controlled by subjecting another finger to the same (monitored) voltage as was received by the experimental finger, since Edelberg (1967) had shown that damage to the peripheral SC effector was more a function of the applied voltage than the applied current.

METHOD

The Ss used in the first experiment were eight paid male college students. Beckman silver chloride electrodes were used with a .07N NaCl electrolyte in a pharmaceutical ointment base (Miller, 1968c). The electrodes were preselected to show less than 0.1 millivolt different in potential. Three of the S's fingertips were wiped with distilled water and then dried. A piece of waterproof adhesive plastic tape with 0.7 cm^2 circular hole in its center (Beckman discs) was then applied to each of the distal phalanges, care being taken to center the hole over the central swirl of the finger print. Any remaining exposed areas of skin on the fingertips were then masked with Scotch tape. An adhesive corn pad (Dr. Scholl's) with a 3/8 inch diameter hole, was then placed over each of the exposed areas of skin. The corn pads were filled with electrolyte and the three electrodes were attached firmly with Scotch tape. In all except the last two sessions of the experiment, one common reference (or inactive) site was used for all electrodes.

In the last two sessions, three independent reference sites were prepared after interaction problems were discovered with the use of a common reference. These effects do not influence the major findings, however. The skin underneath the reference site(s) was first prepared by Shackel's (1959) method of skin drilling. (The cornified epidermal layer was removed and a shiny membrane exposed.) A corn pad was placed over the drilled site, and then the electrode applied in the same manner as at the active sites.

Skin conductance was measured directly using a constant voltage circuit. A constant 0.5 volt was impressed between the electrodes through a 2000 ohm series resistance, and the signal across this resistor was fed into a six channel Beckman type R Dynograph having an input impedance of over 2.5 megohms. With the use of calibrated preamplifier settings and a zero-suppression control, SC could be recorded with sensitivity exceeding $\pm$ .02 micromhos, although recording was usually done at a sensitivity allowing accuracy to $\pm$ 0.1 micromhos.

In preliminary studies, the polarity of the voltage across the skin was periodically reversed. When the active electrode was connected to the positive pole of the battery the tonic SC levels seen were approximately 10% higher than when the polarity was reversed. This rectification effect has been previously reported by Lykken, Miller & Strahan

(1968). However, since the effects seemed relatively constant over time, in all experiments reported in this paper the positive pole of the battery was always connected to the active electrode.

After the electrodes were attached, S was seated in a reclining lounge chair in a thermostatically controlled audiometric chamber. The ambient temperature was kept at approximately 72°F. The S was then instructed to either cough, scratch himself, or take deep breaths at one minute intervals in order to elicit SCRs and maintain tonic SC at a reasonable constant level. SC was then recorded continuously for thirty minutes. At the end of the thirty minute control period of recording, S was asked to come out of the audiometric chamber and the electrodes were removed from two of the three fingers. The corn pads were then carefully removed leaving the tape and discs in place and the electrolyte was wiped off. This left the finger tips with a constant area of exposed skin for IPS. Iontophoresis proceeded simultaneously in both fingers. One finger was placed in a solution of either 1, 10, or 100 mg/cc atropine sulphate, while the other was placed in an equinormal solution of NaCl in distilled water. Iontophoresis of the experimental (atropine) finger lasted for intervals of 1.7 minutes, 5 minutes and 15 minutes. Three current densities of .11 m Amp/cc^2, .33 m Amp/cc^2, and 1.0 m Amp/cc^2 were

used for each IPS interval. Atropine was introduced into the finger from the positive pole of the battery. The circuit was completed through a silver electrode placed in the mouth. In this way, SC reference sites were not contaminated by current flow. Since it seemed likely from previous considerations (noted above) that the relevant parameter to control for IPS electrical effects was voltage, the voltage dropped across the experimental finger was monitored continuously and the current flowing through the control finger was adjusted so that the voltage dropped across it equalled that dropped across the experimental finger. At the end of the period of IPS, S's fingers were carefully dried, new corn pads were applied and electrodes were replaced. S was then returned to the audiometric room, given the same instructions as before, and SC was recorded for at least another ninety minutes.

Unfortunately, although a wide variety of dependent measures have been used to quantify phasic SC records, little agreement exists on which measure (e.g. response latency, amplitude, duration, or number) most clearly reflects variations in the underlying psychological variable. Edelberg, (1964, 1967) has studied and discussed the problem, and the procedures used in the present study to quantify the results are in general agreement with his recommendations.

The data were analyzed as follows. The mean tonic

level during two four-minute intervals within the last fifteen minutes of the control session was called the control tonic level (CTL). The sum of all phasic activity during the same two intervals used to determine the CTL was called the control phasic level (CPL) (see Fig. 1). Similar measures were obtained during the first four minutes of each fifteen minute interval of recording after iontophoresis, and are called the experimental tonic (ETL) and phasic (EPL) levels, respectively. Once these scores were calculated, a measure of the control tonic activity of each finger relative to any other was determined by taking ratios, i.e.

$$\frac{\text{CTL (Saline)}}{\text{CTL (Control)}}$$

$$\frac{\text{CTL (Atropine finger)}}{\text{CTL (Control)}}$$

$$\frac{\text{CTL (Atropine finger)}}{\text{CTL (Saline)}}$$

Analagous ratios were determined for CPLs, and for EPLs and ETLs. Experimental effects were determined by calculating the per cent change in the experimental ratios relative to the control ratios. Ratios were used rather than difference scores to correct for variations in SC range across sites. For example, consider two sites having SC ranges of 2 to 12 μ mhos, and 6 to 36 μ mhos respectively. If S is maximally aroused, the difference between the two sites will be 36 - 12 = 24. Their ratio on the other hand will be 12/36 = 0.33. If their state of arousal is now cut in half, the SC levels seen would be 7 and 21 μ mhos. Their difference

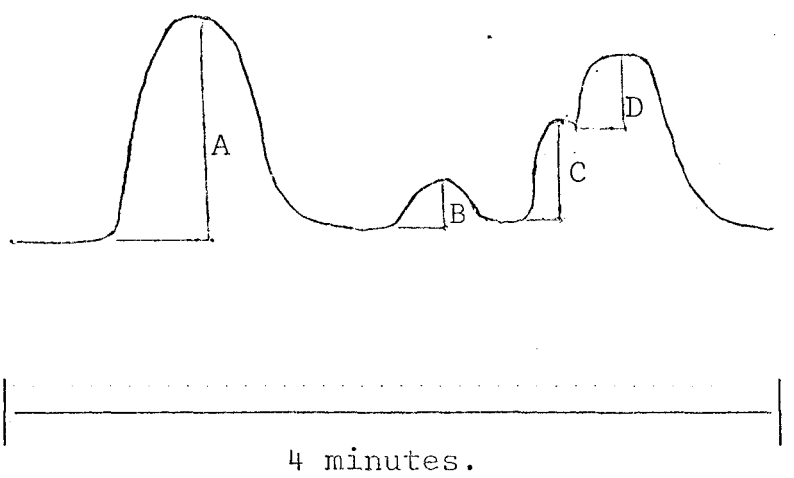

FIGURE 1. Measurement of SC responses.
The sum of all phasic activity during a four-minute interval equals the sum of the perpendicular heights of the SC responses (measured from the base of each response to its peak). $\Sigma_T = A + B + C + D$

now is 14 μ mhos, but, their ratio is still 0.33. Ratios therefore give results which more clearly reflect changes in "arousal" across Ss than do difference scores. Even the use of ratios has its limitations however, for this type of analysis presumes that the function relating arousal and SC tonic level is similar for the two sites throughout the range of SC scores. Although such a statement would seem to be a close approximation to the truth, empirical evidence is lacking. Nonetheless, since difference scores were clearly unacceptable, ratios were used in order to minimize error. Finally, experimental effects were determined by calculating the percent change in the experimental ratios relative to the control ratios. This procedure has been previously used by Edelberg (1964) and Wilcott (1964).

RESULTS & DISCUSSION

In preliminary studies with the use of atropine by IPS difficulty was encountered in eliminating all SCRs. This was surprising because previous investigators (Lader & Montagu, 1962; Montagu, 1958; Wilcott, 1964; Venables & Martin, 1967) had reported that all SCRs were eliminated using a 1 or 2 milliamp current for approximately five minutes over a large area loosely defined, for example, as "...the distal half of the finger," (Lader & Montagu, p.127). Since the area used for IPS in the present experiment was very much smaller (about 1/10th the size), and all current flow

was through the identical tissue used in the subsequent recordings, it was expected that low current levels would introduce enough atropine into the skin to replicate the results noted by other recent researchers. When this failed to be the case, three final steps were taken to insure that a sufficient dose of atropine was entering the skin. Firstly, the concentration of atropine in the iontophoresis solution was raised to twice that used by Wilcott (1964). This maneuver was not expected to have much of an effect, since it would not increase the dose administered for a given current level if the only positive ions in solution were atropine ions. However, on the chance that a few stray positively charged ions were in solution the atropine concentration was doubled to further decrease the probability that other ions were entering the skin. Secondly, the IPS current density was increased to just below the pain threshold. Finally, the duration of IPS current flow was increased. All these procedures however still failed to eliminate SCR activity in seven out of eight Ss even when IPS was continued for intervals up to thirty minutes. Generally speaking SCRs of 1 μ mho were often seen after IPS of atropine for thirty minutes. At this point, one S was iontophoresed with 1.4 milliamp/cc^2 current for ninety minutes to see if that would eliminate SCR activity, however, small SCRs were still observable. These SCRs were reduced to approximately 0.1 μ mho. Figures 2 and 3 show some typical results. The

duration of IPS was fifteen minutes at 1.4 m Amps/cc^2 for this S. Current effects were determined by comparing the changes in control and experimental ratios of SC for the saline finger vs. the control finger over time. The effect of atropine was determined by similar comparisons between the saline and atropine fingers. Considering the restricted IPS area, the current level and duration used guaranteed that a very much larger amount of atropine entered the skin than was considered sufficient to eliminate all SCRs by previous Es, yet the results show that although tonic SC is depressed, as has been previously reported, phasic SC activity was depressed by no greater than 42%. How then does one explain the fact that no fewer than four Es have found that SCRs are eliminated by IPS with atropine? The answer probably lies in the fact that previous Es have used very few Ss. It is a well known fact that inter-subject susceptibility to the action of various drugs is extremely variable. Therefore it may be that recent Es have simply used Ss whose responsiveness to atropine would fall on the high end of a dose sensitivity curve. This would seem to be a reasonable interpretation since in the present experiment although atropine eliminated all phasic SC activity in 1 S, in 7 other Ss degrees of activity still persisted.

Two possible conclusions can be drawn from the fact that IPS of atropine often fails to eliminate SCRs. The first conclusion is that IPS is an inefficient procedure

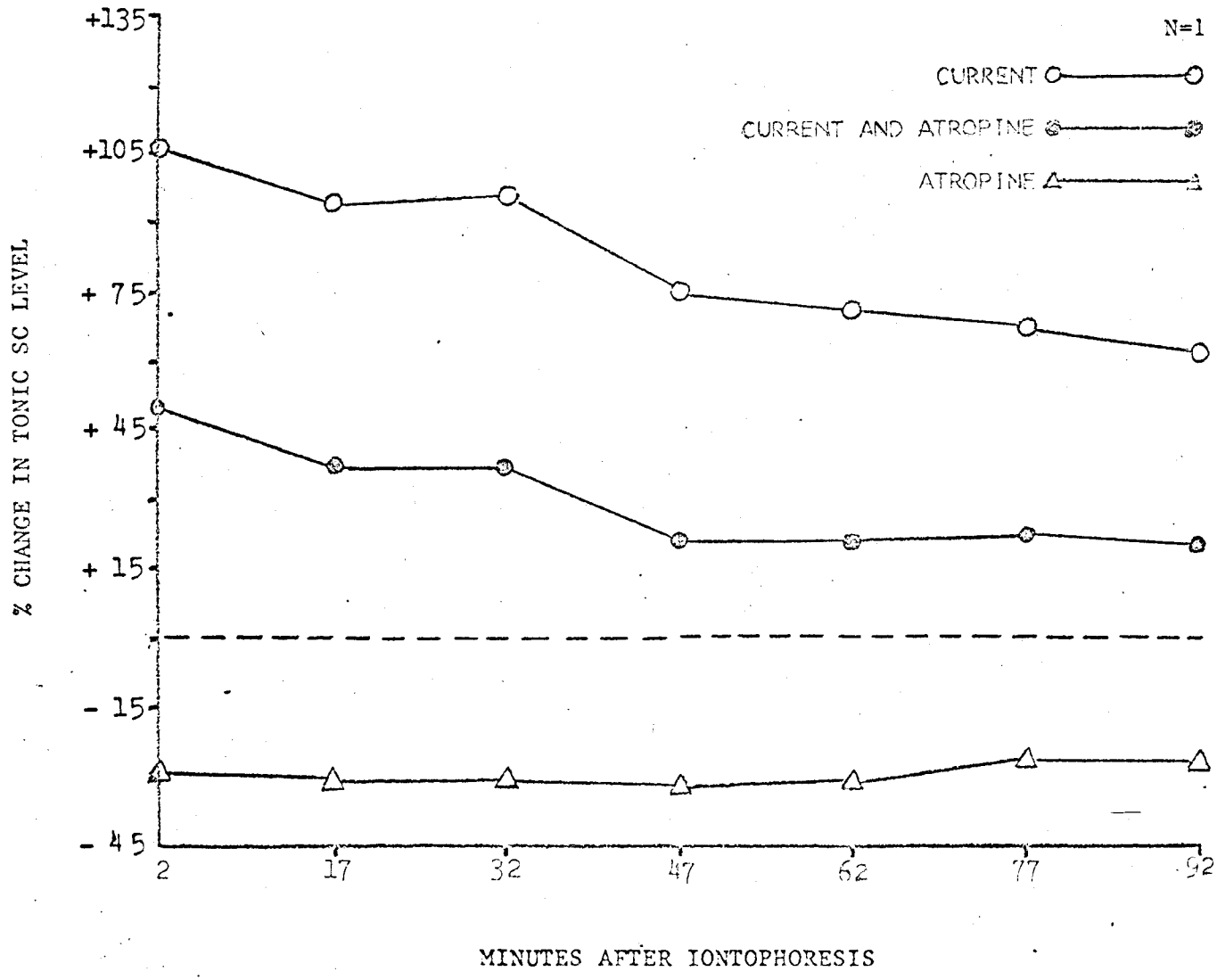

Fig. 2 The effects of iontophoresis of atropine (1.4 mAmp/cm^2 - 15 min.) on tonic SC.

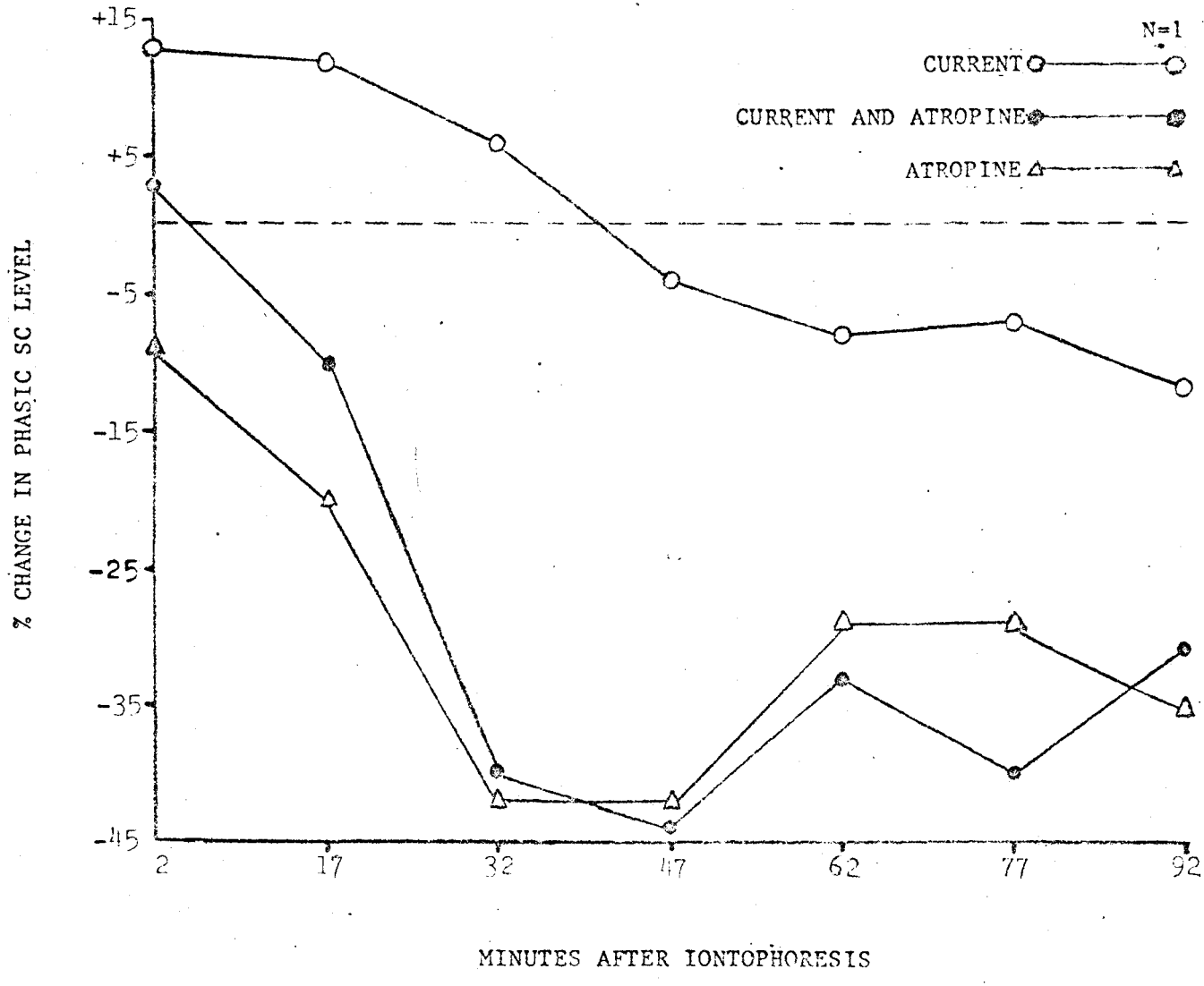

Fig. 3 The effects of iontophoresis of atropine (1.4 mAmp/cm^2 - 15 min.) on phasic SC.

since it is often unable to produce a sufficient local concentration of atropine to eliminate SCRs. The second and perhaps more interesting interpretation is that the persistence of SCRs does not reflect an inadequate local concentration of atropine but rather, it may signal the possible existance of an adrenergic or, to be more conservative, a non-cholinergic, component underlying the physiological activation of the SCR. Experiments to be cited later in the text will deal with these possibilities.

If one re-examines Figure 3, it will be noted that insofar as phasic responses are concerned, it would seem that IPS of saline alone causes no significant effects. On the other hand, IPS current and voltage effects on tonic SC are quite striking. Invariably, the effects of the applied IPS current and voltage were to increase SC tonic level in all Ss. The literature on the effect of current and voltage on tonic SC is, as usual, contradictory. Thus, Montagu (1958), Lader & Montagu (1962), and Wilcott (1964) report that IPS causes no change in tonic SC. As Wilcott (1964, p.57) says, "The effects on Sw (sweating) and SR were the same. For seven of the nine Ss tested there was no effect on basal (SR) levels or (SR) responses." However, Wilcott also found two Ss whose "...SR basal level and responses were reduced more than 50% as compared to the control side. For both of these Ss it appeared that the current produced some damage to the palmar skin. During current flow they both reported

a burning sensation at the palm requiring that the current be turned down several times. This was not the case with the other Ss. It thus appears that when there was no damage to the palmar skin, the current had no effect on Sw and SR" (1964, p.57). In the present experiment current levels were kept below the pain threshold, and no physiological damage (burns etc.) was ever reported or seen, however, tonic SC was consistently elevated.

Venables & Martin (1967) have stated that the effects of IPS cause a decrement in tonic SC, while ion size effects cause an increment in tonic SC (N=1). In the present laboratory IPS has been studied using distilled water and such ions as Li^+, Na^+, K^+, and H^+. Although the existence of a small ion effect was suggested, the effects were not consistantly related to ion size over this small range. Furthermore IPS caused a large increment in tonic SC even when electrophoresis of distilled water was used. This would suggest that ion size effects were not critically involved in elevating tonic SC when NaCl was used as a control. However, since none of the previous Es controlled area during IPS, the results across experiments are not comparable and hence it is impossible to determine the cause of this discrepancy. It should be noted though that in the present experiments the IPS current density and duration used was undoubtedly higher than that used by any

other of the above mentioned Es. It may be that current and voltage effects are minimal when the current density and voltage drop across the skin during IPS are kept below some damage threshold. Finally, it should be noted that in agreement with the literature, atropine has been found to decrease SC tonic levels. This decrease, however, is only with respect to the saline finger, since, as shown in Figure 2 tonic SC in the atropinized finger increases when it is compared to the untouched control.

EXPERIMENT 2

The Effects of Atropine Administered by Injection on SC.

Because the use of IPS to administer a high dose of atropine had been so time consuming, and since IPS caused large current and voltage effects, it became desirable to study the effects of subcutaneous injections of various drugs on SC in the laboratory. This technique was not without its own problems, as one could well imagine. Thus, difficulties were encountered in developing injection techniques, maintaining sterile equipment, minimizing pain etc.; however, since it provided a quick method for studying drug effects that were free of large and possibly confounding voltage and current effects, it seemed to be worth the extra effort.

METHOD

Ss were six paid male college students. The recording

procedure was the same as in Experiment 1. Due to the sensitivity of the finger tips to pain, corn pads and electrodes were always placed on the middle phalanges. In addition, the fingers were always splinted to help prevent movement artifacts. At the end of the thirty minute control period, S was given either 1 or 2 subcutaneous injections. Sterile, disposable syringes, calibrated in hundredths of a cubic centimeter, and fitted with 3/8 inch long, 30 gauge stainless steel needles were used for the injection. An attempt was made to keep the injection depth uniform, although the problems involved in accomplishing this feat are considerable. Various subjective and objective observations suggest that the degree of success obtained was only moderate. In two cases the control finger was injected first and received 0.1 cc of physiological saline under the recording electrode. In four cases a control injection was not administered. Immediately afterward, the experimental finger was injected with 0.1 cc. of atropine sulphate 0.8 mg/cc, also under the recording electrode. Recording was then continued for at least another sixty minutes.

RESULTS

Ss usually reported a transient (1 or 2 minutes) local soreness at the atropine injection site. This was often accompanied by local redness and vasodilation, however, these symptoms disappeared in a few minutes. At no time

did any S report any systemic symptoms (large doses of atropine produce symptoms such as dry mouth, dry skin, thirst, dizziness and double vision). The effects on tonic and phasic SC were relatively identical for all Ss. Results for a typical S are shown in Figures 4 & 5. Almost immediately, phasic SC and tonic SC began to decrease and within fifteen to forty minutes no SCRs could be observed in the atropinized finger although large SCRs were clearly evident in the control finger. During this interval, the recording sensitivity of the amplifier for the atropinized finger was usually increased until it was two to ten times that of the control finger, but no phasic SC activity could be elicited. It should be noted at this point that four of the six Ss used in this experiment had been used in the previous study on the effects of IPS of atropine on SC. In none of them were we able to eliminate all SCR activity, with IPS even though current densities of 1.4 mAmp/cm^2 were run for as long as ninety minutes. This would indicate that IPS is not as efficient a procedure for producing a high local concentration of drug ions in the skin as was previously thought.

EXPERIMENT 3

The Effects of IPS on SC Levels

At this point, the whole question of the use of IPS to administer drugs was reconsidered. In addition to

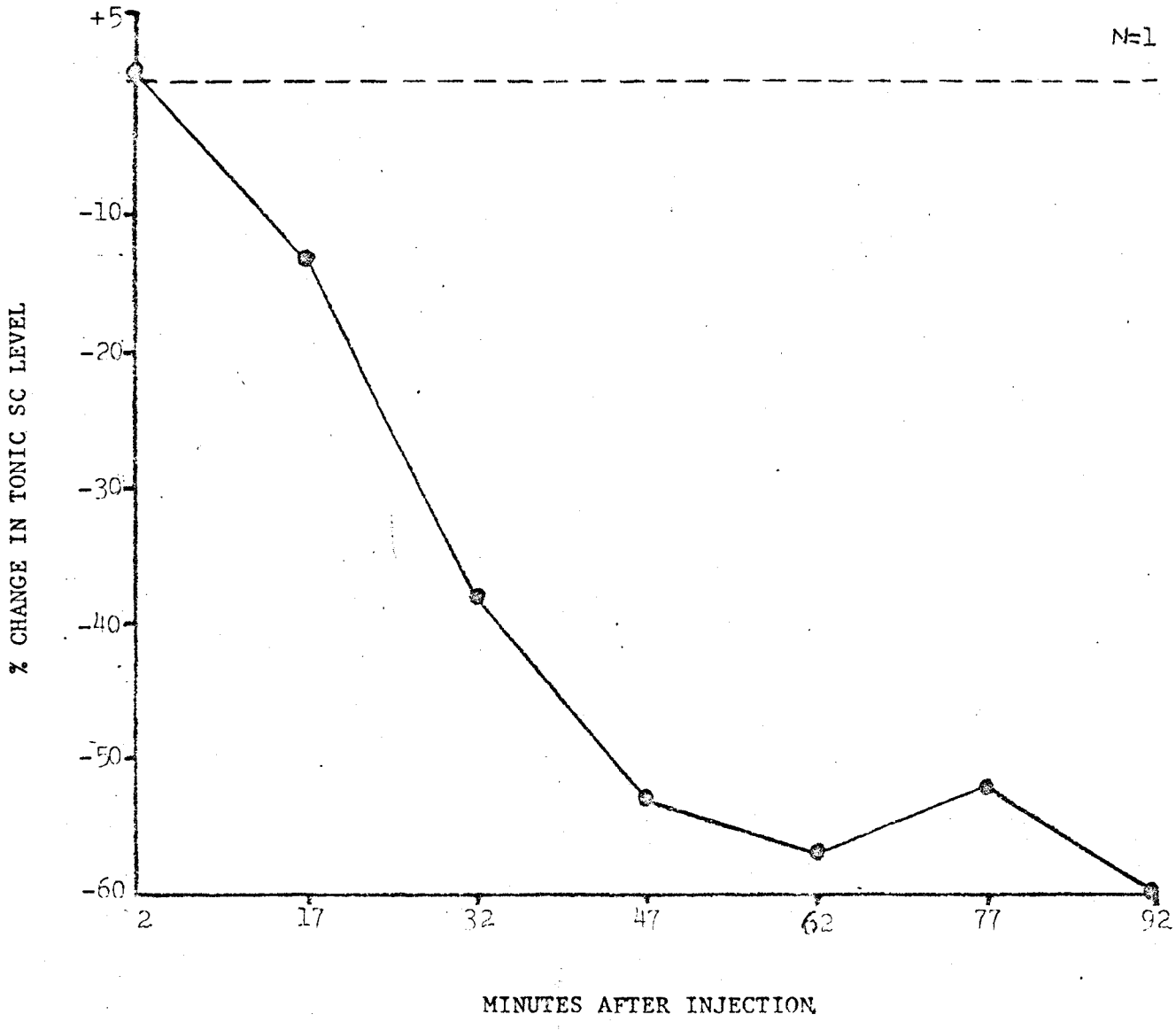

Fig. 4 The effects of injection of atropine (0.1 cc at 0.8 mG/cc) on tonic SC.

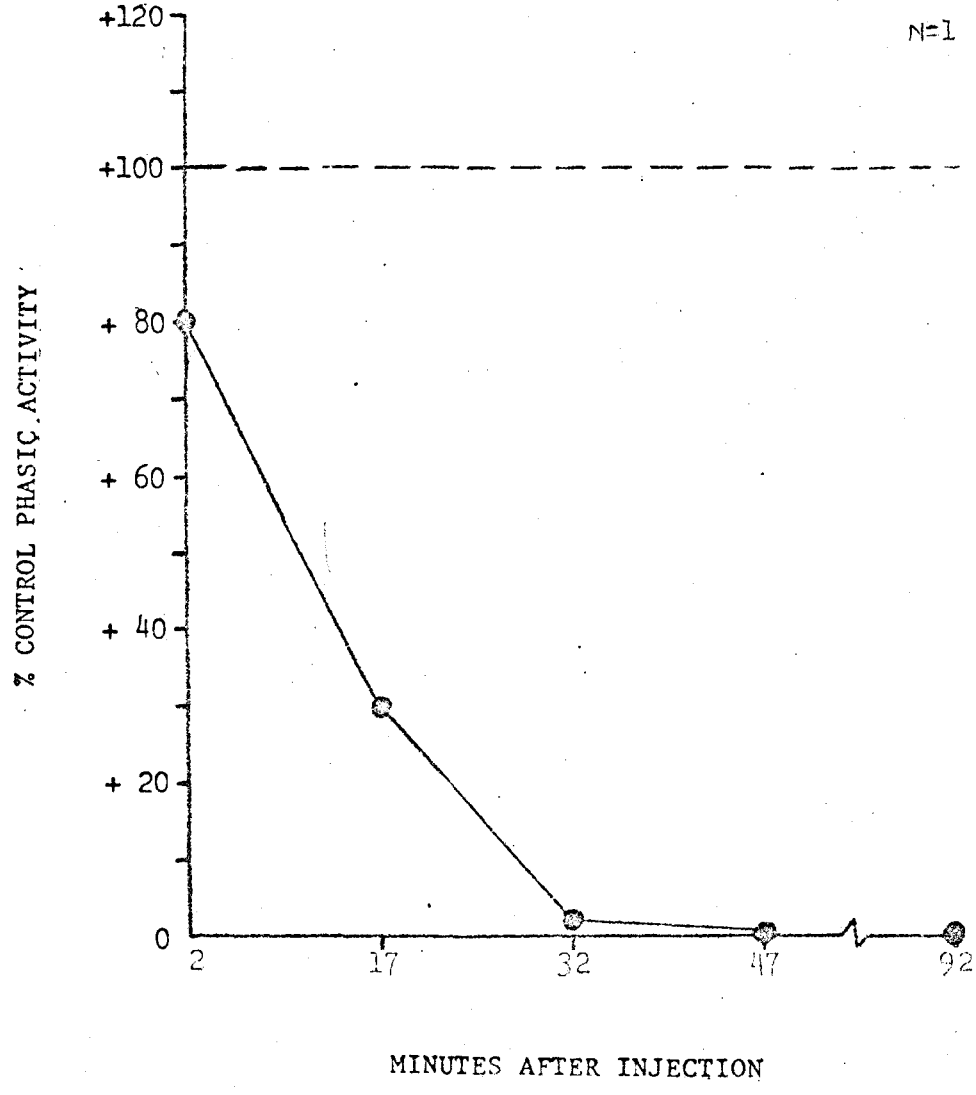

Fig. 5 The effects of injection of atropine (0.1 cc at 0.8 mG/cc) on phasic SC.

the question of efficiency, it seemed that IPS raised SC to levels far above the limits normally observed during variations in psychological "arousal". The skin can be represented electrically by a model (Thomas & Korr, 1957) in which the sweat glands act as variable resistances in parallel. The capacitance of the skin is considered to be in parallel with these resistive units. (See Figure 3). Therefore, increased SC could reflect either maximal stimulation of the sweat glands by IPS current to an extent never seen physiologically, or, it might reflect tissue damage. If tissue damage was involved, the SC effects noted could be due to destruction of either the capacitance or resistance of the skin, or both, since the electrical resistance of the skin is actively maintained. Therefore one final experiment in this series was performed in order to help E reach a final decision about IPS.

METHOD

Only one S, a paid male college student, was used in this experiment. Recording procedures were the same as in Experiment 1, except that independent reference sites were always used. On two successive days, SC was recorded from the same areas on three fingertips for an initial fifteen minutes. Then two of the fingertips received a subcutaneous injection of 0.1cc acetylcholine chloride 10^{-2} g/cc (Miochol; Smith, Miller & Patch). Invariably this caused

a sudden sharp increase in tonic SC. When the increase in tonic SC due to the injection asymptoted, another 0.1 cc of acetylcholine was injected. This occasionally caused another slight increase in tonic SC level. When the effects of the second injection had asymptoted, a third 0.1 cc of acetylcholine was injected, and invariably this did not cause a further increment in tonic SC. The SC maximum (SC_{max}) obtained in this way from both fingers was noted. On the third day, the identical areas of skin were prepared as in Experiment 1. Control recordings of SC were obtained for thirty minutes. Then one electrode and corn pad was removed and that finger was iontophoresed with distilled water using a current density of 1.4 mAmps/cm^2 for sixty minutes. After the end of the IPS period, the electrode was replaced and SC recordings taken for five to ten minutes. At that time, both fingers were injected with ACh using the same procedure as described above. One week later, the procedures used on the third day above were repeated, except that IPS proceeded for only fifteen minutes.

RESULTS

The SC_{max} obtained from each finger is shown in Table 1. The SC_{max} obtained during the first two days provide a measure of the reliability of the procedure, which seems to be quite high. As is immediately apparent, IPS increases tonic SC far above the level that can be

achieved using ACh (which is the main neurohumoral transmitter to the sweat glands). In fact, after IPS, ACh has no visible effect on tonic SC. The score in block 6 of Table 1 may be confusing since it suggests ACh has lowered the SC_{max} found after IPS; however, it only reflects the fact that the tonic SC observed immediately after IPS was higher than the tonic SC when the ACh injection began, i.e. tonic SC dropped during the interval before injection. When the injection was actually administered, ACh had no effect.

Since SC levels observed after IPS were much higher than those observed after injection of ACh, it is clear that some non-physiological process is going on during IPS. Whether this process is due to super-normal excitation of sweat glands or if it is due to destruction of resistive and/or capacitive membrances is unclear. However, the latter seems to be a more likely choice since the excitatory effects of IPS would probably diminish rapidly when the current was turned off. Since the SC effects noted were prolonged, it seems likely that physiological damage occured. Identical arguments pertain to the finding that ACh has no SC effect after IPS. Other investigations of ACh induced SC maximum will be discussed later in the text.

DISCUSSION

To sum up the results briefly, atropine, when

	Finger #1	Finger #2
Day 1	10.0 μʊ	10.3 μʊ
Day 2	10.7 μʊ	10.2 μʊ
Day 3 After IPS (60 Min.)	30.8 μʊ	-
Day 3 After ACh	30.8 μʊ	11.3 μʊ
Day 10 After IPS (15 Min.)	19.0 μʊ	-
Day 10 After ACh	18.0 μʊ	12.6 μʊ

TABLE 1

Normal SC levels and SC levels obtained after ACh and/or IPS.

administered by subcutaneous injection, eliminates all SCRs and decreases tonic SC considerably. However, when it is administered by IPS, although tonic SC decreases, (relative to an IPS saline control) it has been found to be impossible to eliminate SCRs in certain Ss. The contradiction in the literature on atropine effects has thus been reflected in the present data. However, it seems clear that the cause of the contradiction lies in the fact that IPS is an inefficient procedure, since if an adequate dose of atropine is administered by local injection, all SCRs are eliminated.

Methodological problems and inconsistencies are probably also partly responsible for the discrepancies in the literature. For example, at the outset of an experiment, E was faced with the problem of whether to use a constant current IPS system, a constant voltage IPS system, or a modification of one of the above systems as used in Experiment 1 of the present paper. Regardless of the procedure chosen however, it seems unlikely that either the current or voltage effects on sweat glands in one finger can be duplicated in a second finger unless the sweat glands in the second finger are in the same state of activation (i.e. their SC is the same). This is seldom the case.

Another potential problem in finding an adequate control has been noted by Martin & Venables (1967). They

suggest that if SC is in part caused by a semipermeable membrane, as seems likely, then forcing large organic drug ions through this membrane during IPS is likely to cause effects due to ion size only. As such, an ideal control solution would contain an isomer of the experimental drug having exactly the same ionized size, but having none of its pharmacological properties. Unfortunately however, such ions are rarely found[5] and preliminary data in the present E's laboratory partially support Martin & Venables contention that it may be an important parameter to control.

A third problem lies in the fact that as yet, no one has differentiated between the electrical effects of IPS and the chemical effect of the ion induced at the "control" site. Despite the fact that empirical evidence is not available, considering the importance of sodium and potassium in maintaining electrochemical equilibrium across nerve membranes, the use of sodium or potassium chloride as control IPS ions may not be a prudent procedure - yet these chemicals are commonly used.

Finally, as the results of Experiment 3 would suggest, the effects of even moderately prolonged exposure to the voltage and current effects of IPS raise tonic SC far above that level which can be elicited behaviorally or pharmacologically. Because pharmacological stimulation probably excites the vast majority of receptors on the sweat glands,

it seems likely that IPS causes real physiological damage since the resistance of the skin is not an ohmic resistance but rather reflects an actively maintained electromotive force in opposition to the applied current. In such a system, if current and voltage effects were activating the electrodermal membranes physiologically, you would expect SC to asymptote at a level somewhere near the SC level caused by a receptor saturating dose of the main neurohumoral transmitter. However, in Experiment 3 it was shown that, after IPS, tonic skin conductance levels are very much higher than those elicitable by ACh. This would suggest that the membranes responsible for maintaining tonic SC have been altered.

If this is the case the degree of damage caused may depend on the tonic SC level of the skin prior to IPS. For example, considering a simplified model of the skin in which capacitance is ignored, the size of the voltage drop across the skin during IPS for a given constant current level would depend on its SR. The SR of a given sweat gland depends on the size of the gland and its state of activation which are both variable. However, for areas of skin containing an equal number of sweat glands the larger the SR, the greater the voltage drop across the skin, and hence, as Edelberg (1967) has shown, the greater the damage. Differences in the tonic SR of different areas of skin used as the experimental and control IPS sites might hence result in varying degrees of damage and

different recovery rates. This would tend to further invalidate the effectiveness of a "control" IPS site.

In summary then, there are at least five prerequisite conditions which should be met before IPS can be used with confidence to administer drugs in the skin, until such time when considerably more parametric data on IPS effects are available.

1. The SC of the areas of skin to be iontophoresed should be nearly identical.

2. A pharmacologically inactive control ion having the same size as the ionized drug of interest should be used.

3. The physiological damage caused to skin membranes must be small and equal at both sites (i.e. voltage drop and current duration should be kept below the damage threshold).

4. The recovery rate from electrical effects must be identical for both sites.

5. The iontophoresis procedure must be efficient in producing an adequate local concentration of the drug.

Since it seems that these conditions are rarely, if ever,

met, this casts serious doubt on the quantitative and perhaps even qualitative reliability of previous research on SC which used IPS. In light of these numerous methodological problems, the use of IPS would seem to be inadvisable and results obtained thereby would seem to be questionable. Therefore, the inescapable conclusion seems to be that the use of IPS to administer drugs in the skin should be abandoned in the type of experiments central to this paper.

CHAPTER 3

ADRENERGIC INVOLVEMENT IN SC

EXPERIMENT 4

The SC Effects of Bretylium Administered via IPS and Injection

Since it appeared that drug effects obtained using IPS as a procedure were unreliable, another experiment was performed. In the first part of the experiment bretylium was administered by IPS while in the second part it was administered by local injection. By comparing the results it was hoped that we would be able to evaluate results obtained using IPS and in addition, it was hoped that the experiment would shed light on the possible existence of an adrenergic mechanism in the innervation of sweat glands since the final effect of the nicotinic blockade caused by bretylium is a secondary adrenergic blockade.

METHOD

The recording procedure in this experiment was identical to that in Experiment 1, except that separate inactive (drilled) sites were always used. In the first part of this experiment the Ss were three paid male college

students. There were five experimental sessions. For the experimental finger a 2% solution of bretylium in distilled water (Darenthin; Burroughs-Wellcome) was used, while the control finger was iontophoresed with distilled water. A constant current system of IPS was used to make the results more comparable to those of Lader & Montagu (1962). The IPS current lasted for forty-five minutes at a density of 1.1 milliamps/cm^2. Recording then continued for sixty minutes.

In the second part of the experiment, the Ss were four paid males ranging in age from 20 to 25 years. There were eight experimental sessions. The procedure used was the same as used in Experiment 2 except all Ss received control injections of physiological saline having the same pH as bretylium (7.0). Four injections were administered to each S. The first injection was 0.1 cc physiological saline. Then 0.1 cc of bretylium having concentrations of 5×10^{-3} g/cc, 5×10^{-4} g/cc, and 5×10^{-5} g/cc were injected subcutaneously in the middle phalange of three other fingers of the same hand. These injections were all approximately isotonic. Recording was then continued for ninety minutes.

RESULTS

With the doses of bretylium used, Ss never reported either immediate or delayed local or systemic symptoms.

The mean per cent change in tonic and phasic SC levels caused by bretylium administered by IPS over five sessions is shown in Figure 6. The phasic means noted are qualitatively representative of the responsiveness to bretylium of all Ss. Tonic measures showed considerable variability, both qualitative and quantitative. Bretylium caused a large decrement in total phasic SC activity, while tonic SC activity showed a moderate initial increment followed by a small decrement. Figures 7 and 8 show the mean per cent change in tonic and phasic SC scores recorded when bretylium was introduced via local injection. In seven of eight sessions, tonic SC scores remained remarkably constant for the entire ninety-minute recording session. In the means shown in the figure, with the exception of one point, all scores deviated by less than 10% from the control level. This result was contrary to that found when bretylium was administered by IPS. On the other hand, phasic SC scores agreed more closely with those obtained using IPS and show a clear dose response differentiation. In all Ss the highest dose of bretylium used initially caused a large decrement in phasic SC activity. Toward the end of the session however, the effects diminished. In three of four Ss, initially, the dose of 10^{-4} g/cc bretylium seemed to cause a slight decrement in phasic SC; however, this was followed by a prolonged increase in phasic SC. The lowest dose of bretylium

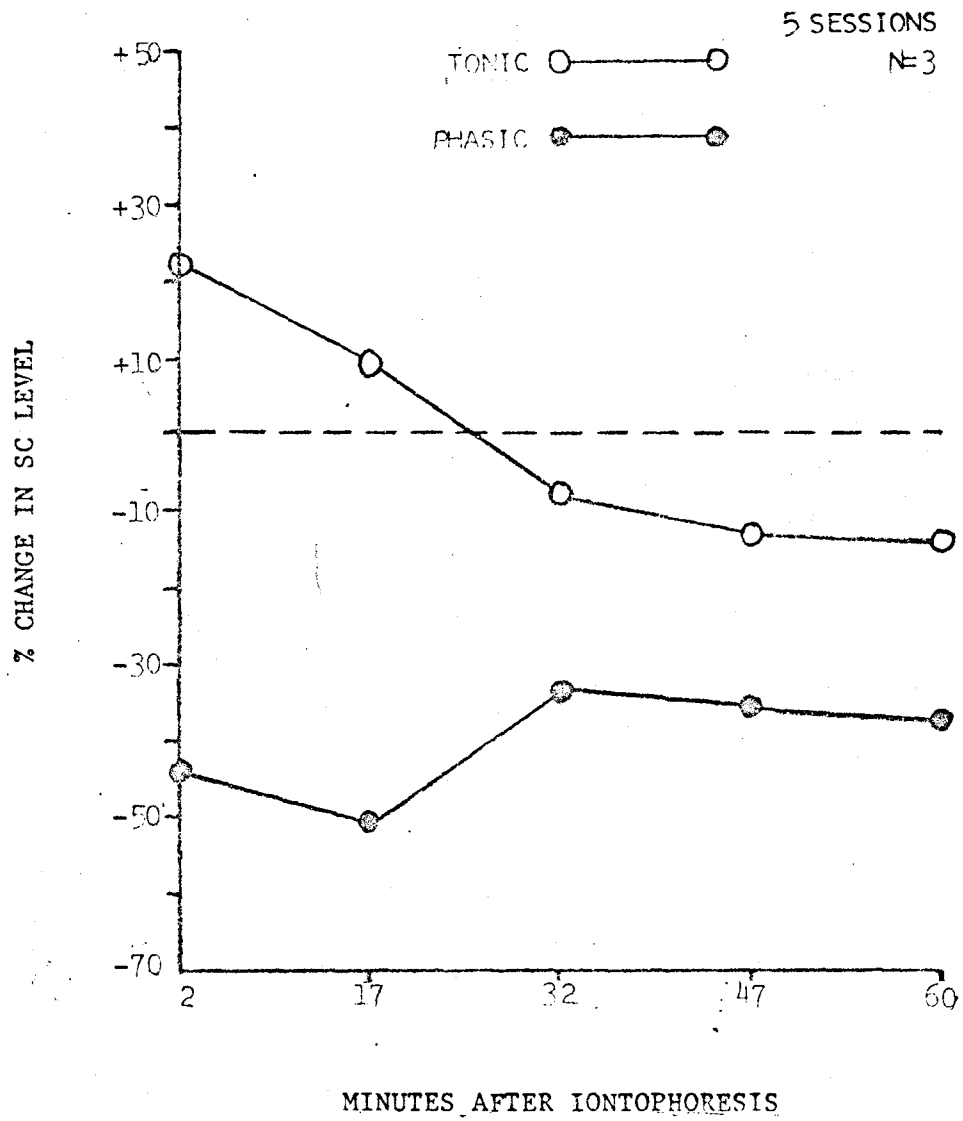

Fig. 6 The effects of iontophoresis of bretylium (1.1 mAmp/cm^2 - 45 min.) on tonic and phasic SC.

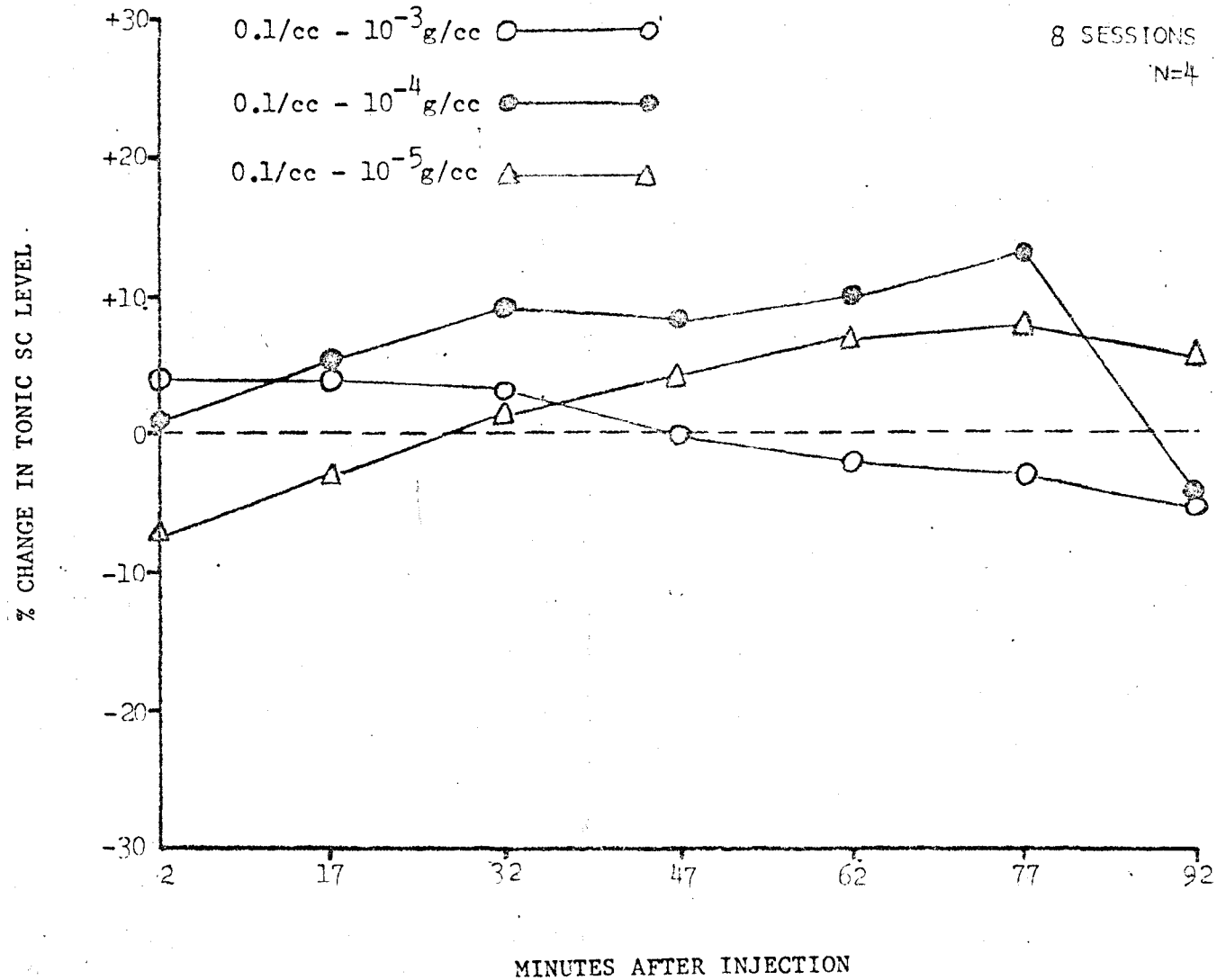

Fig.7 The effects of injection of bretylium on tonic SC.

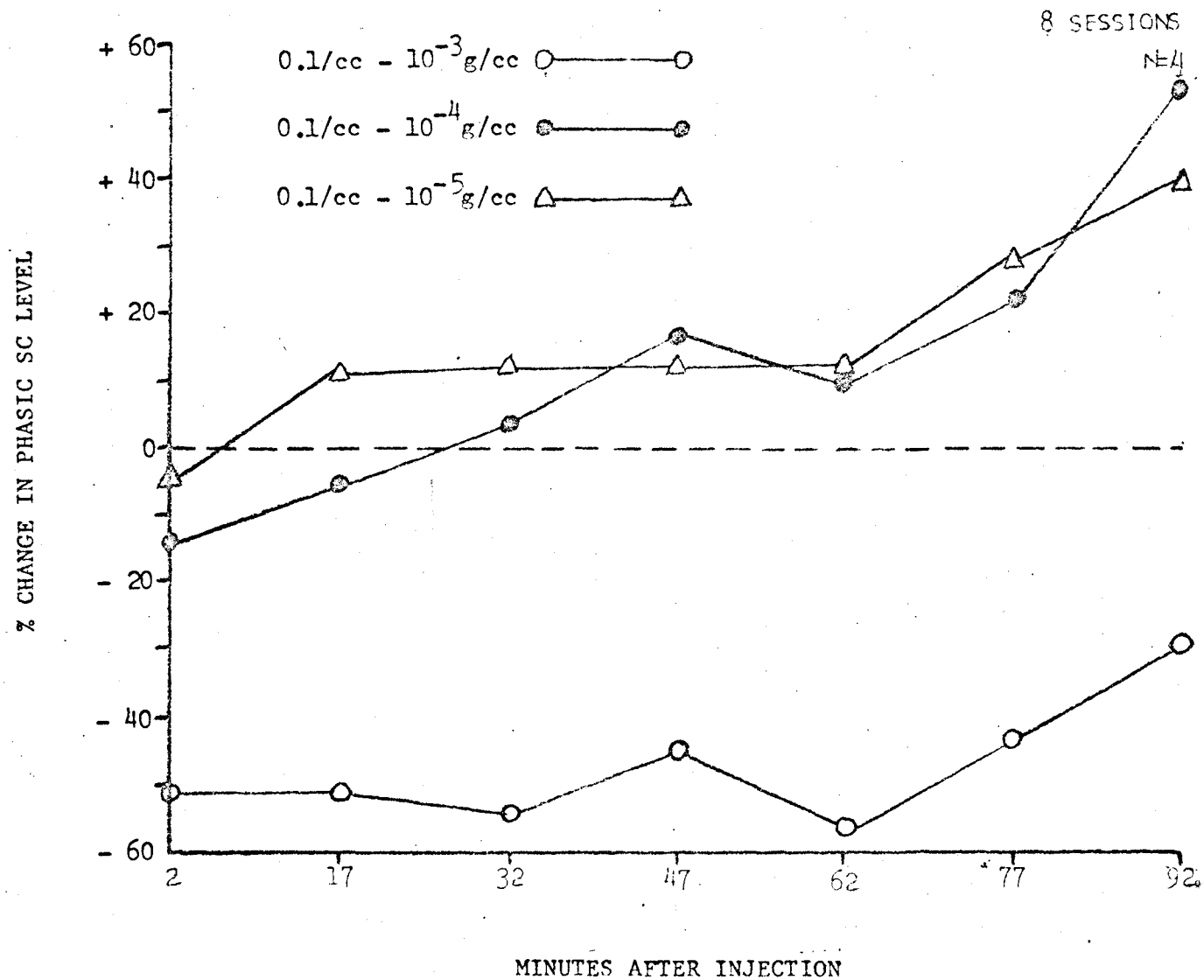

Fig. 8 The effects of injection of bretylium on phasic SC.

caused small but erratic effects at first; however, like the dose of 10^{-4}g/cc it also caused an increment in phasic SC over time. This pattern was seen in six of eight sessions.

DISCUSSION

As expected, the effects of bretylium on SC were erratic when a comparison of results across methods of administration was made. The results are shown in Figures 6, 7, and 8. In all Ss the effects of bretylium on phasic SC were qualitatively similar when the time-response effects for the largest injected dose were compared to the time-response effects obtained after IPS. Nonetheless, IPS of bretylium seems to have caused bizarre effects on tonic SC which were different from any other seen. Potentially, it could be argued that the dose of bretylium administered via IPS was not comparable to the others. However, considering the similarity in phasic SC effects in the above noted comparison, it seems more likely that the lability in tonic SC scores obtained after IPS reflects methodological and artifactual error. This seems particularly likely in view of our knowledge that IPS increases tonic SC above physiological levels. When this occurs the resulting "injury" effects and recovery processes might mask any drug effects, or a lack thereof.

In the present experiment, bretylium was noted to have

an effect (decremental) on phasic SC levels which has not previously been reported. In fact, Lader & Montagu (1962) have claimed that bretylium does not have any effect on SC. Exactly how they arrived at this decision remains unclear, but in any case our results are not directly comparable since their observations were not made until twenty-four hours after bretylium was administered via IPS, when the symptomatic effects of adrenergic blockade were quite obvious. This decremental effect is quite interesting in that it was unaccompanied by any appreciable change in tonic SC level. This suggests that tonic and phasic SC may be independent.

Since the effects of an adrenergic blockade caused by bretylium would have included vasodilation and since the adrenergic blocking effects of bretylium have been reported to be delayed, Ss were questioned and observed to see if immediate or delayed local vasodilation occurred, but none was reported or seen. Unfortunately, therefore, since in the present experiment simultaneous plethysmographic data on bretylium injection effects were unavailable, it can not be concluded that the effects observed had an adrenergic aetiology. Thus, for example, it is theoretically possible that the reduction in phasic SC noted was caused by a local anaesthetic effect which bretylium is known to have (Goodman & Gillman, 1965) although one is left with the difficult problem of explaining the lack of effect on tonic SC. Since

this is the case, a more extensive discussion of the results obtained would be purely speculative, and will therefore be omitted.

EXPERIMENT 5

The Effects of Epinephrine on SC

Since a clear understanding of the local effects of EPI on SC seemed essential to an understanding of neurohumoral transmission to the sweat glands, this problem was investigated.

METHOD

The Ss were three paid males ranging in age from twenty-one to twenty-five years. There were five experimental sessions. The recording apparatus used was the same as in the previous experiments. At the outset of the experiment, seven active and seven inactive electrodes were attached to the palm and forearm of one hand respectively. The reference sites at the forearm were previously prepared using Shackel's (1959) method of skin drilling. Ss were instructed to elicit GSRs at one-minute intervals by coughing, deep breathing, scratching etc. After recording SC for a thirty-minute control period, S received six subcutaneous injections under the electrode sites. The first, third, and fifth injection contained 0.1 cc of saline adjusted to have a pH of 2.35, 5.0, and 6.0. The second, fourth, and sixth

injections contained 0.1 cc EPI having a concentration of 10^{-3} g/cc, 10^{-5} g/cc and 10^{-7} g/cc. The pH of the saline control solutions was made identical to that of their respective experimental solution because it was determined in preliminary sessions that changes in the pH of saline injections had effects on phasic SC activity. The injections were administered over a fifteen minute interval.

After these injections had been administered SC was monitored for at least another ninety minutes while adrenergic sweating was investigated in the S's other hand. Sweating was observed by the method of Wada (1950). Briefly, a 2% iodine-absolute alcohol solution was painted on the skin and a mixture of starch in castor oil was daubed on when the iodine was dry. "When sweating occurs, spots or rings of black-stained starch grains appear at the pores of functioning sweat glands and can be seen in a transparent layer of the starch-castor oil mixture." (Wada, 1950, p.376). Preliminary work showed that adrenergic sweating could not be easily visualized in most Ss using this method unless spontaneous sweating was inhibited. Therefore, Ss received two subcutaneous injections of 0.1 cc atropine sulphate 0.8 mg/cc. Approximately fifteen to forty minutes after the injection of atropine no sweating was visible under ten power magnification. At this time 0.1 cc saline having a pH of 2.35 was injected subcutaneously into the center of the non-sweating area of the control site. Immediately

afterward, the experimental site received a subcutaneous injection of 0.1 cc EPI 10^{-3} g/cc, also in the center of the non sweating area. The areas injected were homologous to those injected on the other hand. Sweating was observed with a 10x magnifying glass. It's duration was determined by repeatedly wiping off and reapplying the starch and castor oil mixture.

RESULTS

The dose of 10^{-3} g/cc EPI usually caused Ss to complain about a sharp stinging localized pain. This usually lasted for two to five minutes. Vasoconstriction was seen around the injection site almost immediately and extended into most of the forefinger as the session progressed. There was no discernible spread of vasoconstriction into any other areas. The dose of 10^{-5} g/cc EPI also usually caused transient pain and some vasoconstriction, but this was barely visible around the electrode site. The dose of 10^{-7} g/cc EPI seldom caused pain and did not cause any visible vasoconstriction around the electrode site although vasoconstriction may have occurred under the electrode.

The effects of EPI on phasic and tonic SC are shown in Figures 9 and 10. Only the highest dose of EPI caused any increase in tonic SC. Unlike ACh, EPI (10^{-3} g/cc) did not cause a sharp increase in SC immediately after injection. Rather a small, slowly rising increment was seen. This

occurred during the first fifteen minutes after the injection and was followed by a slow decline in tonic SC. Initially the dose of 10^{-5} g/cc EPI seems to cause no effect; however, a slow decline in tonic SC also followed. The lowest dose of EPI caused a small initial decrement in tonic SC, but seemed to have little or no effect after fifteen minutes. These effects were seen in all Ss. All doses of EPI caused a decrement in phasic SC responses. Initially, the degree of response decrement was inversely proportional to the concentration of the dose administered, but fifteen minutes after the injection the relationship reversed, and the degree of phasic blockade was directly related to the concentration of EPI administered. This relationship was seen in all five sessions when a comparison of the effects of the highest and lowest dose of EPI was made. The dose of 10^{-5} g/cc EPI however, had erratic SC effects.

In the hand being observed for sweating effects, 10^{-3} g/cc EPI caused prompt adrenergic sweating to occur within five minutes of the injection. The pH control site occasionally showed a few tiny drops of sweat immediately after the injection, but it ceased within the first two minutes. Adrenergic sweating on the other hand actively continued throughout the length of the recording session (50-75 min.). However, the amount of adrenergic sweating was small when compared to adjacent spontaneous sweating. Adrenergic sweat appeared as discrete droplets at the

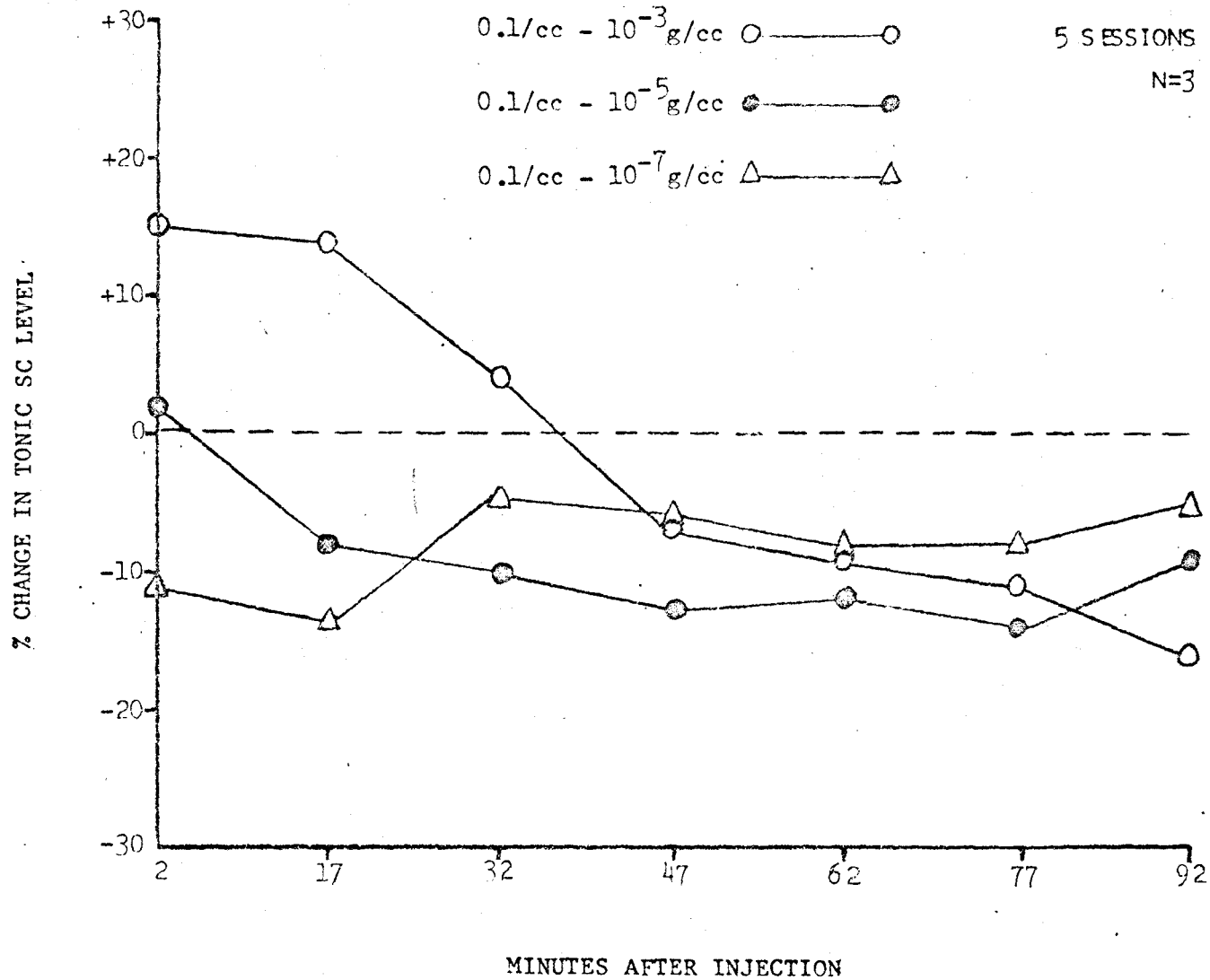

Fig. 9 The effects of injection of epinephrine on tonic SC.

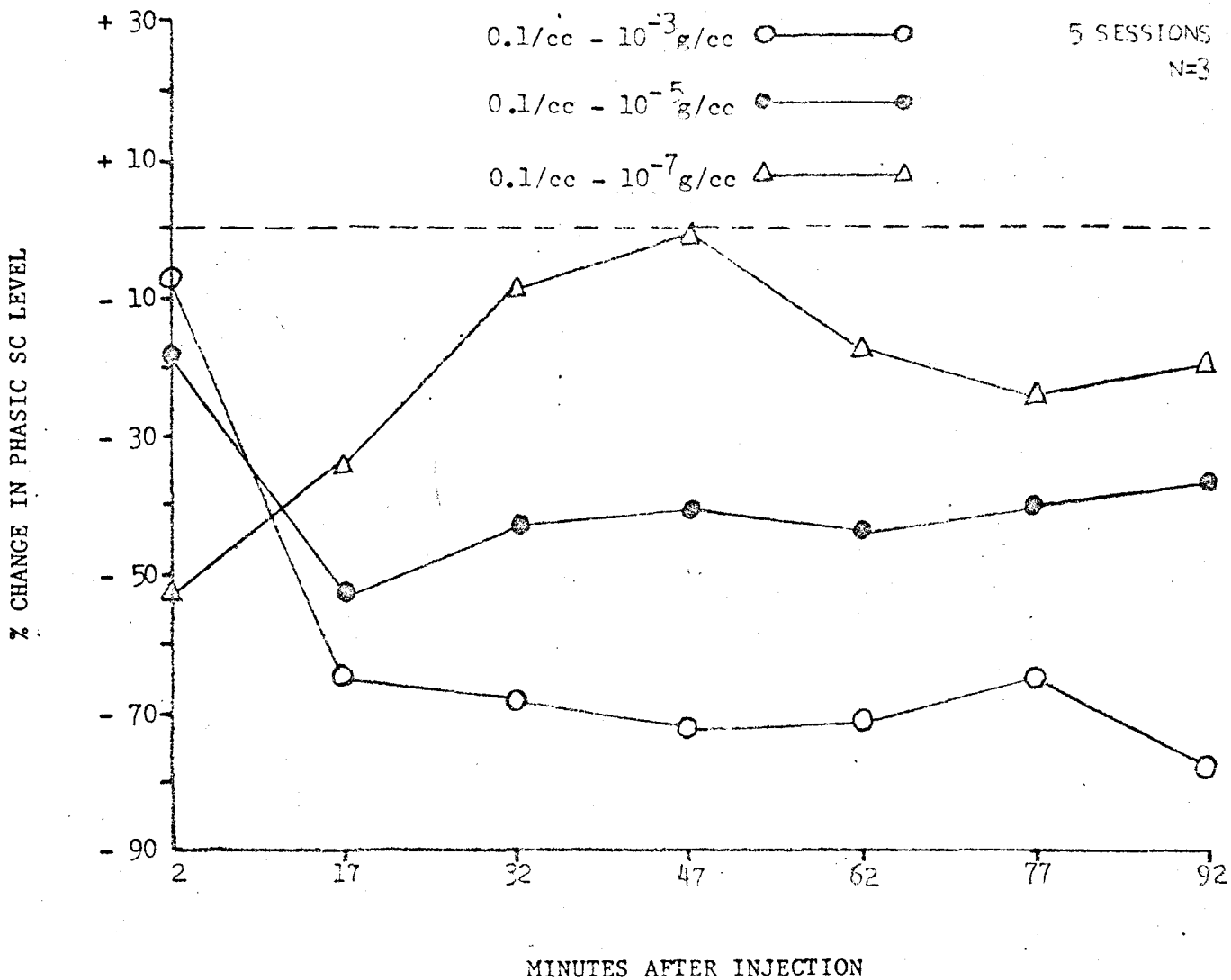

Fig. 10 The effects of injection of epinephrine on phasic SC.

injection site at first, and then spread into the same areas where vasoconstriction was observed.

Figures 11 and 12 show the effects of changes in pH on tonic and phasic SC. Insofar as tonic SC levels are concerned, at only one point was there a greater than 10% deviation from the control level. However, phasic SC response changes were extremely labile. Generally speaking, the greater the acidity of the solution, the greater was the increment in phasic activity that was seen, until at pH 2.35, a drop in phasic activity was observed after the first fifteen minutes. This dissociation of tonic and phasic SC again suggests that the responses may be independent (i.e. see Figures 7 and 8).

DISCUSSION

In agreement with previous research on the effects of systemic doses of EPI on SC, the present experiment demonstrated that non-systemic doses of locally acting EPI generally cause a small decrement in tonic SC over time. However, an initial excitatory EPI effect was observed with the highest dose which had not been reported in the literature. This effect was relatively small, hence it was not surprising to find in later pilot studies that EPI had little or no effect when used in conjunction with ACh or atropine to try and raise SC maxima or minima obtained using the same procedure as in Experiment 2. EPI effects

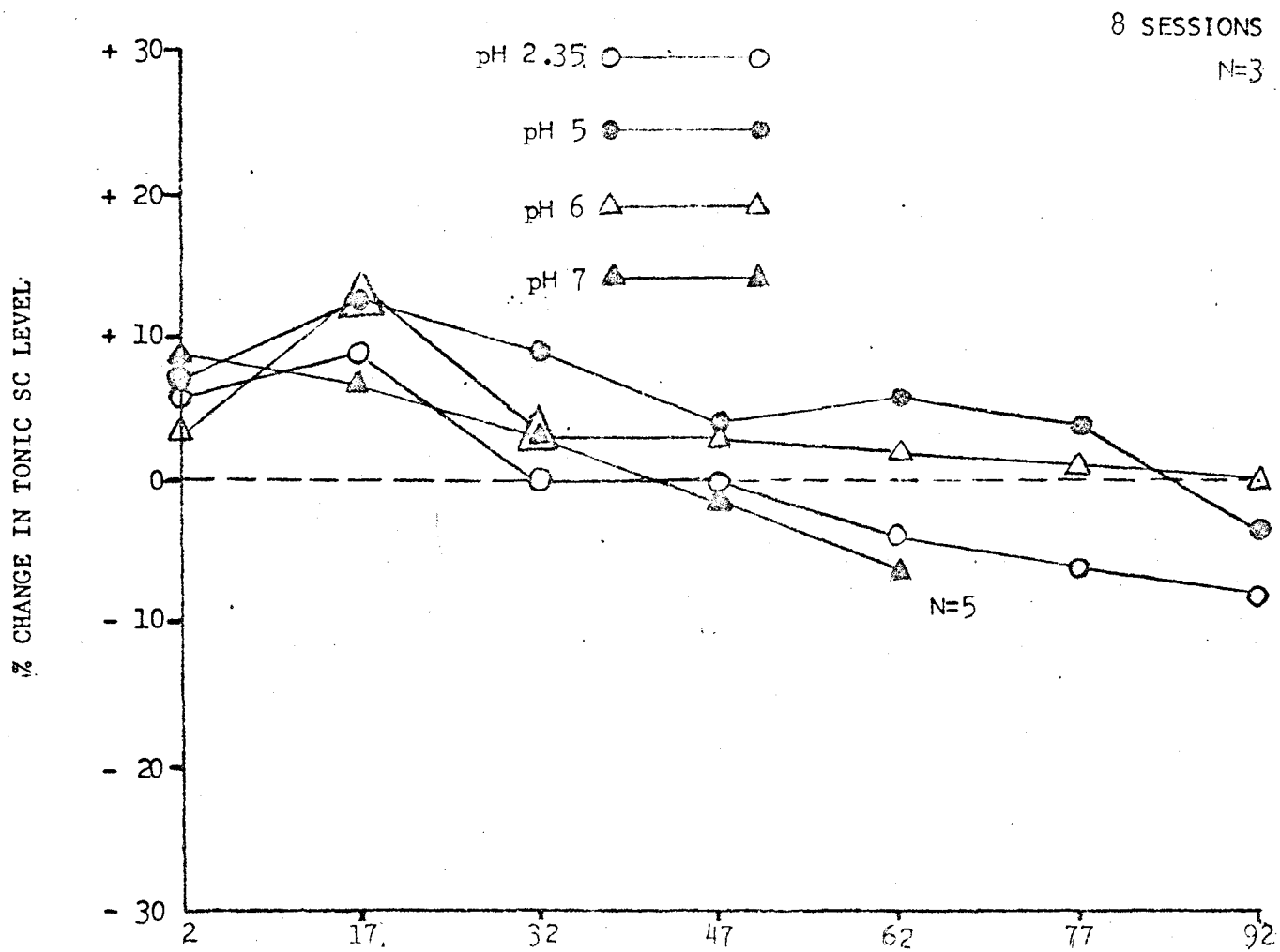

Fig. 11 The effects of changes in pH on tonic SC.

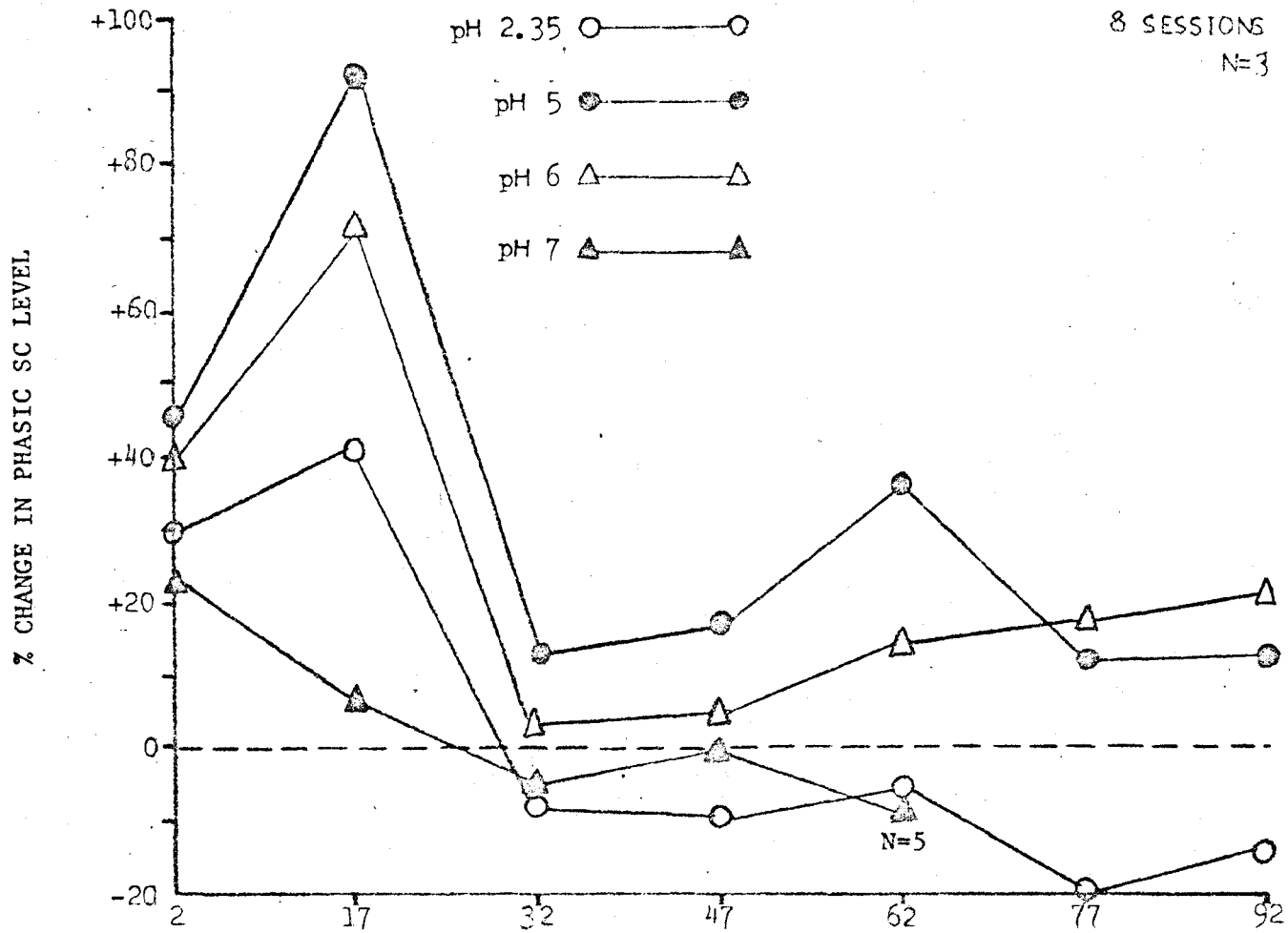

Fig. 12 The effects of changes in pH on phasic SC.

on phasic SC (diminishing) agreed with those found by Densham and Wells (1927). The pattern of initial tonic and phasic SC dose-response curves however suggests that two processes, one inhibitory and one excitatory are interacting. In light of the fact that a large dose of EPI causes a transient increase in tonic SC level while a small dose causes a decrement in tonic SC, the peculiar inversion of dose-response effect seen in phasic SC fifteen minutes after EPI injection might be due to an interaction of these two opposing processes. The excitatory effect may be due to a direct action of EPI on the sweat glands, while the inhibitory effects could be due to such things as decreased blood flow and its concomitant temperature drop and/or change in metabolism due to decreased oxygen levels following vasoconstriction. It is quite probable that the effects of vasoconstriction would have to be taken into consideration since many researchers (Wilcott, 1958; 1962; Carmichael et al, 1941; Goadby & Goadby, 1941) have found that exsanguination abolishes sweating and severely reduces SCRs. A drop in skin temperature has also been found to have similar, though less severe, effects (Maulsby & Edelberg, 1960). Another possibility that should be mentioned finally,is that EPI may be directly antagonizing the effects of ACh, as often happens in other parts of the body.

The observed results might be seen if the sweat glands are represented by a model having a few excitatory

adrenergic receptors, surrounded by a plexus of vasculature having very many vasoconstrictive or "inhibitory" receptors. A large dose of EPI would excite many "excitatory" receptors, but it also would excite many more inhibitory receptors. The sum of their activities would be the observed initial effect. As time progressed, though, excitatory effects would reach some kind of equilibrium, but inhibitory effects would be cumulative as an increasing oxygen and temperature drop following prolonged vasoconstriction became more and more debilitating. A very small dose of EPI on the other hand would excite very few or no "excitatory" receptors on a strictly probablistic basis and its whole effect would be inhibitory. With time however, EPI would diffuse away in the blood and recovery would take place. A moderate dose of EPI would be expected to have effects somewhere between these extremes. If one examines the first and last points of all curves on Figure 7, one sees that this type of result was observed.

In light of our knowledge that sweat gland function plays an important role in maintaining SC tonic and phasic levels, it was somewhat surprising to see a large drop in SCR amplitude and a small drop in SC tonic level despite the fact that active sweating occurred in response to a high dose of EPI (in the same site where atropine had been previously administered). These results suggest that sweating and SC changes may be somewhat independent. This

conclusion was also reached by Edelberg (1964) and Wilcott (1964); however, they arrived at this decision after noting that SCRs were seen while sweating was abolished. In the present experiment, the opposite effect was seen; i.e. although moderate sweating was observed, SCRs were diminished. It appears therefore that SCRs can be partially dissociated from sweat gland activity. However, if the model described above is correct, one might expect to see both sweating and a drop in tonic and phasic SC if some sweating due to a powerful effect of EPI on a few sweat glands was superimposed on a more powerful overall drop in sweat gland activity due to lack of oxygen following vasoconstriction. Thus the present evidence suggesting the independence of sweat gland activity and SC levels must be considered to be tentative.

In summary then, it would seem that despite the post hoc arguments and interpretations noted above, several lines of evidence suggest that adrenergic sweating is not a physiologically relevant phenomenon in the study of SC. For example, atropine has been found to block all SCRs. In addition atropine has been seen to lower tonic SC to less than 1 μ mho in several Ss who were known to display adrenergic sweating after injections of EPI. Since these muscarinic effects are so great, little remains for any adrenergic component to influence. In addition, only an unphysiologically high dose of EPI was effective in raising tonic SC. This dose certainly caused more vasoconstriction

than would ever be seen under normal conditions. This also argues against the existence of a natural adrenergic component.

On the other hand, the possibility was considered that EPI-induced vasoconstriction prevented its own distribution to the sweat glands. Therefore an attempt was made to cause adrenergic sweating by releasing any endogenous EPI which might be stored at the neuro-effector junction. Amphitamine was used since it is known to act by releasing norepinephrine (Burns, 1965, 1968). When a small dose was injected into the forearm, sweating was observed; however, later results showed that this sweating was blocked by a previous injection of atropine. Since adrenergic sweating is unaffected by atropine, amphetamine-induced sweating appears to be cholinergic. Whether this is a direct or indirect effect is unknown. At this point this pilot study was terminated.

Finally, even the effects noted after injections of bretylium did not support an adrenergic hypothesis. For the moment therefore, although a final decision as to the existence of an adrenergic component in sweat gland innervation may be held in abeyance, one must conclude that the probability that a significant adrenergic component is involved is low.

Since the existence of any adrenergic component would be of considerable theoretical interest(re. the Burn-Rand hypothesis), further investigation of this problem may take two approaches. First of all an attempt will be made to design equipment which will monitor pulse volume and SC from the same site simultaneously. Temperature effects can then be controlled using a water bath and it may be possible to control for a local oxygen debt by using some kind of restrictive bandage on the control site. However, the most promising possible method of attack may involve the use of false adrenergic transmitters. A false transmitter is "... held in the same storage sites as norepinephrine, released by nerve stimulation, and depleted by drugs which deplete the physiological transmitter...,(T)he activity of most adrenergic false transmitters is far less than that of norepinephrine." (Kopin, 1968, p.378). Already such drugs as octopamine, metaraminol, and α-methyl-DOPAmine have been identified as false adrenergic transmitters. If the skin was primed with a dose of one of these drugs and it replaced the normal stores of nor-epinephrine, then in effect one would have blocked any adrenergic component in the skin. Hopefully any EPI released by the drug would diffuse away in the blood and one could then observe SC effects which were free of confounding vasoconstrictive effects. This could possibly provide a method whereby a clearer understanding of the physiological basis of SC activity could be determined.

CHAPTER 4

EXPERIMENT 6

Range Correction and the Psychological Relevance of SC Scores

Since the results of previous experiments had shown that adrenergic agonists and antagonists had little or no effect on tonic SC, only ACh and atropine were used in the final experiment in order to elicit SC maxima and minima, respectively.

METHOD

Five paid males ranging in age from twenty-one to twenty-five years were used as Ss in this experiment. The Ss were brought to the laboratory at 11:00 p.m. and SC was monitored throughout the night from the middle phalanges of three fingers of the same hand, using the same procedure as in Experiment 3. The Ss were awakened in the morning around 10:00 a.m. Injections were not administered until approximately thirty to forty-five minutes after S was awakened when S seemed thoroughly awake. At that time S received 0.1 cc atropine sulphate 0.8 mg/cc subcutaneously under one recording electrode. The pain involved during

the injection usually caused tonic SC to rise in all fingers. At this time S was encouraged to elicit SCRs and raise his tonic SC level by vigorously coughing and taking deep breaths. While this occurred, E inserted a second syringe needle subcutaneously under a second recording electrode. When the tonic SC response seemed to level off, E administered three injections of 0.1 cc acetylcholine chloride 10^{-2} g/cc (Miochol: Smith, Miller & Patch) until the pharmacological effects of ACh had asymptoted. The injections were separated by approximately two to five minute intervals. The tonic SC_{max} elicited just prior to the ACh injections was called the normal SC_{max} (N-SC_{max}) while the SC_{max} elicited after ACh was called the pharmacological SC_{max} (P-SC_{max}). Recording was then continued for one hundred and twenty minutes. The lowest SC level observed during this interval was called the pharmacological SC_{min} (P-SC $_{min}$) while the SC_{min} observed during the night of sleep was called the normal SC_{min} (N-SC $_{min}$).

RESULTS

The injection of ACh usually caused Ss to report a localized stinging pain which was transient. Throbbing was also occasionally reported and was usually accompanied by signs of local vasodilation. All symptoms terminated within a few minutes after the injections. The effects of ACh and atropine on tonic SC are shown in Table 2. N-SC_{max}

and P-SC_{max} are very similar for all within S comparisons. The same is also true for N-SC_{min} and P-SC_{min}; however, these results may be misleading since in all cases the SC of the atropinized finger was still decreasing slightly when the session was terminated. In four out of five Ss P-SC_{min} was lower than N-SC_{min}. In S #3 this relationship is reversed. However, this S had been exposed to the effects of atropine frequently and it seems likely that he had developed a tolerance to atropine which was not seen in the other Ss. Atropine injections, as reported previously, eliminated all SCRs. The latency of this effect was variable; however, it usually occurred within forty-five minutes after injection. Acetylcholine also caused SCRs to be markedly diminished and occasionally it eliminated all SCRs. This occurred immediately after injection and continued for approximately thirty to sixty minutes. During this interval tonic SC in the finger injected with ACh returned to approximately normal.

DISCUSSION

The results obtained in this experiment suggest that pharmacologically induced SC maxima have considerable psychological relevance. On the other hand, it seems likely that the similarity between sleep induced and pharmacologically induced SC minima was in part a function of the decision on when to end the session, because when SC recordings

	$N\text{-}SC_{max}$	$P\text{-}SC_{max}$	$N\text{-}SC_{min}$	$P\text{-}SC_{min}$
S_1	3.8 μʊ	4.3 μʊ	0.8 μʊ	0.55 μʊ
S_2	9.7 μʊ	10.3 μʊ	4.2 μʊ	3.8 μʊ
S_3	19.7 μʊ	20.6 μʊ	5.0 μʊ	5.9 μʊ
S_4	8.55μʊ	10 μʊ	2.6 μʊ	1.8 μʊ
S_5	9.5 μʊ	10.3 μʊ	3.3 μʊ	2.3 μʊ

TABLE 2

Normally (N) and pharmacologically (P) induced SC maxima and minima.

were continued for very long intervals (four to eight hours) after injection, a small but continued decline in SC was sometimes seen. The fact that atropine induced minima are regularly lower than those found during sleep indicates that even during sleep, some measure of "arousal" is reflected in SC tonic levels. Data presented by Wang (1957, 1958) have shown that intraspinal influences help maintain skin potential responses in decerebrate cats. To the extent that his data are comparable to the present ones, it may be that the tonic "arousal" seen during sleep in humans may also reflect a spinal component. In such an event, the peripheral pharmacological assessment of SC_{min} may necessarily underestimate the normal minimum output level.

Thus it seems likely that at least one factor (SC_{max}) in Lykken et al's (1966) range correction equation can be estimated pharmacologically. However, whether or not this would help improve the correlation between various psychophysiological response measures and be of value in the range correction formula is an empirical problem. The use of atropine to estimate SC minima will have to be investigated further since it may be that SC minima recorded at some fixed interval of time after an atropine injection (two hours in the present experiment) may provide a more reasonable estimate of Ss true SC_{min} than the SC_{min}

obtained when atropine effects have asymptoted, although it seems unlikely that this would be consistent in cross-sectional research. Furthermore, the psychological relevance of a SC_{min} obtained during sleep is open to question since "...it is not at all clear that the (SC) minimum obtained during a full nights sleep would be optimal for RC since the minimum value obtained while the S is still awake (or just crossing the sleep threshold) might seem to best represent the lower end of the activation continuum usually of interest." (Miller, 1968b).

It should also be noted in passing that the use of drugs to elicit SC minima and maxima provides a potential approach to the study of the effects of variations in tonic SC level upon SCR response size, i.e. the "Law of Initial Values" (LIV) (Wilder, 1957). It may provide an improvement over previous techniques, especially insofar as SC is concerned (The LIV theoretically applies to all autonomic measures), since as Miller (1968b) has noted, the LIV is essentially a within S statement, yet invariably the study of it has been cross-sectional in approach. This leads to confusion since a comparison of SC response sizes across Ss for a given tonic SC level has little significance unless the Ss SC ranges are identical, or have been adjusted for variation in range using the RC. The use of drugs like ACh or atropine to find Ss SC range would alleviate this problem. Failure to take this consideration into mind may

explain why the published research on SC and the LIV has been contradictory. Thus, Hord, Johnson & Lubin (1964) found that the LIV does not hold for SC recordings, while Sternbach (1960) found that it does.

Potentially, it would seem that drugs could also be used to cause variations in SC tonic level; however, there are problems involved in using this type of approach. For example, in the present experiment it was noted that soon after an injection of ACh, SCRs diminished in amplitude. This may have been initially due to the effect of the LIV, but the SCR effect continued even when tonic SC began to recover toward normal. This type of response has been frequently noted after a large dose of ACh has been applied to smooth muscle and has been accredited to a "desensitization" of the receptors to neurohumoral action (Paton, 1960). Thus ACh and presumably other parasympathomimetic drugs may have a direct effect on SCR response amplitude which would be confounded with the study of the LIV.

Finally, it should be noted that tonic and phasic SC seem, at least to some extent, to be independent of one another in experiments cited in this paper since it has been frequently found possible to manipulate either tonic or phasic SC extensively without effecting the other to any great extent. Although this evidence is by no means conclusive, it would tend to support Hord et al's (1964)

results, and it presents an interesting area for future research.

CHAPTER 5

SUMMARY

In the present paper several pharmacological studies of skin conductance (SC) were performed in order to achieve the following four goals:

(1) To study the effects of cholinergic and adrenergic agonists and antagonists in a generalizable model of the autonomic nervous system.

(2) To investigate the physiological basis of SC activity.

(3) To clarify the contradictory pharmacological literature on SC.

(4) To explore, in preliminary fashion, the possibility that the psychological relevance of SC could be improved through a range-correction based on pharmacologically determined minimum and maximum output levels of the peripheral SC effector (SC_{min} and SC_{max}).

CHOLINERGIC STUDIES

The effects of atropine (a cholinergic muscarinic blocker) on skin conductance (SC) were studied in order to clarify the contradictory pharmacological literature. It was found that atropine decreased tonic SC in agreement with recent reports. When atropine was administered by iontophoresis (IPS) the contradictory effects on SC responses (SCRs) noted in the literature were reflected in the results, even though several different techniques were used to optimize the efficiency and reliability of IPS. When atropine was administered by local, subcutaneous injection however, SCRs were always completely eliminated. The conclusion was reached, therefore, that IPS was an inefficient procedure for achieving an adequate local concentration of atropine in the skin. In addition, it was noted that IPS at the current levels and durations used, caused a substantial artifactual increase in tonic SC.

In another experiment, SC tonic levels obtained after IPS of water for various intervals were compared to SC maxima obtained after injections of acetylcholine (ACh). IPS was shown to raise tonic SC far above levels achieved with large doses of ACh. Mechanisms for this effect were discussed, methodological problems with the use of IPS were noted, and it was concluded that the use of IPS to administer drugs in the skin was highly inadvisable if

relatively high local concentrations were necessary.

ADRENERGIC STUDIES

The effects of bretylium (an "adrenergic" blocker) were studied. When bretylium was administered by IPS the SCR effects seen (decremental) were qualitatively similar to those seen after a high dose of bretylium was injected into the skin. Injections of bretylium caused little or no effect on tonic SC; however, tonic SC changes seen after IPS of the drug were large and erratic. These results supported the conclusion, previously drawn, that IPS was un unreliable procedure. Unfortunately, peripheral manifestation of adrenergic blockade were not seen. Because the latency of bretylium's adrenergic blocking effects is usually quite long (e.g. twenty-four hours), while the SC effects observed reached their greatest amplitude soon after injection, it was concluded that the aetiology of the SC effects noted was probably not adrenergic. Potential interpretations were discussed.

The effects of EPI on sweating and SC were also studied. EPI caused slight sweating which was not antagonized by atropine. The doses required to produce active sweating also produced considerable vasoconstriction. All doses of EPI which were used caused SCRs to be reduced. These results suggested that sweating and SC changes might be partially independent. High doses of EPI caused an

initial increase in tonic SC which diminished to below control levels over time. A low dose caused an initial drop in tonic SC which recovered. The pattern of initial phasic SC dose-response curves showed that initially SCR decrement was inversely related to the concentration of the dose of EPI administered, however fifteen minutes later the two factors became directly related. This suggested that two processes, one inhibitory, and one excitatory were interacting. When EPI was injected on top of a cholinergically produced SC_{max} or, a SC_{min} produced by atropine, little or no effect was seen.

In a pilot study, the effects of amphetamine on adrenergic sweating were investigated. Subcutaneous injections of the drug, which is believed to cause its peripheral effects by releasing endogenous epinephrine (EPI), were found to cause sweating. This sweating however was blocked by a prior injection of atropine. Since atropine does not block EPI-induced sweating the conclusion drawn was that amphitamine was having a cholinergic effect. A final decision on the possible existence of an adrenergic component in sweat gland innervation was postponed, although it was concluded that the probability that such a component might have physiological significance was low.

THE PSYCHOLOGICAL RELEVANCE OF SC RANGE

Injections of ACh were used to increase SC tonic level. These injections produced an immediate large increase in tonic SC up to a functional ceiling. The ceiling effect was a reliable one and the SC_{max} obtained thereby exceeded but generally approximated the SC_{max} observed during "stress". When the pharmacological SC_{min} obtained after an injection of atropine was compared to the SC_{min} obtained during a night of sleep, the pharmacological SC_{min} was found to be lower than the sleep induced SC_{min} although the scores were quite close.

When the effects of pharmacological manipulation of SC range were noted, the conclusion was drawn that the peripheral SC effector has considerable influence on behaviorally induced SC_{max}. Peripheral restrictions, however, may have less of an effect on SC_{min}. The potential significance of these results for use in Rose & Lykken's range correction method (Lykken, Rose, Luther, & Maley, 1966) were discussed. In addition, some implications for a pharmacological approach to the study of the Law of Initial Values were also noted.

FOOTNOTES

1. ACh is known to have two classes of action. One is called muscarinic because the actions are mimicked by muscarine. The other class of activity is called nicotinic because the effects are mimicked by nicotine. Muscarinic receptors are usually found in smooth muscle and glands, while nicotinic receptors are usually found in skeletal muscle and sympathetic post-ganglionic nerve endings.

2. The effects of ACh are described as "cholinergic".

3. The effects of EPI (and nor-epinephrine) are called "adrenergic" because a popular proprietary name for EPI is Adrenalin. The neurohumor released at organs innervated by the sympathetic nervous system is usually nor-EPI. However, although innervation to the sweat glands is classified as sympathetic, the neurohumor released is ACh.

4. IONTOPHORESIS: A method for administering drugs into the unbroken skin. This is accomplished by applying a voltage of known polarity across an area of skin which has been immersed in an ionized solution of a drug. Drug ions having the appropriate charge will be repelled from the voltage source and driven into the skin.

5. Atropine is made up of a combination of d- and l-hyoscyamine. The molecular size of the two ions is identical, however, d-hyoscyamine has much less pharmacological activity. Martin & Venables (1967) have used the two ions to study ion size effects.

APPENDIX A

DATA FOR FIGURE 2

% Change in tonic SC due to

Current, Current & Atropine, & Atropine.

Minutes after Injection	Current % Change	Current & Atropine % Change	Atropine % Change
2	+ 106	+ 50	- 28
17	+ 94	+ 37	- 31
32	+ 96	+ 37	- 31
47	+ 76	+ 21	- 32
62	+ 72	+ 21	- 31
77	+ 68	+ 22	- 27
92	+ 62	+ 20	- 27

DATA FOR FIGURE 3

% Change in phasic SC due to

Current, Current & Atropine, & Atropine.

Minutes after Injection	Current % Change	Current & Atropine % Change	Atropine % Change
2	+ 13	+ 2	- 9
17	+ 12	- 10	- 20
32	+ 6	- 40	- 42
47	- 4	- 44	- 42
62	- 8	- 33	- 29
77	- 7	- 40	- 29
92	- 13	- 21	- 35

DATA FOR FIGURE 4

% Change in tonic SC due to injection of atropine.

Minutes after Injection	% Change
2	+ 1
17	- 13
32	- 38
47	- 53
62	- 57
77	- 52
92	- 60

DATA FOR FIGURE 5

% Control Phasic SC activity.

Minutes after Injection	% Control Activity
2	79
17	30
32	2
47	0
62	0
77	0
92	0

DATA FOR FIGURE 6

% Change in tonic SC due to IPS of Bretylium.

Minutes after Injection	% Change
2	+ 22
17	+ 9
32	- 8
47	- 13
62	- 14

% Change in phasic SC due to IPS of Bretylium

Minutes after Injection	% Change
2	- 44
17	- 50
32	- 34
47	- 35
62	- 37

DATA FOR FIGURE 7

% Change in tonic SC due to injection of Bretylium.

Minutes after Injection	10^{-3} g/cc % Change	10^{-4} g/cc % Change	10^{-5} g/cc % Change
2	+ 4	+ 1	- 7
17	+ 4	+ 6	- 3
32	+ 3	+ 9	+ 2
47	0	+ 8	+ 4
62	- 2	+ 10	+ 7
77	- 3	+ 13	+ 8
92	- 5	- 4	+ 6

DATA FOR FIGURE 8

% Change in Phasic SC due to injection of Bretylium.

Minutes after Injection	10^{-3} g/cc % Change	10^{-4} g/cc % Change	10^{-5} g/cc % Change
2	- 51	- 14	- 4
17	- 51	- 5	+ 11
32	- 54	+ 4	+ 13
47	- 45	+ 16	+ 13
62	- 56	+ 10	+ 13
77	- 42	+ 22	+ 27
92	- 29	+ 54	+ 41

DATA FOR FIGURE 9

% Change in Tonic SC due to injection of EPI.

Minutes After Injection	10^{-3} g/cc % Change	10^{-5} g/cc % Change	10^{-7} g/cc % Change
2	+ 15	+ 2	- 11
17	+ 14	- 8	- 13
32	+ 6	- 10	- 5
47	- 6	- 13	- 6
62	- 9	- 12	- 8
77	- 11	- 14	- 8
92	- 16	- 9	- 5

DATA FOR FIGURE 10

% Change in Phasic SC due to injection of EPI,

Minutes after Injection	10^{-3} % Change	10^{-5} % Change	10^{-7} % Change
2	- 7	- 18	- 52
17	- 64	- 52	- 34
32	- 68	- 43	- 9
47	- 72	- 41	- 1
62	- 71	- 43	- 17
77	- 65	- 40	- 24
97	- 78	- 37	- 20

DATA FOR FIGURE 11

% Change in tonic SC due to changes in pH.

Minutes after Injection	pH 2.35 % Change	pH 5 % Change	pH 6 % Change	pH 7 % Change
2	+ 6	+ 7	+ 4	+ 9
17	+ 9	+ 13	+ 13	+ 7
32	0	+ 9	+ 3	+ 3
47	0	+ 4	+ 3	- 1
62	- 4	+ 6	+ 2	- 6
77	- 6	+ 4	+ 1	-
92	- 8	- 3	0	-

DATA FOR FIGURE 12

% Change in phasic SC due to changes in pH.

Minutes after Injection	pH 2.35 % Change	pH 5 % Change	pH 6 % Change	pH 7 % Change
2	+ 30	+ 45	+ 40	+ 23
17	+ 41	+ 92	+ 72	+ 6
32	- 8	+ 13	+ 4	- 5
47	- 9	+ 17	+ 5	- 9
62	- 6	+ 36	+ 14	- 6
77	- 20	+ 12	+ 17	-
92	- 14	+ 12	+ 21	-

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