THE PHARMACOLOGY OF SWEATING[1,2]

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As the physiology and biochemistry of the skin attains increasingly greater significance, it is inevitable that attention should be directed to the sweat glands. Their reactions to naturally occurring substances as well as to administered agents assume both theoretical and applied significance. Although structural and functional information concerning the sweat glands has been accumulating for many years, there remains a deficit of organized knowledge concerning the pharmacology of the sweat forming and secreting apparatus. Even though the important relationships of acetylcholine, epinephrine, and other naturally occurring substances with the process of sweating have been studied by many investigators, it is surprising indeed that very few firmly established principles may be clearly stated concerning these relationships.

Although we have not been able to find a comprehensive review of the literature in this field, literally scores of papers have been published in which the action of drugs on the sweat glands is ancillary. It is impossible for us to review and properly credit all such work. It is our purpose, rather, to focus attention upon: 1) certain gaps in our knowledge, 2) points which may have been tacitly assumed rather than scientifically established, and 3) avenues of research which offer promise of rewarding information.

STRUCTURE AND FUNCTION OF THE SWEAT GLANDS

The sweat glands are simple tubular glands, the secretory portion forming a closed coil situated either intracutaneously or subcutaneously. The majority of glands are of the small, eccrine type which function primarily in the regulation of body temperature through their relationship to evaporative heat loss. Larger secretory elements, the apocrine glands, located in the axillary, pubic and areolar regions, are of debatable function. Shelley and his co-workers however are progressively developing a significant body of information concerning them.

Under high magnification of the eccrine sweat gland, there is revealed a vitreous membrane upon which at least two types of cells are based. The innermost cells serve as the secretory elements which empty into the lumen of the gland. The more external cells are very similar to smooth muscle cells but have ectodermal origin. These cells are spindle shaped and contain numerous longitudinal fibrils

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and rodlets, a property similar to that of smooth muscle in general (18). They are arranged in a spiral fashion around the sweat gland, and because of their oblique arrangement around the axis of the duct, they could act in both a longitudinal and circular direction upon the lumen of the duct (180). Way and Memmesheimer (214) have considered these cells to be contractile elements, and Hurley and Shelley (95) claim to have directly observed peristalsis in the apocrine gland duct due to contraction of the myoepithelium. The delivery of sweat to the skin surface is a cyclic process (4, 17, 172), the intensity and frequency of individual cycles depending upon the thermal drive.

Emotional excitement may also elicit the appearance of sweating, particularly upon the palmar and plantar surfaces. If the environmental temperature is properly adjusted to such a threshold level that generalized sweating may be easily elicited, emotional excitement, deep breaths, or startling, will cause sweating from most of the skin surfaces. It is equally true however, that even in a cold environment, sufficiently intense pain or emotional reaction may be accompanied by "drenching sweats" from the general cutaneous surfaces.

It is tempting to account for the outpouring of sweat on the basis of a secretory pressure created by the secreting cells together with a contractile pressure set up by the myoepithelial elements. Experimental proof of such an hypothesis is only fragmentary. The difficulties of direct experimentation are obvious, and histological preparations leave much to be desired in the final interpretation of normal function *in situ*. If both functions could be demonstrated, one might logically expect differential pharmacologic influences upon the secretory and the contractile elements. In addition, drugs may be differentially active upon the neuroglandular junction, the axon, or specific portions of the nervous system which control sweating. Conceivable variations induced in the vascular supply of a given group of sweat glands by various pharmacologic agents may alter the output of sweat. Chemical agents which increase the flow of impulses in the sudomotor nerves, or directly excite the gland cells may be expected to increase the output of sweat. Those substances which tend to block or inhibit impulses in the efferent sweat nerves or which block transmission from nerve ending to glandular elements should, conversely, decrease the output of sweat.

Contrary to the impression frequently expressed that thermoregulatory sweating occurs simultaneously over the entire cutaneous surface, it has been conclusively shown that gross variations in sweating may differentiate one region of the skin from another (92, 177). It is also evident that large variations in the number of sweat glands per unit area exist (173, 215). This is of utmost importance when evaluating a response to a given pharmacologic agent.

Little attention has been paid to an important phenomenon recognized by Kuno (113) and described by Rothman (189) as "conditioning" of eccrine glands. This refers to the variation in sweat gland response to a given stimulus under different conditions. Environmental temperature is a significant "conditioner". Response to acetylcholine and related compounds is much more pronounced in a warm environment than in the cold (10). Sweating is induced by heat (113) or drugs (156) much less readily in winter than in summer. In our own experience we

have been impressed by great variation in response to injection of identical amounts of nicotine and other drugs on different occasions and under different conditions. Rothman (189) believes such differences may be accounted for on the basis of varying responsiveness of the sweat glands resulting from a higher "nerve tonus". Although the term "nerve tonus" seems ill defined, it is true that the phenomenon represented may satisfactorily account for a number of variations in responsiveness of the "conditioned" glands. In his introduction to a symposium on neurohumoral transmission (140) Loewi recently emphasized the importance of the state of cells as one of the factors which determines their reactions.

INTERPRETATION OF SWEATING EXPERIMENTS IN ANIMALS AND MAN

It is indeed unfortunate that suitable sweating experiments may not be easily carried out on common laboratory animals. Although a few workers argue that animals such as the dog possess sweat glands which are distributed generally over the body surface, most agree that they are present only on the pads of the feet. This is true of most of the small furred animals adaptable to laboratory care. Certain larger animals such as the horse possess functional sweat glands distributed over the general body surface, but maintenance costs of such animals are generally prohibitive. Much work has been done on the response of sweat glands in the footpad of the cat. If these glands are comparable to those on the plantar and palmar surfaces of man (a point which cannot be made with finality) slight if any thermal responsiveness may be attributed to them. Until this point is clarified, it is necessary to study the action of drugs upon thermal sweating in the skin of man, and the limitations imposed by this requirement are obvious.

A review of the literature dealing with the influences of various drugs on thermal sweating, reveals important difficulties in quantitative comparison; namely, the great variety in methods of drug administration and response evaluation. Drugs have been administered orally, intravenously, intra-arterially, intracutaneously, sub-cutaneously, topically and by iontophoresis. Likewise, methods of measurement varying from direct visual observation to colorimetric and gravimetric techniques have been employed. Additional difficulties arise from the large variation in response of particular skin regions on which observations have been made. Palmar and plantar areas may react quite differently from other areas. Again, the subcutaneous injection of pilocarpine or methacholine elicits profuse sweating on the head, neck and upper chest, but sometimes sweating on the lower extremities is restricted to sharply circumscribed areas (133). Most of the original observations of Langley and his contemporaries were made by direct visual observation, with and without the use of an auxiliary lens.

Roth (188) and Robinson (185) have outlined the most commonly employed methods for the detection of sweat, and it is not our purpose to describe them here. It is important simply to call attention to the great differences in detection processes. Undoubtedly many pharmacologic effects have been missed due to insensitivity of techniques employed and many subtle variations have not been noticed because of the inability of the method to record differences. With notable exceptions (3, 16, 142, 147) few comparative studies have been carried out in

which different pharmacologic agents have been carefully administered and controlled in an attempt to elucidate functional behavior of the sweating mechanism. Because of the difficulty in interpreting reports in which widely varying techniques, and grossly different volumes and concentrations of pharmacologic agents have been employed, we have attempted to compare the responses of normally innervated sweat glands to representative cholinomimetic and adrenomimetic drugs. Compounds were injected intracutaneously, needle bevel up, in a volume of 0.02 ml. delivered from a 27 gauge needle and a ¼ cc. tuberculin syringe. This injection resulted in the production of a wheal of relatively constant diameter (5 to 6 mm.). The iodine-starch-paper technique (172) was employed throughout, since this technique has proved to be the most sensitive and reproducible of all the procedures which we have tried. Our procedure consisted of the intracutaneous injection of the test substance, always accompanied by control injections of saline (0.9 per cent sodium chloride) taken from the same supply as that used for dilution, into the volar surfaces of the forearm. The test papers were applied for each successive fifteen second interval through the first two to five minutes immediately following the injection. After this period, the papers were applied for each successive 30 second interval until approximately ten minutes had elapsed, and then at five or ten minute intervals until the sweating response disappeared. It was thus possible to compare the rapidity of onset, the intensity, and the duration of the response and the size of the area involved. Only those records comparing responses to a few representative drugs are shown in figure 1.

SYMPATHETIC CHOLINERGIC INNERVATION OF THE SWEAT GLANDS

The presence of secretory nerves to the sweat glands was established over seventy-five years ago by the direct stimulation of the sciatic nerve in experimental animals (165) or the severed nerve stump in an amputated limb (107). In 1886, Gaskell (64, 65) described the general structure of the sympathetic nervous system and, a few years later, Langley (119–122) described specifically the secretory fibers supplying the sweat glands in the feet of the cat.

The general pattern of origin and distribution of fibers of the sympathetic nervous system remain essentially as described by Langley, Gaskell and their contemporaries. Important additional pathways have been described in recent years however, and reference to them must be included since they account for many of the discrepancies which have appeared in the surgical and physiological literature over the past thirty years. Direct synaptic connections between pre- and postganglionic fibers within and about the spinal nerves completely by-pass the sympathetic trunk, and are not interrupted by conventional surgical sympathectomy (116). Many so-called "sympathetic denervations" have been unsuccessful because of the persistence of these pathways when greater or lesser portions of the sympathetic trunk have been removed.

The demonstration by Langley that the secretory nerves took anatomical origin in the thoraco-lumbar portion of the autonomic nervous system seemed anomalous, since the excitatory action of pilocarpine and muscarine, together with the blocking action of atropine, were well known even at this early date.

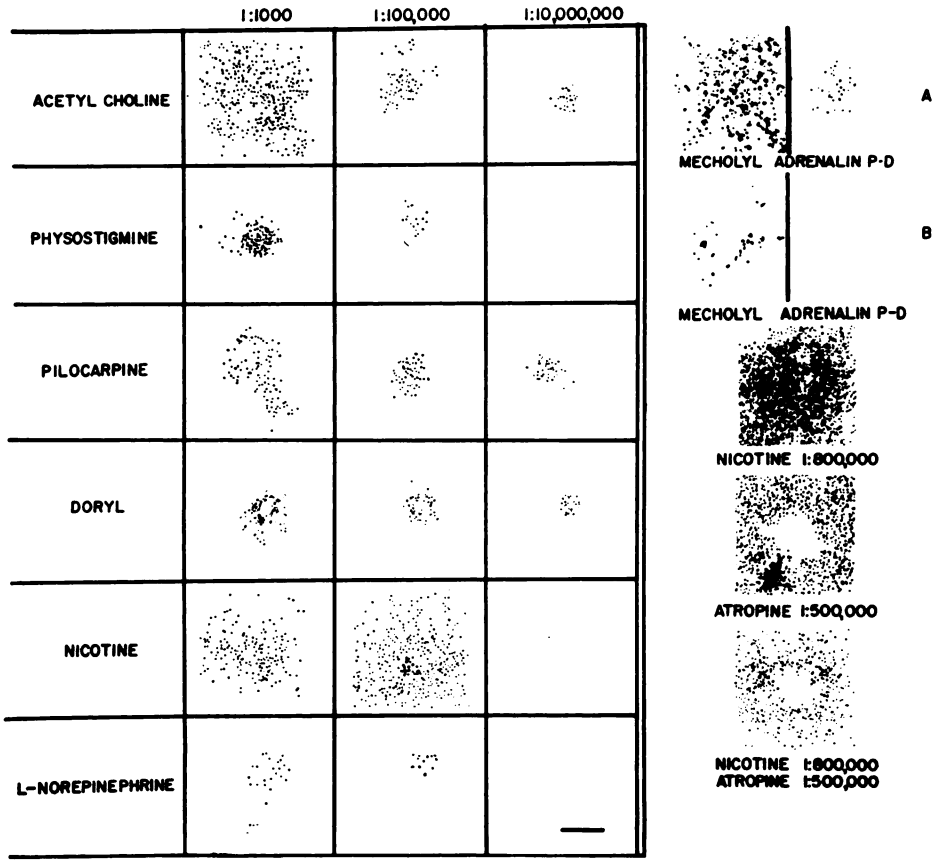

FIG. 1. *Sweating responses to intradermal injection of representative drugs into the volar surface of the forearm.* Responses were recorded by the iodine-starch-paper technique and the records carefully retouched with india ink for purposes of photographic reproduction. The calibration line at lower right represents 1 cm. in the original records, and may be employed to indicate the presence or absence of peripheral spread of sweating around the injection wheal (5 to 6 mm. diameter) in the center of the field. All of the compounds were diluted in physiological saline as indicated at the top, except for the first solution of carbachol (Doryl) which was 1:4000 instead of 1:1000. At the extreme right the comparative responses to methacholine (Mecholyl) and Parke Davis & Co. adrenalin (1:1000) are shown on the normally innervated (A) and sympathetically denervated (B) forearms. The sweating response to 1:800,000 nicotine was taken from the same subject who showed the nicotine sweating to the left, in a cool room in which no reflex sweating was present. The inhibiting action of atropine, on the other hand, was shown during profuse thermal sweating by the same subject. Finally, the combined injection of atropine and nictoine was made in the cool room as before.

Many authorities suggested that, like other vegetative organs, the sweat glands were supplied with double autonomic innervation (1, 2, 81, 86, 117). The apparent discrepancy between anatomical innervation and pharmacodynamics of the sweating mechanism continued to puzzle physiologists for over fifty years. Such

discrepancy resulted in the functional terminology "cholinergic" and "adrenergic" to differentiate transmission at synapses and effector systems (42).

In 1906, Dixon was so impressed by the correspondence between the effects of the alkaloid muscarine and the response to vagal stimulation that he advanced the important idea that the vagus nerve liberated a muscarine-like substance which acted as a chemical transmitter of its impulses (47). He concluded that "excitation of a nerve induces the local liberation of a hormone which causes specific activity by combination with some constituent of the end-organ, muscle, or gland". Dixon's hypothesis met with such skepticism that he was discouraged from following his idea. In the same year (1906) Hunt announced his studies on the physiological action of acetylcholine and other choline derivatives (94). It was not until 1921, however, that Loewi (139) published the first of a series of papers in which the first real proof was furnished for the chemical mediation of nerve impulses. This chemical transmitter had the characteristics of acetylcholine (141). Loewi and his co-workers also found that heart muscle contained an esterase which could cause the rapid hydrolysis of acetylcholine into the practically inactive choline and acetic acid. This accounted for the remarkably evanescent action (44). It is extremely interesting that acetylcholine has not been positively identified in the skin, but its presence is strongly indicated by presumptive evidence which will be reviewed in subsequent paragraphs. It should also be mentioned that not all authorities are convinced of the transmitter role of acetylcholine (69).

While attempting to extend the relatively new concept of a "chemical mediator" of the nerve impulse across the neuromuscular and the neuroglandular junction, Dale and Feldberg presented a preliminary report in 1934 (45) and later in the same year published what has come to be the classic identification of acetylcholine in the mediation of impulses to the sweat glands (46). These workers artificially perfused the foot-pad of the cat in such a way that the venous effluent could be collected and tested against the eserinized leech muscle. When the abdominal sympathetic trunk was stimulated electrically so that beads of sweat appeared on the hairless pads, the venous fluid was shown to contain 2.5 to 10 microgm. of a material very similar to, if not identical with acetylcholine. It is of great interest that only four such experiments were made. In one of these experiments ligatures were tied around the base of the pads in such a way that circulation to the sweat glands was stopped completely, although circulation to the remainder of the foot remained intact. Stimulation of the sympathetic trunk in this preparation produced intense vasoconstriction in the foot, but the venous fluid remained free of acetylcholine. The control foot, with pad circulation intact, showed vigorous sweating and accumulation of the acetylcholine-like material when the abdominal sympathetics on the control side were stimulated. It was concluded from these studies that in spite of their sympathetic origin the sudomotor nerves in the cat were cholinergic. These significant experiments upon the chemical transmission of nerve impulses to the sweat glands were not pursued further by either of the authors (56) nor to our knowledge by any other investigators. Because of their extensive experience with acetylcholine and the devel-

oping concept of "chemical mediation", they believed the sudomotor nerves in man were also cholinergic. Dale (43) observed, "we cannot perform an experiment of this kind in man, but the cholinergic nature of the nerve supply to human sweat glands is clearly indicated by their failure to respond to adrenaline, their response to pilocarpine with profuse secretion, and their paralysis by atropine". It is interesting that the first of these three indications has proved incorrect.

Almost simultaneously with the reports of Dale and Feldberg, Megay (149) reported a substance in human sweat which exerted a "vagomimetic" action on the frog heart, the blood pressure of the cat, the frog rectus and the leech preparation. Its action on the rectus muscle and the leech preparation was augmented by physostigmine and its action on heart and blood pressure was inhibited by atropine. Megay concluded that the material was probably acetylcholine, and comparison of its action with that of acetylcholine indicated a concentration of 0.1 to 0.2 microgm./ml. of sweat.

In 1936 Feldberg and Guimarais (57) observed small amounts of acetylcholine in the venous outflow from the cat's foot following potassium injection. It was not certain however, whether the acetylcholine arose entirely, or only in part from the sweat glands, since other tissue including skeletal muscle conceivably could have contributed small amounts.

The fibers supplying the sweat glands were thus identified as cholinergic although anatomically they pass to the periphery via sympathetic pathways. According to the neurohumoral theory, the chemical mediator liberated at the sudomotor ending is acetylcholine, and it acts directly on the sweat gland. Precisely how or where this compound acts on the sweat gland remains unknown. Shelley and Hurley (195) report that the myoepithelial element of the apocrine sweat gland definitely does not respond to acetylcholine (96), but a great preponderance of indirect evidence suggests that such cells in the eccrine glands do respond. Until proven otherwise, it seems reasonable to assume that this humoral mediator acts to excite the secretory cells as well.

NICOTINIC AND MUSCARINIC ACTIONS OF ACETYLCHOLINE

The similarity in action between acetylcholine and muscarine on autonomic effector organs, smooth muscles and glands gave rise to the term "muscarinic actions of acetylcholine" to distinguish them from the effects on ganglia and striated muscle. The alkaloid nicotine stimulates ganglion cells initially before paralyzing them. Acetylcholine likewise has the ability to stimulate ganglion cells in low concentration and to depress them in high concentrations. This biphasic action of nicotine and acetylcholine is also noted on skeletal muscles. Thus the actions of acetylcholine on ganglion cells and striated muscle have been termed "nicotinic".

The double action of acetylcholine was first so designated by Dale in 1914 (41). At that time he characterized the muscarinic actions as purely peripheral in origin, unaffected by large doses of nicotine, but readily abolished by atropine. He further pointed out that acetylcholine and quaternary ammonium bases also possess nicotine-like actions which may be observed when the muscarine-like

action is excluded by atropine. This action can itself be suppressed by large doses of nicotine and curare.

THE ACTION OF ACETYLCHOLINE AND NICOTINE

In view of the fact that acetylcholine is presumed to be the neurohumoral transmitter at the sudomotor ending, its direct introduction into the immediate tissue environment of the sweat gland should be expected to elicit secretion and discharge of sweat onto the skin surface. The sweating response is most intense within the limits of the injection wheal and appears within 5 to 15 seconds after injection (34, 35, 100, 101, 191, 210). It has also been reported that an extension of the response occurs around the periphery of the wheal so that sweating may be apparent in an area having a diameter of 2 to 10 cm. around the site of injection, the response persisting from a few seconds to as long as five minutes, depending upon the concentration of the drug and the level of excitability of the glands. The sweating responses occur in much the same area as the local red reaction due to direct vasodilator effects of the drug along with the axon-reflex flare in the periphery (137).

If, however, acetylcholine is injected into skin which has been anesthetized previously by the local infiltration of procaine, sweating appears only on or near the wheal. It was concluded from these experiments that sweating within the procainized area was due to the direct action of acetylcholine on the sweat glands (the muscarine-like effect) while sweating in the skin surrounding the wheal of a non-procainized area was due to the nicotine-like action of the drug. The widespread response around the site of injection of 1:1000 acetylcholine in figure 1 illustrates this response. In low concentrations only the direct muscarine-like actions are manifest.

Having observed this dual action of acetylcholine when injected into the skin, Coon and Rothman (34, 35) and Wada *et al.* (210) substituted solutions of nicotine or lobeline and observed a widespread sweating (and pilomotor, 190) response identical to that noted in the area surrounding the acetylcholine wheal except that the response lasted for a longer period. It appears that these compounds are destroyed much more slowly than acetylcholine. The sweat response to nicotine was also abolished by infiltration of the injected area with procaine or by mixing procaine with nicotine solution before injection (36, 100).

We have encountered considerable variation in response to intradermal nicotine. The subject represented in figure one gave a maximal response with nicotine in a concentration of 1:800,000 (see extreme right of figure) with considerably less sweating when higher concentrations were injected. These results essentially confirm those reported by Coon and Rothman. Other subjects, however, gave maximal responses with 1:1000 and showed lesser reactions with lower concentrations. One of our subjects showed but minimal sweating in response to any concentration of nicotine, but this same subject showed minimal sweating in response to all of the drugs employed. It is interesting that he sweats profusely while exercising in a warm environment.

The widespread response to nicotine and acetylcholine was originally inter-

preted by Coon and Rothman (36) to indicate the operation of an axon reflex in the excitation of sweat glands some distance from the site of injection. In this hypothesis, it was assumed that impulses arise at a point along the course of a sudomotor fiber in a peripheral ramification of the autonomic nerve and proceed from that point in both directions (*i.e.*, efferently and antidromically) to spread efferently throughout the arborized peripheral distribution of the axon. A constant pattern of response is explained by such an assumption. Considering (a) that the area of direct stimulation (diameter of the wheal) does not immediately exceed the diameter of 0.5 to 1.0 cm. and (b) that the area of response may exceed 5.0 cm., the phenomenon can hardly be explained in any other way. Sweat responses to direct faradic stimulation of the skin (11, 176, 216) elicited a similar widespread excitation of sweat glands in an area as much as 6.0 to 8.0 cm. from the point of electrode application. Our interpretation, along with that of Coon and Rothman, supports the suggestion of Lewis (131) that the spread of excitation occurs through an arborization rather than a network of autonomic nerve fibers. It must be acknowledged however, that impressive data are accumulating in favor of a syncytial nerve network in the terminal innervation of the sweat glands (143, 163, 164, 170).

Data supporting the concept of an axon reflex initiated by drugs with nicotine-like action (36) were based on the following evidence: (a) local anesthetics abolish the sudomotor axon reflex when injected locally. On the other hand, procaine blockade of a nerve trunk did not abolish the response in the resulting anesthetized region. (b) Immediately after sciatic nerve section or extirpation of the lumbar and sacral sympathetic trunk in the cat, there was no impairment of the "nicotinic" sweating response in the hind paws. (c) The excised toe pads of anesthetized cats showed an outbreak of sweating provided the nicotine injections were made within three minutes after excision. After this interval there was no longer any reaction to nicotine, but pilocarpine (which possesses chiefly the muscarine-like activity) remained effective.

It is of interest that in the sudomotor axon reflex set up by drugs having a nicotine-like action, the "receptor point", which may perhaps be the nerve ending or the fiber itself, behaves in a fashion similar to an autonomic ganglion cell in that it is stimulated by small concentrations and paralyzed by large concentrations of such drugs. Thus according to this hypothesis, when optimal stimulating concentrations of acetylcholine or nicotine are injected intradermally, the nicotine-like action of the drugs sets up at the "receptor point" an impulse which travels to all connected nerve endings. It is pertinent that Brown and Gray (15) demonstrated a direct chemical stimulation of sensory nerve endings by acetylcholine and nicotine although they cite numerous unsuccessful attempts to excite nerve axons directly with these compounds.

It is immediately evident that this view focuses attention upon nicotine as a direct axon stimulator, a view not universally accepted by pharmacologists (15), and seemingly in contradiction to the early demonstration (127) that nicotine acted on ganglion cells, but failed to affect fibers passing through a ganglion without synapse. Therefore, we attempted to determine the site of the stimulating

action of nicotine in the following way. After determining the concentration (1:800,000 in this subject) of nicotine which gave optimal stimulation without evidence of block (figure 1), a solution containing this concentration of nicotine together with 1:500,000 atropine was injected into the volar surface of the forearm. This concentration of atropine separately was capable of completely blocking thermal reflex sweating. The results of this injection revealed a definite block of sweating on the wheal but "axon sweating" still appeared in the periphery. Our results confirm the concept that nicotine actually does excite the sudomotor axon or some peripheral portion of the branching axon system. It is assumed that the atropine in the injected solution blocked transmission at the neuroglandular junction within the area of the wheal, but did not completely block transmission along neurones which did not synapse. The reduction of "axon sweating" in the periphery suggests that atropine also blocked a part of the peripheral system, or at least altered the ability of the axon system to be stimulated by nicotine.

It has been observed repeatedly (76, 101, 144, 210) that axon reflex sweating produced by the nicotine-like action of acetylcholine was inhibited by tetraethylammonium, a known ganglionic blocking agent, although Issekutz *et al.* (100) could not confirm the observation. Peripheral erythema and piloerection are also inhibited by this compound (49) and Douglas (48) states, without giving the evidence, that hexamethonium abolishes axon sweating.

In consideration of these reactions to ganglionic blocking compounds, a possible alternative to the concept of a "receptor point" along the course of the axon is the possibility of participation of peripheral ganglia situated in the skin. Such ganglia have been suggested repeatedly to explain the action of acetylcholine and nicotine upon peripheral blood vessels, and Braeucker (13) postulated such cells in the nerve control of the sweat gland. J. H. Burn (21) discusses the constrictor action of acetylcholine as well as nicotine upon perfused vessels of the rabbit ear and points out that a colleague, Kottegoda, has shown these effects to be abolished by tetraethylammonium and by hexamethonium. The indisputable demonstration of such cells in appropriate relationship to sweat glands would account for many facts which now appear to be anomalous: 1) the stimulating action of nicotine and related compounds; 2) the intracutaneous blocking action of ganglionic blocking agents; 3) the apparent failure of degeneration and hypersensitivity of sweat glands to develop following sympathectomy and 4) the anomalous response of sympathetically innervated structures to acetylcholine. The great difficulty in making such interpretations lies in *the lack of agreement on histologic evidence of such ganglia.* There are those histologists who believe however, that the autonomic interstitial cells of Cajal actually do represent such ganglion cells (143, 150, 163 and others quoted by these authors).

Whether ganglia, "receptor points", bare axons or axon endings are concerned in these responses, it is clear that much investigative work remains to be done before many experimental findings may be adequately understood.

It is of interest that the sudomotor fibers which responded to nicotine were more sensitive to local anesthetics than were sensory fibers (36). Cocaine, mixed

in a concentration of 1:200,000 with an otherwise effective dose of nicotine, totally inhibited the sudomotor response, yet had no apparent effect on sensory fibers. Issekutz *et al.* (100) found that cocaine also blocks the reflex excitation of sweating in response to local heating, and concluded that very small, myelinated or non-myelinated fibers are concerned in the efferent portion of the reflex arc. These observations are in accordance with the fact that the smaller the diameter of the nerve fiber, the greater its susceptibility to chemical anesthesia.

In 1942 Kahn and Rothman (106) demonstrated a distinct and interesting difference in the sweating responses of men and women. Intracutaneous injections of acetylcholine (or methacholine) gave moderate or strong local sweating in 95 per cent of the men tested, whereas only 10 per cent of the women so responded. Sweating was slight or absent in the majority of women tested. The authors could not account for the difference on the basis of atmospheric differences nor anatomical differences in density or distribution of sweat glands. Greater sweating in men has also been shown in response to thermogenic stimuli (91). Studies of heat loss under basal conditions (85) demonstrated that men sweat at a lower temperature, and at any given temperature, men sweat more than women. It was suggested that women have a lower metabolic rate than men and therefore required less evaporative cooling. With this background of information, Gibson and Shelley (70) investigated specifically the sexual and racial differences in response of the sweat glands to acetylcholine and pilocarpine. Employing the iodine-starch-paper technique (173) these workers observed that the individual spots over each functional sweat pore were smaller and fewer in number in the female subjects as compared with males. These workers also demonstrated more marked sweating responses in the negro (both male and female) as compared with whites. Gibson and Shelley were unable to account for the sexual variations in sweating on either an anatomic or physiologic basis. Although hormonal variation may possibly account for these reactions to acetylcholine and pilocarpine, there is no evidence for this hypothesis.

Janowitz and Grossman (102) furnished additional information when they showed that intracutaneous acetylcholine in relatively high concentrations (1:10 to 1:500) produced stronger sweating responses in the male than in the female. Further, with solutions more dilute than 1:500, sweating was very slight or absent in the female but remained moderately heavy in the male until very dilute solutions were employed. It seemed clear from these data that sweating thresholds to injected acetylcholine were much higher in women than in men. Chalmers and Keele (26) noted that the threshold concentration of acetylcholine required to activate sweat glands varied from 10^{-3} to 10^{-6} in different subjects, but these authors could find no differences between the sexes, nor in the thresholds of hyperhidrotic patients (23).

THE ACTION OF PILOCARPINE ON NORMAL SWEAT GLANDS

The alkaloid pilocarpine prepared from South American plants of the genus Pilocarpus appears to have been administered experimentally for the first time in 1874 by the Brazilian physician Coutinhou who demonstrated its marked

sudorific effect (89). Since then his observations have been extended both in animals and in man (113), but the manner in which pilocarpine elicits sweating is still incompletely understood. It acts upon the sweat glands directly in a manner similar to muscarine, and shows none of the biphasic characteristics of nicotine. In 1932 Cushing (40) suggested the drug acted centrally on a parasympathetic center in the diencephalon. He produced generalized vasodilation, sweating, salivation and vomiting by the intraventricular injection of pilocarpine, and noted the reaction was not obtained in patients in whom the hypothalamus had been damaged. It was known that direct warming of the region around the corpus mamillaria elicited sweating and that sweating could be abolished by atropine (86). List and Peet (133) concluded that the action of pilocarpine differs, depending upon whether the drug is injected into the skin or into the cerebral ventricles. When administered by the former route it acts peripherally, and by the latter route it produces a central effect.

Sweating responses elicited by pilocarpine have been reported in many animals as well as in man. Although most common laboratory animals have sweat glands only on the footpads, they have been studied in an effort to determine the manner in which pilocarpine acts to elicit sweating. Luchsinger (145) demonstrated sweating of long duration in response to subcutaneous injections of the drug in both the cat and the horse, and Gasnier (68) has shown a similar response in the rabbit, Eimer (51) in the dog, and Muto (153) in the calf.

Introduction of pilocarpine (either by injection or ion transfer) into the skin of man (16, 114, 147) elicited prompt sweating in the immediate area of injection without extension into the periphery. It has been found to be effective in dilutions ranging up to 1:10,000,000. When injected in a large dose (16 mgm.) subcutaneously, profuse sweating is induced over the entire body (218).

Figure 1 illustrates the sweat gland responses to pilocarpine as compared with other compounds. Sweating is generally confined to the area of the wheal illustrating its direct muscarine-like action on the glandular elements, but in high concentration (1:1000) intradermal injections were frequently marked by discrete sweat channels leading away from the wheal as the drug was collected and transported via lymphatics.

Pilocarpine was for many years the most widely used agent for the stimulation and testing of sweat gland activity, but because of its undesirable side effects, it is gradually being replaced by other parasympathomimetic agents.

RESPONSES OF "DENERVATED" SWEAT GLANDS TO PILOCARPINE AND RELATED COMPOUNDS

Reflex thermal sweating as well as sensory, vasomotor and somatic motor responses may be temporarily abolished by the procainization of a peripheral nerve trunk. However, sweating responses to the direct cutaneous injection of pilocarpine persist in a procainized limb, so it must be presumed that pilocarpine acts distal to the site of nerve block. After surgical section of the peripheral nerve, with adequate time allotted for degeneration of the sweat fibers, the sweating response to pilocarpine is greatly reduced or completely abolished (79, 80, 124,

133, 145). This evidence, showing peripheral action of pilocarpine, was commonly interpreted to indicate that this drug acted on the terminal arborizations of the sudomotor fibers (132). Langley and Anderson (125) however, observed free sweating to pilocarpine as long as 6 weeks after sciatic nerve section although denervation did result in reduction. These workers concluded therefore, that pilocarpine acted directly upon the sweat gland cells, probably upon a "receptive substance" in them.

Braeucker (13) reported positive sweating responses to pilocarpine for as long as 10 months after sympathectomy, although the intensity of response was considerably less than normal. He concluded that the drug acted upon a "nerve plexus in the skin".

Burn's carefully conducted experiments illustrate further the lack of unanimity of opinion concerning the precise site of activity of pilocarpine (19). He injected pilocarpine into the loose skin of the flank of young kittens, and observed that following sciatic section there was usually a short period in which sweating on the foot pad became more intense in response to injection of the drug, followed by a variable period in which secretion was definitely diminished. This observation confirmed that of Langley, but Burn felt that the loss of sweating was not due primarily to loss of secretory fibers, but rather to degeneration of fibers in the mixed peripheral nerve which controlled circulation. This view was further elaborated in 1925 (20) when he showed that the sweating response to pilocarpine persisted as long as histamine evoked a vasodilator response and that the eventual loss of activity was correlated with degeneration of motor fibers to the leg muscles. It was shown a few years later however (59) that in cases of lesions of peripheral nerves the vasodilator response to pilocarpine is retained whereas sweating is abolished.

Hinsey and Cutting (93) supported the contention of the importance of somatic motor fibers by the combination of abdominal sympathectomy (L_2 through L_7 or S_1 and deafferentation by cutting the dorsal roots from L_4 through S_2. Pilocarpine in these cats induced essentially similar sweating in both the normal and "denervated" footpads up to 2 years after operation. Recent experiments have proved that not only the somatic motor but also accessory sympathetic pathways remain intact in this sort of preparation (90, 175). Wilson (217) could not confirm the significance of the motor nerves and concluded that sweating induced locally by injection of pilocarpine is due to direct action of the drug upon the gland cells.

After cervicodorsal ganglionectomy List and Peet (133) observed pilocarpine sweating on the face. They suggested that cholinergic fibers course along certain cranial nerves to innervate cutaneous blood vessels, and when pilocarpine (or methacholine) is introduced it acts on the cholinergic endings of such fibers causing them to release sufficient acetylcholine to activate neighboring denervated sweat glands. Their tests were carried out however, only nine days to two weeks following operation, and it is possible that although nerve fiber degeneration had occurred, the reactive portion of the cell had not lost its capacity to be stimulated. Such an area might correspond to the motor end plate in skeletal muscle.

List and Peet expressed the belief that anhidrosis was not due to degeneration

of the sympathetic fibers. From this conclusion, together with the assumption that lesions in the spinal cord may disturb pilocarpine sweating, Craig (39) studied a number of patients with spinal lesions. He concluded however, that there was no constant relation between diminished sweating and diminished sensibility.

In 1942 Hyndman and Wolkin (98, 99) reported significant differences in the response of sweat glands to pilocarpine following preganglionic as opposed to postganglionic denervation. After the former, pilocarpine induced free sweating up to at least two years after operation. After the latter, the pilocarpine test performed two months or longer after operation revealed an area of anhidrosis which agreed precisely with that outlined by thermoregulatory anhidrosis. These authors felt this result might even be employed to differentiate the two types of operation. Similar results were reported by Simeone *et al.* (197) in the cat where the response of sweat glands was reduced following post-ganglionic denervation but not completely abolished. This result has been further confirmed (36, 106, 142, 182) following sympathectomy in man. At the upper right of figure 1 is shown a comparison of responses to methacholine and epinephrine of normally innervated sweat glands and those denervated 3 months previously. In this patient the right upper extremity was denervated by extirpation of the 1st through 4th thoracic ganglia, and three months later (at the time of this test) this area of the forearm was found to be completely free from thermal reflex sweating when the patient was exposed for 1½ hours in a climate chamber at 47°C. It is important to mention that the iodine-starch-paper technique (173) was employed in this test for residual sweating, and a few scattered sweat spots were detected in neighboring areas of the forearm. In our experience other commonly employed tests have failed to reveal minimal sweating responses (and thus minimal residual innervation) in such patients.

The significant differences in intensity of response between the normally innervated left side and the almost completely denervated right side illustrate the remarkable reduction in response to intradermal parasympathomimetic drugs by denervated sweat glands. There is also shown in this figure a comparison between the reaction by normally innervated and by denervated glands to intradermal injection of epinephrine (Parke, Davis & Co., Adrenalin). Similar failure to respond to epinephrine by denervated skin was reported by Janowitz and Grossman (103).

Thus the literature is replete with conflicting evidence upon the site of action of pilocarpine and similar parasympathomimetic agents as well as upon the presence or absence of response of sweat glands deprived of their innervation. Histological examination of sweat glands following denervation (peripheral nerve section as well as sympathetic ganglionectomy) reveals additional confusion. Tower and Richter (206) reported that "denervated" sweat glands of the footpad of the cat, though atrophic, were not actually degenerated. Clark (27) could find no signs of atrophy in the sweat glands of either the dog or the cat a few years following sympathectomy, and Löfgren (142) and Gurney and Bunnell (77) could detect no histological differences between secreting sweat glands and

those on anhidrotic areas. It is evident, of course, that the relatively gross changes detected by routine histological or histochemical procedures may not rule out the possibility or even the probability of subtle changes not as yet detected through available techniques. Finally, on the basis of the phenomenon called "contact sweating", it has been claimed (99) that sweat glands are capable of functioning "several years after complete sympathetic denervation". Although neither thermoregulatory nor pilocarpine sweating were detected in the test area by these workers, moisture did accumulate when two skin areas were brought into direct contact. It was felt this represented activity of the "denervated" sweat glands rather than accumulation of water of diffusion (insensible perspiration), but the experimental evidence does not appear to be convincing.

Careful examination of each of the reports concerning the presence or absence of sweat gland response following denervation, coupled with our own observations following ganglionectomy of varying extensiveness has led us to conclude that many, if not most, of the studies in reality dealt with incomplete denervations. Except for those instances of peripheral nerve section including all peripheral sudomotor fibers, it may not be concluded without experimental demonstration, that a complete denervation has been accomplished. This is certainly true when the conventional L_2-L_3 ganglionectomy is performed for denervation of the lower extremity, or T_2-T_3 ganglionectomy is done for denervation of the upper extremity (28, 161). Indeed, extirpation of the entire ganglion trunk may fail to eliminate all sympathetic control of sweating on the upper and lower extremities. The presence of intact functional synapses between pre- and postganglionic pathways within the spinal nerves can account for significant and sometimes profuse sweating.

In spite of anatomical difficulties in accomplishing complete denervation (a difficulty overcome in experimental animals by peripheral nerve section and in certain cutaneous regions in man by sufficiently extensive ganglionectomy) the evidence seems to favor the conclusion that sweating responses to pilocarpine and other cholinomimetic agents are definitely decreased or even abolished, following sympathetic denervation. Such a decrease in responsiveness of an autonomically innervated structure represents an important exception to Cannon's law of denervation.

SWEATING RESPONSES TO PHYSOSTIGMINE

Physostigmine (eserine) exerts its principal influence in the body by inhibiting the action of cholinesterase in body fluids and tissues. Since cholinesterase is responsible for the rapid destruction of acetylcholine, physostigmine preserves acetylcholine and prolongs its pharmacologic action. This is true of both the muscarine-like and nicotine-like actions of acetylcholine.

Some workers believe that physostigmine also exerts a direct effect on muscle and gland cells. It has been shown, for example (73), that after physostigmine has depressed serum cholinesterase activity to a given level, additional amounts of the drug will continue to cause response of effector organs proportionate to the dose without further depression of esterase activity. One may object to this

evidence, however, on the basis that serum cholinesterase is being studied rather than tissue cholinesterase, and it is the latter which ultimately determines the rate of acetylcholine hydrolysis and the effectiveness of physostigmine.

Janowitz and Grossman (102) observed the effects of physostigmine and prostigmine alone and in combination with acetylcholine when injected intracutaneously at daily intervals following postganglionic denervation. Control observations were made on the normally innervated extremity where sweating was always elicited by these compounds. These observers believe physostigmine is capable of direct excitation of local sweating as well as potentiating the action of acetylcholine. They felt Wilson's failure (217) to observe this response to physostigmine may have been due to inadequate methods since he depended upon the simple observation of sweating with a hand lens. Similar stimulating action of physostigmine has been reported by others (16, 67, 147). In none of these experiments did this compound elicit the same intensity of sweating as was observed with acetylcholine or pilocarpine, but when used in combination with acetylcholine, the response was definitely enhanced.

From the data of these reports and from the experience in the author's laboratory (figure 1) it is not possible to determine whether sweating elicited by physostigmine injection is positive evidence of a direct excitor action on the sweat gland, or whether it indicates that acetylcholine is being constantly produced in subthreshold amounts and the anticholinesterase permits its build-up to threshold levels for stimulation. Evidence in favor of the latter view might be adduced from our observation that physostigmine failed to elicit sweating in one of our subjects exposed for a prolonged period in a cool room (20°C). Upon stepping out into a warm environment (33°C) sweating appeared first and with greatest intensity in the physostigmine-treated area. On the other hand, Pfeiffer (169) has pointed out that in neostigmine and physostigmine (as well as in the parasympathomimetic drugs pilocarpine and arecoline) the three fundamental "prosthetic groups"[5] are revealed at the same approximate interprosthetic[5] distances that have been postulated for acetylcholine and its aliphatic homologues. Neostigmine has been definitely shown to have a direct acetylcholine-like action on striated muscle, and it would not be surprising if physostigmine did have a direct stimulating action.

Employing the histochemical method of Koelle (111), Hellman (87,88) has studied the distribution of cholinesterase in the skin of the cat's footpad. This technique revealed a positive response for the pseudo or non-specific cholinesterase around the sweat glands but there was no specific cholinesterase in the area. This appeared to be a peculiarity of the cholinesterase of the sympathetic supply to the sweat glands, since most other cholinergic nerves are characterized by the specific type. Denervation of the sweat glands (stellate ganglionectomy) resulted in virtually complete disappearance of the enzyme. It seemed evident therefore, that the enzyme demonstrated in normal sections was associated mainly with the neuro-effector system of the sweat glands. Similar studies were recently reported by Hurley *et al.* (97) in which the localization of cholinesterase was examined in

[5] More suitable terminology has been suggested to be "pharmaphore groups" and "interpharmaphore distances" (109).

axillary biopsy specimens from three normal adult men. Contrary to the findings of Hellman, these observers report that specific cholinesterase is present in large amounts in the nerve fibers about the secretory acini of the eccrine sweat glands. Significant amounts of cholinesterase were not found in the vicinity of the apocrine sweat glands, in apocrine or eccrine sweat ducts, the sebaceous glands, hair follicles or the epidermis. Employing a manometric method in the assay of enzyme activity, Magnus and Thompson (146) found both true and pseudocholinesterase in human skin. Whether the different results reported by these groups represent species differences in distribution of cholinesterase or variations resulting from manipulation of a rather complicated histochemical technique remains to be established by confirmation from additional investigators.

THE SUDORIFIC ACTIONS OF METHACHOLINE AND CARBACHOL

The evanescent nature of acetylcholine stimulated a search for synthetic choline esters which would be more stable in the body and therefore more persistent in their actions. Of several hundred such compounds synthesized and tested, acetyl-beta-methylcholine (methacholine) and carbaminoylcholine (carbachol) are generally employed clinically.

All glands innervated by cholinergic nerves are stimulated by methacholine, and therefore lacrimation, salivation, and sweating are prominent manifestations of its peripheral action. Sweating is often so pronounced following subcutaneous injection of relatively large doses that the underclothing becomes drenched (203). Generalized sweating caused by subcutaneous administration of this compound is inhibited by atropine and enhanced by neostigmine or physostigmine (155, 156, 158, 166). Like the response to pilocarpine, sweating is no longer induced by methacholine after interruption of the postganglionic innervation of the sweat glands (see figure 1). Repeated intradermal injections of methacholine or a steady intradermal infusion evokes progressively decreasing outputs by the sweat glands until a refractory state is reached, and it has been suggested that this decrease represents fatigue or exhaustion of the glands (205), a point not firmly established.

Methacholine is relatively free from the nicotine-like effects of acetylcholine with retention of most of the muscarinic effects. Thus, sweating is profuse within the actual site of injection with little if any axon sweating in the periphery. Since methacholine is destroyed slowly, its distribution by the lymphatic system is readily demonstrated (176). Long, narrow channels of activated sweat glands were observed radiating away from the site of injection, these channels branching and uniting to form very discrete sweating patterns on the skin surface as the compound diffused out of the lymphatics to excite the sweat glands locally. Since methacholine, like alkaloids, takes a positive charge, it may be driven into the skin by ionotophoresis resulting in a profuse local sweating and flush reaction.

Carbachol is a powerful parasympathomimetic agent differing from methacholine in that it is somewhat more stable in body fluids and possesses more nicotine-like actions on autonomic ganglia and striated muscle. In sharp contrast to acetylcholine and methacholine, the drug is apparently not destroyed by

cholinesterase and therefore its activity is neither enhanced nor prolonged by neostigmine or physostigmine (73). It was reported that sweating appears later and is of lesser intensity than after methacholine when the two compounds were administered subcutaneously (202). Atropine abolished the muscarine-like but not the nicotine-like effects of the drug.

In our experience (and in that of Brun and Favre (16)) carbachol has proved to be a most potent stimulator of the sweat glands when injected directly into the skin (figure 1). It induces a strong nicotine-like spread of sweating in the periphery of the injection wheal, it blocks sweating in the area of the wheal when used in high concentration, and elicits a typical muscarine-like influence on sweat glands when injected in low concentration. Its action is especially dramatic because of its slow rate of destruction and its easy and rapid spread along lymphatic channels giving rise to discrete sweating patterns radiating away from the central injection wheal.

SWEATING RESPONSES TO FURTRETHONIUM

Furtrethonium (furfuryltrimethylammoniumiodide) is chemically related to other parasympathomimetic agents such as methacholine, carbachol, and acetylcholine and exhibits many of the same effects on the cardiovascular (12, 58) and urinary systems (8). Within a few minutes after subcutaneous injection, a diffuse flush, tachycardia, perspiration and salivation occur. Simultaneously a desire to micturate is frequently reported. The compound was first administered to man in 1940 by Myerson *et al.* (157) who found it to be clinically effective in doses ¼ those required for methacholine. These workers were impressed by its effectiveness in producing sweating, flush and rhinorrhea. They observed that sweating was generalized and lasted for about three quarters of an hour, and sometimes became sufficiently intense to induce a fall in body temperature. They note that the compound could be administered by iontophoresis, and that its action could be prevented by previous administration of atropine. In contrast to the marked synergistic effect of neostigmine and methacholine however, the combination of furtrethonium and neostigmine did *not* enhance the response. This was explained by the fact that furtrethonium is not an ester and therefore it is not affected by cholinesterase. The compound is not rapidly destroyed by the tissues and its effects persist for comparatively long periods of time. Guttman (78) and Jasper and Robb (104) found this compound to be preferable to the more commonly used pilocarpine and methacholine as a test of sweat secretion in man. Because of its stimulating action upon the smooth muscle of the urinary bladder, the compound has been widely employed in the treatment of urinary retention.

SWEAT GLAND RESPONSES TO HEXENE-OL

In clinical trials of the compound hexene-ol (C_6H_9OH), in the treatment of burns, Levine (130) first reported an increased localized sweating in the area of skin to which the compound had been applied. He observed that the warmer the room temperature, the more profuse the localized sweating. There was no hyperemia in the area and he felt that the drug caused sweating by either a direct

action on the sweat glands or a stimulation of the sudomotor fibers. Koppanyi (112) later reported a series of studies designed to analyze the diaphoretic action of the compound. He injected the drug intravenously in doses of 150 to 300 mg/kg body weight, as well as directly into the footpad of cats and noted in every case profuse sweating on the footpads. He then observed the surprising result of intense local sweating when the compound was simply rubbed on human skin. Its sudorific action was abolished by atropine (both in cats and in man) but not by high concentrations of nicotine nor by local infiltration with procaine. Its pharmacologic action is reported to be confined to the sudomotor effectors, and its action is exclusively muscarine-like with no nicotine-like actions. These observations were later confirmed by Sulzberger *et al.* (204) and by Janowitz and Grossman (102), the latter authors further demonstrating that the response could not be elicited in a skin area deprived of its sympathetic innervation.

SUPPRESSION OF SWEATING BY ATROPINE AND PARASYMPATHETIC BLOCKING DRUGS

The major alkaloids of belladonna, atropine and scopolamine, act both on the central nervous system and upon the smooth muscle and secretory glands innervated by postganglionic cholinergic nerves. All the muscarine-like actions of acetylcholine and its esters can be diminished or prevented by atropine and many responses to postganglionic nerve stimulation can be blocked. The site of this action appears to be directly on effector cells and not on nerve endings. The release of chemical mediator is not prevented by atropine, but atropine does prevent the mediator from exciting the cell. Although the anti-secretory activity of atropine and related compounds is not clear (134), Goodman and Gilman (73) suggest that it acts by preventing the chemical mediator (acetylcholine) from penetrating the cell membrane and combining with a "receptive substance" within the cell. Suppression of sweating appears to be the main feature in the production of "atropine fever", although it is possible that the drug may have a direct action on the central nervous system. In atropine poisoning in infants, the temperature may reach 109°F. However, animals which do not sweat show no fever after atropine.

While studying the secretory innervation of the sweat glands in cats, Ott and Wood Field (165) observed the excitant action of muscarine on denervated glands and noted that such sweating could be stopped by atropine. They demonstrated that muscarine can, by peripheral action, excite the sweat glands, and that atropine, also by peripheral action, can arrest it. These authors also state (without giving literature reference) that Koppe and Ringer had proved that muscarine also excited an increased perspiration in man and that Ringer and Fothergill had proved that atropine prevents perspiration in man. In 1880 Tweedy and Ringer (207), while comparing the mydriatic properties of atropine and homatropine, reported that atropine was a more powerful depressant of sweating (induced by pilocarpine injection) than homatropine.

In more recent observations (167, 211, 212), potentials recorded from the skin of the footpad of the cat during direct electrical stimulation of the sympathetic trunk have shown that atropine consistently produces complete sudomotor

paralysis. Patton concluded (as did Dale and Feldberg), that the sudomotor innervation in the cat is entirely cholinergic. Kuno (114, 115) showed that atropine may be administered by iontophoresis and that reflex thermal sweating is locally depressed. Although atropine abolishes reflex sweating it fails to block completely the response of sweat glands to the direct action of local radiant heat (174). Kadatz (105) found atropine to be a most effective inhibitor of sweating on local skin surfaces. Its local effectiveness when injected intradermally in dilute solutions is illustrated in figure 1.

The systemic administration of atropine (38, 179, 186) reduces general body sweating by only 40 to 50 per cent. In these experiments the drug caused severe cardiovascular reactions before reaching a high enough concentration at the sweat glands to cause complete anhidrosis. Sweating can be arrested on small skin areas for several days by intradermal injection of from 0.01 to 1.0 ml. of atropine (1:100,000 dilution) without danger of systemic action (136).

Since scopolamine is closely related to atropine structurally, it might be expected to have an action very similar to that of atropine in blocking the action of cholinergic fibers. We have found but few references relative to its action upon the sweat glands. In a clinical report, the drug depressed sweating rate in normal man by approximately 35 per cent (63).

In a careful comparative study of the effect of fifteen anticholinergic drugs on sweating, Shelley and Horvath (193) showed that scopolamine and atropine are by far the most effective in controlling sweating. None of the compounds possessed sweat gland specificity. Tachycardia, cycloplegia, xerostomia, etc. are effects that appear concomitantly with desired anhidrosis when the compounds are given orally. To secure complete abolition of sweat gland response to either thermal or pilocarpine stimulation it was necessary to administer 10.0 mg. atropine sulfate with consequent widespread parasympathetic blocking effects. Thus these authors pointed out that anhidrosis is not a therapeutic result of systemically administered anticholinergic drugs, but a sign of overdosage.

When administered by iontophoresis into local areas of the skin, scopolamine proved the most effective in eliminating sweating with atropine and homatropine next in effectiveness. The newer synthetic agents had little or no effect. Scopolamine induced anhidrosis in an area two to three times the size of the electrode; always a larger area than produced by atropine. Partial anhidrosis in the scopolamine area lasted from 1 to 10 days. Surprisingly, sweating was also reduced by the simple topical application of scopolamine, and remained depressed for several days.

During the course of treatment of a group of patients with peptic ulcer and other gastrointestinal disorders, Grimson *et al.* (75) noted the effectiveness of methantheline in suppressing excessive sweating in several patients. Subsequently these workers treated four hyperhidrotic patients with this compound and obtained effective control. Pharmacologic studies indicate that methantheline is a true anticholinergic drug in that it 1) antagonizes the action of acetylcholine at the parasympathetic nerve endings, 2) blocks the action of acetylcholine at autonomic ganglia, and 3) in toxic doses has a curare-like action on skeletal

muscle innervation (151). Further studies indicated that medication with methantheline effectively controlled hyperhidrosis in 90 to 95 per cent of patients examined (14, 219). However, a number of undesirable side reactions, the tendency to develop tolerance in some patients, and the fact that the drug must be administered indefinitely in order to have continuous effectiveness limited the usefulness of the preparation.

Still another quaternary amine, diphemanil is an effective parasympathetic blocking agent with more prolonged action and fewer side effects than methantheline. The actions of the two compounds were compared in hyperhidrosis, but neither consistently controlled sweating in all patients (159, 160, 187, 220). Zupko and Prokop (221) carried out carefully controlled experiments on hyperhidrotic and upon normal subjects, quantitatively measuring the sweat outputs from seven different cutaneous regions during the administration of four additional parasympathetic blocking agents (propantheline, oxyphenonium, methsespolamine,and Darstine [5-methyl-4-phenyl-1(1-piperidyl)-3-hexanol methyl bromide]) for periods varying from six weeks to eight months. These studies indicated the order of maximal effectiveness in controlling hyperhidrosis under the experimental conditions described was as follows: methantheline, methsespolamine, oxyphenonium, propanthaline, diphemanil, and Darstine. None of the compounds proved to be ideal therapeutically as anhidrotics.

Ringer and Moreshead (181) described the action of narcissia, an alkaloid obtained from the bulb of the common daffodil. In many respects its action resembled that of atropine, for it dried the mouth, checked perspiration, dilated the pupil and quickened the pulse. It antagonized the effect of muscarine and pilocarpine on the frog's heart. It is interesting that most of these actions were reversed if the extracts were made after flowering of the plant.

THE ACTION OF GANGLIONIC BLOCKING DRUGS

In view of the clinical significance of attempts to control hyperhidrosis by way of ganglionic blockade, brief reference to recent use of hexamethonium compounds will be made. It was observed by Burt and Graham (22) while testing penta- and hexamethonium compounds in the treatment of hypertension and peripheral vascular disease that sweating was reduced in normal subjects, and excessive sweating was rapidly controlled in one case of hyperhidrosis. Following this lead, Sommerville and Macmillan (198) have treated six patients by the oral administration of 1250 mg. of hexamethonium daily. All six of their cases were satisfactorily controlled initially, but one half appeared to develop tolerance over a period of a few months. Chalmers and Keele (26) have also controlled four out of six cases of hyperhidrosis with 750 mg. of hexamethonium daily. After each dose (250 mg. orally) sweating was reduced within 15 minutes and remained so for 3 to 4 hours. Neither placebos nor tolazoline had such effects. It was the opinion of both these groups that oral hexamethonium was worth trying in cases of hyperhidrosis before resorting to sympathectomy.

During the examination of patients before and after sympathectomy, Cox and Randall (37) have been greatly impressed with the remarkable speed of action of,

and the completeness of blockade of sweating induced by intravenous injections of hexamethonium. While recording sweating by either the iodine-starch-paper or the desiccating capsule techniques (178) in a hot room (where sweating on normally innervated parts was profuse) the drug was injected, and sweating was observed to stop on all surfaces under observation (up to 18 areas) before the termination of the injection (30 to 60 seconds). Sweating remained completely surpressed for 10 to 30 minutes and then gradually recovered over the following hour. In our present limited experience, the local sweat-blocking action of hexamethonium injected intradermally has not proved convincing.

In addition to the actions of hexamethonium, it has been reported that other agents (dibenamine, tetraethylammonium, and tolazoline) may decrease sweating because they may interrupt the normal impulse flow at different points along the sympathetic pathway. Adequate confirmation is not yet available to establish the validity of such reports, and attention is directed to the discussion of epinephrine-induced sweating in the following section.

THE ACTION OF EPINEPHRINE AND RELATED COMPOUNDS

In his classic papers on the actions of epinephrine (52, 53) Elliott reported that human sweat glands were not excited by this substance, and the subsequent demonstration of the cholinergic nature of the sweat fibers together with their suppression by atropine seemed to support this conclusion. Langley at first failed to detect sweating in response to injected epinephrine in the human hand (123) and observed very slight or no sweating in the footpad of the cat (128).

Similar failure to elicit sweating in man (9, 192) and in the isolated perfused limb (168) have been reported. However, positive sweating responses to administration of epinephrine have been observed repeatedly in experimental animals such as the cat (62), the horse and sheep (153), and the rabbit (66). Ergotamine is reported to block sweating induced by epinephrine. In 1917 Muto (154) produced generalized sweating in the horse by the intravenous injection, and local sweating by subcutaneous injection, of both pilocarpine and epinephrine. The pilocarpine sweating was stopped by atropine but not that induced by epinephrine. Langley (126) confirmed these observations but observed that the response to pilocarpine was generally more copious than that to epinephrine. Bacq (4b) noted that the injection of normal serum into the horse resulted in no sweating response, but if a solution of epinephrine (1:100,000 optimal conc.) was added to the serum, sweat secretion definitely resulted. Thus earlier literature reveals evidence both for and against epinephrine-induced sweating.

During recent years evidence has accumulated to show that at least a fraction of the eccrine sweat glands in man will respond to epinephrine (60). In 1937 Kuno and Kashiwabara (115) observed prominent blanching over the epinephrine wheal and stated "just on that portion, numerous very small sweat drops could be seen for an hour or two".

In 1948 Haimovici (82) reported that intravenous phenylephrine induced moderate sweating responses, and that dibenamine blocked not only the effects of injected phenylephrine but also prevented or greatly suppressed spontaneous

palmar sweating. Since dibenamine was considered a sympathetic blocking agent Haimovici concluded that the suppression of sweating represented an epinephrine blocking effect and that there exists, therefore, an adrenergic component in the nervous control of sweating in man.

Simultaneously with Haimovici's report, Kisin (110) suggested that epinephrine induced a sweat response even in dilutions as high as 10^{-8}. In rapid succession, these observations were confirmed and amplified. Sonnenschein *et al.* (199, 200) studied the results of intradermal injections of epinephrine, phenylephrine and l-nor-epinephrine, each of these compounds eliciting a local sweat response in a majority (but significantly, not in all) subjects. No sexual or racial differences were apparent. The response commenced within 2 minutes after injection and lasted up to 2 hours, and it closely approximated the area of vasoconstriction. Preliminary intradermal injection of atropine or tetraethylammonium had no effect on the epinephrine response, but again, dibenamine and ergotamine caused marked inhibition. Patton (167) failed to demonstrate blockade of sweating in the cat's footpad by dibenamine during direct stimulation of the lumbar sympathetic trunk. Atropine, however, did produce complete sudomotor paralysis. Although varying widely in intensity of response, 21 of 30 subjects showed definite sweating following injection of synthetic epinephrine (199, 208). Haimovici extended his studies to additional epinephrine-like compounds (83, 84) essentially confirming previously reported observations. He noted however, that unlike acetylcholine-induced sweating, that elicited by epinephrine is not constantly observed. While 84 per cent of his subjects gave a positive response, 16 per cent failed to do so. A similar percentage of Manuila's subjects showed a positive response to epinephrine administered by iontophoresis (147). He also pointed out that, contrary to common belief, vasoconstriction induced by epinephrine is not incompatible with secretory activity of the sweat glands, but it did appear that epinephrine-induced sweating is considerably less intense than that induced by acetylcholine or methacholine.

The accumulation of evidence indicates that the postganglionic sympathetic transmitter is probably nor-epinephrine (54, 55, 55b, 57). Barnett (7) has pointed out that sweating is a prominent feature in the symptom complex of patients with phaeochromocytoma, and considerable evidence indictes that the predominant vasoconstrictor substance present in the tumor tissue is nor-epinephrine (72). Barnett (6) has demonstrated the sudorific effect of intradermally injected nor-epinephrine.

It has been demonstrated (201, 209) that epinephrine in concentrations from 1:1000 to 1:10,000,000 may excite sweating when injected intradermally. Sonnenschein and his group found the effect difficult to demonstrate in palmar skin. They also observed the curious phenomenon of inhibition of spontaneous sweating by epinephrine, the inhibition in some instances lasting for many hours, sometimes long beyond the duration of obvious vasoconstriction. It is of interest here that Wada *et al.* (210) showed inhibition of nicotine sweating by the preliminary intradermal injection of epinephrine.

Although confirming the essential facts of epinephrine stimulation of sweating

and its inhibition by dihydroergotamine and tolazoline, Chalmers and Keele (24) challenged the opinion that there is an adrenergic component in the innervation of human sweat glands. They also make the significant observation that sweating which occurs during hypoglycemia is completely blocked by local injection of atropine, and therefore cannot be explained as an example of epinephrine-induced sweating. In a later paper (25) these authors noted that contrary to the earlier reports of Haimovici, neither reflexly induced thermal sweating nor mental (emotional) palmar sweating could be inhibited by either dihydroergotamine or tolazoline, whereas both types of sweating could be completely suppressed by atropine. They feel that intravenously administered dibenamine may have produced its effect through a central depressant action and that it therefore provided no support for the concept of an adrenergic component in the nervous control of sweating.

Sweating due to the direct cutaneous administration of epinephrine or nor-epinephrine appears to be a real phenomenon (see figure 1). The response, although of lesser magnitude than that induced by cholinomimetic compounds is not the result of injection of fluid *per se* as indicated by the lack of effect of saline diluent alone. Moreover, the intensity varies generally with the concentration of the sympathomimetic agent. Those responses reported as a result of systemically administered drug or naturally occurring epinephrine or nor-epinephrine are difficult to evaluate since their site of action may not be accurately determined. Responses to local cutaneous injection of epinephrine need explanation. It is not likely that mere contraction of the myoepithelial elements could account for the continuous activity of the sweat glands lasting in some instances for several hours. Numerous experiments have shown that ischemia itself is not causally related to the sweating and epinephrine does not act through the liberation of acetylcholine in the tissues since atropine fails to influence epinephrine sweating. It does not appear that an axon reflex is involved since neither tetraethylammonium nor atropine influences it. The only explanation which seems plausible at present, then, seems to revolve around the direct action of the compounds upon the secretory cells themselves (201). It would appear that both acetylcholine and epinephrine may act upon the same glands, and that the cells may respond to both agents.

Do these observations prove the existence of an adrenergic innervation of the human sweat glands? Many workers (26, 135, 201) emphatically believe they do not. The mere fact that sweat glands are sensitive to an agent which appears to be a neurohormone for other structures does not necessarily imply a physiological role in this situation. Thus a physiological adrenergic sudomotor system has not been established, and it does not yet appear tenable to conclude that adrenergic nerves are concerned in the control of thermal or emotional sweating.

The very recent reports by Hurley and Shelley (95, 96, 195, 196) focus attention upon related but anatomically different sweat units, the apocrine sweat glands. Epinephrine and nor-epinephrine have been shown to be powerful pharmacologic stimuli for the apocrine sweat gland (18) and pain and emotional excitement are most effective physiologic stimuli (194). The latter authors also

report that the myoepithelial elements of the apocrine sweat gland are under control of adrenergic fibers of the sympathetic nervous system and respond to sympathomimetic stimuli. Examination of axillary sweat gland activity revealed two different kinds of secretion differing greatly in appearance and resulting from totally different stimuli. One secretion, a viscid, turbid, white liquid, appeared following epinephrine injections, whereas a clear watery fluid was noted in response to acetylcholine. Emotions that cause profuse eccrine sweating do not produce axillary odor; those that result in axillary odor do not initiate profuse sweating. Drugs that inhibit one type of axillary sweating do not inhibit the other (136). Evidence was presented to indicate that the apocrine glands form the whitish or milky product, whereas the clear aqueous secretion results from eccrine glands. These observations do not support the report of Olivet and Nauck (162) that pilocarpine and epinephrine are without effect on the myoepithelium and that atropine causes contraction.

Thus the possibility exists that in emotional or psychic sweating commonly observed on palmar and plantar surfaces and in the axilla, there may be an adrenergic control over the apocrine component of such sweating, but evidence at the present time seems to support best the hypothesis of cholinergic innervation of the eccrine sweat glands. Such a view seems compatible with the observations of apparently paradoxical sweating in the axilla and on the palms and soles of subjects exposed to a cold environment (15 to 23°C) by Glaser and Lee (71).

THE COMPARATIVE EFFECTIVENESS OF SUDORIFIC AGENTS

In a recent series of experiments, Brun and his co-workers examined the sweat-inducing properties of over one hundred compounds when introduced into the skin by the process of ion transfer (iontophoresis) (16, 108). Thirty-five of these compounds, the majority of which were parasympathomimetic agents with a few sympathomimetic substances, induced sweating of greater or lesser intensity. When compared on the basis of duration of sweating response and total amount of sweat produced, some inconsistencies appeared as to the relative potencies of the different drugs. In general, however, carbachol, trimethylammonium iodide and methacholine proved to be the most powerful of the parasympathomimetic sudorific agents, with pilocarpine, arecoline, neostigmine, tetraethylammonium, acetylcholine, benzoylcholine, choline and physostigmine following in the stated order.

Of the sympathomimetic agents, all showed sudorfic properties comparable only to the weaker parasympathomimetic compounds. Glaukosan and l-epinephrine proved to be the most effective, with l-nor-epinephrine, adrenalone and d-epinephrine following in progressively declining potency.

Although we did not test the sudorific effectiveness of precisely the same group of drugs as listed by Brun and co-workers, we can confirm the relative stimulating ability of many of those listed above. As tested in our laboratories, a sequential listing of all compounds tested (in descending order of effectiveness) would be as follows: carbachol, methacholine, furtrethonium, pilocarpine, nicotine, acetylcholine, physostigmine, lobeline, l-epinephrine, and l-nor-epinephrine.

THE ACTION OF ADRENAL CORTICOIDS ON THE SWEAT GLANDS

It is well known that fully acclimatized man produces a larger volume of sweat during performance of work in the heat than does unacclimatized man. Unacclimatized man in a temperate climate produces sweat which contains about 4.0 gm. of sodium chloride per liter of sweat; diet, climatic season, degree of activity, etc., causing some variation from this figure. Full acclimatization to heat reduces the loss of sodium chloride by about 60 to 70 per cent. If the daily intake of salt is abruptly reduced, there is first an abrupt reduction in urinary excretion of salt, followed in about 24 to 36 hours by a sharp reduction in salt concentration in the sweat (29-33). Under conditions imposed by Conn and his group, in acclimatized men, the limit of the sweat glands' ability to conserve salt produced values of 0.25 to 0.35 gm./liter of sweat. The reduction in salt concentration in sweat during the process of acclimatization to heat is elicited by a salt deficiency developed during profuse sweating in the initial response to heat (29, 148, 183, 184).

Conn and his co-workers observed that during acclimatization to heat there occurred a negative nitrogen balance quite independent of nitrogen intake. The pattern of a negative nitrogen balance and falling concentration of sodium chloride in sweat and urine suggested a sudden increase in adrenocortical activity (32). Daily administration of desoxycorticosterone acetate (DOCA) produces a sharp decrease in urinary Na and Cl, but this effect lasts for only a few days after which the urinary levels rebound to higher than normal levels in spite of continued administration of the drug. Na and Cl in the sweat are also lowered markedly about 18 to 36 hours after administration of DOCA (118) and in spite of the tendency for the kidney to "break through" the salt-lowering effect of DOCA on the urine, the sweat glands continue to secrete a fluid dilute in Na and Cl as long as DOCA is administered. This long latency period between administration of DOCA and appearance of sweat gland response probably accounts for previous failures to detect this action of adrenal cortical extracts (50, 152). The sharp fall in NaCl concentration in sweat produced by DOCA occurs in the absence of any change in blood levels. This was interpreted to indicate that the sweat glands perform active osmotic work in reabsorbing these elements, and that the process is stimulated by the pharmacologic activity of DOCA.

Thus, according to Conn and his group, the effects during acclimatization and administration of DOCA are similar as far as Na and Cl content of sweat and urine are concerned. Excepting for a few variations in results and interpretation, recent experiments have generally confirmed the conclusions of this group (118, 129, 138, 184). Both Locke *et al.* (138) and Conn (30) have further strengthened the hypothesis by showing that the sweat salt concentration in untreated Addisonian patients was considerably in excess of normal values, and that these values were reduced to normal by administration of DOCA (30). Conversely, sweat sodium and chloride values in patients with a hyperactive adrenal cortex (Cushing's syndrome) were considerably lower than may be observed in normal subjects (30).

The effect of adrenocorticotropic hormone (ACTH) in decreasing the concentration of sodium and chloride in sweat is similar in all respects to that induced by

DOCA (29, 33, 213). Although the precise relationship between the process of acclimatization and the ketosteroids has not as yet been demonstrated in man, the conclusion seems justified that ACTH stimulates increased adrenal elaboration of salt-active corticoids, and that the mechanism by which man adapts himself to physical work in the heat is related to this activity of the pituitary.

MISCELLANEOUS

A number of workers have observed that sweating may be effectively depressed by the action of formalin. Griesbach (74) stated that simply painting concentrated (35 per cent) formalin on the foot leads to complete absence of sweating on the foot and a great diminution in sweating throughout the body. Kuno and Kashiwabara (114) applied 10 per cent formalin to the skin by ion transfer techniques and observed that sweating was suppressed for as long as six days. Prompt clinical remission in cases of hyperhidrosis has been obtained with similar administration of both formaldehyde and copper sulfate (61). Several applications of formaldehyde at 2-day intervals will suppress sweating for two to four weeks (171).

The action of the antipyretic drugs in accelerating processes of heat dissipation in febrile patients is well known. The salicylates (acetylsalicylic acid, sodium salicylate) are probably the best known antipyretics, and profuse sweating has long been associated with their use in combating fever. The fact that sweating is not a prominent accompaniment of salicylate administration in the absence of fever (5) has led many to the conclusion that the compound acts directly upon the hypothalamic "thermostat" when thermogenesis is in excess of thermolysis (73). Evidence indicates the salicylates act primarily upon the central nervous system and not directly upon the peripheral sweat mechanism. Although little information is available, it appears that other antipyretic agents such as acetanilid, acetophenetidin, antipyrine and aminopyrine act in much the same manner as the salicylates.

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