STIMULATION OF THE SWEAT GLANDS IN THE HAIRY SKIN OF THE DOG BY ADRENALINE, NORADRENALINE, ACETYLCHOLINE, MECHOLYL AND PILOCARPINE*

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There is as yet little information regarding the sweating in the hairy skin of the dog. Goltz and Ewald (1), in 1896, noticed that transection of the cervical spinal cord in dogs caused a remarkable sweating almost all over the body surface except the head. Schindelka (2) described Barbey's observation that a manifest sweating was seen on the general body surface of the dog which had been run over by a wheel, and two cases of unaccountable hyperhidrosis of the dog, one of which was of his own observation. According to Marek (3), certain kinds of dogs (American naked dog and sky-terrier) are capable of sweating on the general body surface.

Frank and Voit (4), in 1903, reported that the systemic administration of pilocarpine led to a perceptible wetness and an increase of water evaporation in the hairy skin of a dog, which they attributed to an augmented activity of the sweat glands. Similar results were obtained by Eimer (5). Kato (6), using the Minor method, studied the sweat response in dogs to some drugs administered systemically. He observed sweating on restricted areas of the frontal aspect of the abdomen in 2 out of 10 dogs after the administration of adrenaline, in 5 out of 11 after pilocarpine, and 12 out of 15 after pituitrin.

Nevertheless, since Luchsinger's description in 1883 (7), it has been generally believed until recently that the dog does not sweat on the hairy skin. In our preliminary report (8) we described the sweat response in the hairy skin of the dog to some sudorific drugs and direct radiant heat. The present paper gives a fuller account of the results obtained from the experiments, which were limited to the drug sweat response and some histologic observations. The results of the experiments on direct heating of the skin will be described in detail elsewhere.

MATERIALS AND METHODS

Forty-three mongrel dogs and 2 fox terriers, aged about 1 to 8 years, were used. The tests were carried out in all seasons of the year.

The dogs, non-anesthetized, were fastened to animal board either in supine or in prone position, and the hairs of the areas to be examined were cut as short as possible with scissors. In nearly all instances, the frontal aspects of the thorax and abdomen, and the ventral surface of the thigh were chosen as the most suitable areas for observations. In some cases, however, the lateral or dorsal aspects of the thorax and abdomen were also tested.

Sweat secretion was visualized by the iodine-starch method of Wada and Takagaki (9). Briefly, the skin was painted first with 2 to 3% iodine in absolute alcohol and allowed to dry, and then covered with a mixture of corn starch powder and castor oil (about 1:1 in volume). Sweating was recognized by the appearance of black spots at the sites of functioning sweat glands.

The sudorific effects of the following drugs were studied: L-adrenaline hydrochloride (Sankyo Co., 1:1000), DL-noradrenaline hydrochloride (Sankyo Co.), acetylcholine chloride (Roche), Mecholyl chloride (Merck), pilocarpine hydro-

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chloride (J. P.), and nicotine (Merck). These drugs were dissolved in 0.9% NaCl solution to various concentrations, and 0.1 or 0.2 ml of each solution was injected intradermally. Control injections were made with 0.9% saline solution.

The skin biopsies for the histologic study were taken under narcosis with morphine. The local anesthetics such as cocaine or procaine were not used, since they were found to cause local sweating when injected intradermally. Care was taken to minimize the mechanical stimulations to the sweat glands. All of the skin specimens were fixed in 10% formalin, and serial sections in paraffin were made either tangentially or vertically at 8 to 12 microns. These sections were stained with routine hematoxylin and eosin.

RESULTS

Spontaneous sweating

Most of the animals tested did not show any spontaneous sweating on the general hairy skin even at the time when excitement and panting were considerably vigorous. In several dogs, however, a slight sweating was observed to occur spontaneously in some restricted areas, *e.g.*, around the umbilicus, in the median part of the hypogastric region, or in the pubic region. This sweating became evident particularly after violent struggles with panting.

Sweating by adrenaline and noradrenaline

Thirty-seven dogs were tested for local sweat response to intradermal injection of adrenaline. The concentrations used ranged from 10^{-7} to 10^{-3}. A local sweating was produced at the site of injection in 35 out of 37 animals. Of these, 4 dogs occasionally failed to respond even to 10^{-3} adrenaline. A total of 185 tests were made on 37 dogs; 149 showed definite, 25 slight, and the remaining 11 no responses.

The sweating by adrenaline was usually detectable within one minute after the injection. The intensity and extent of sweating generally varied with concentrations of the drug. At lower concentrations such as 10^{-7} to 10^{-6} the response was roughly confined to the injection wheal, whereas at higher concentrations it spread around the wheal along the course of the lymphatic channels, closely approximating the area of vasoconstriction (Fig. 1). The duration of sweating was determined in 7 animals; the majority of the glands stimulated by adrenaline almost ceased to secrete within 10 to 15 minutes after the injection, while some of the glands were still functional, but to a very weak degree, at the end of about 20, 50 and 90 minutes after the injection of adrenaline in 10^{-6}, 10^{-5} and 10^{-4}, respectively.

The control tests with normal saline were made in all of the animals, usually with negative responses. The injection of chloretone which is contained in the commercial solution of adrenaline (Sankyo Co.) was also found to be with hardly any sudorific effect in concentrations of 10^{-4} to 10^{-3}. It must be added that in some sensitive animals, the mechanical stimulations of the skin, such as prickling or stroking with a hypodermic needle led to the appearance of a small number of sweat spots around the site of stimulations. Such animals also often showed a

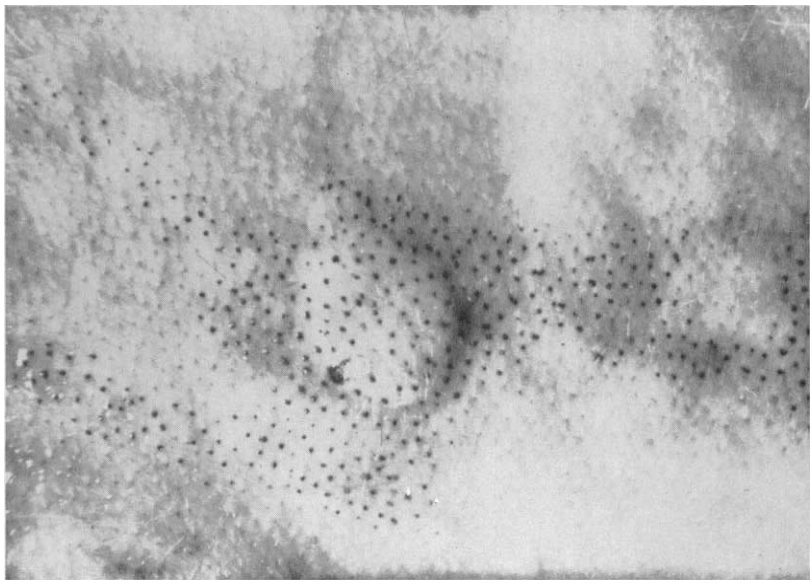

FIG. 1. Sweat response to intradermal injection of 10^{-4} adrenaline in skin of abdomen. Note lymphatic spread around injection wheal. Photographed 25 minutes after injection.

slight sweat response to intradermal injection of normal saline alone, which might be explained as being due to a mechanical stimulation.

The minimal effective (threshold) concentrations of adrenaline for producing the local sweating were repeatedly estimated in 35 dogs on the frontal aspects of the thorax and abdomen, and the ventral surface of the thigh. There were considerable variations with the animals and sometimes in the same animals on different days. In some dogs, regional, though slight and inconsistent, differences were also occasionally observed. In the majority of cases, however, they ranged from 10^{-8} to 10^{-6}, while 10^{-5} to 10^{-4} in several cases. No apparent sexual or seasonal variations were found in the sensitivity to adrenaline.

Intradermal injection of noradrenaline in 10^{-7} to 10^{-3} also produced a localized sweating with vasoconstriction in all 5 dogs tested. The threshold concentrations for sweating were almost similar to those of adrenaline; the range was from 10^{-8} to 10^{-6} in 5 dogs on the ventral surface of the thigh and frontal aspect of the thorax.

Sweating by acetylcholine, mecholyl and pilocarpine

Acetylcholine in 10^{-6} to 10^{-3} was tested in 26 dogs, and the sweat response was obtained in 24 dogs, while 2 of them occasionally showed no response even to 10^{-3} acetylcholine. A total of 127 tests were made, of which 104 showed definite, 19 slight and the remaining 4 doubtful or no responses. The onset of the sweating by acetylcholine was, as a rule, somewhat earlier and its duration was shorter than those by adrenaline at identical concentrations. The threshold concentrations of acetylcholine were determined in 24 dogs on the ventral surface of the thigh and frontal aspects of the thorax and abdomen. The results were 10^{-10}

to 10^{-8} in the majority of cases, but 10^{-7} to 10^{-3} in several cases. The sensitivity to acetylcholine roughly paralleled that to adrenaline: the sweat glands which showed a high sensitivity to adrenaline were also found to be highly sensitive to acetylcholine.

Intradermal injections of mecholyl in 10^{-6} to 10^{-3} were performed in 16 dogs. A total of 66 tests were made and all of them showed positive response. The threshold concentrations of mecholyl, determined on 16 dogs, in the frontal areas of the thorax and abdomen ranged from 10^{-8} to 10^{-6} in the majority of cases, while 10^{-5} in a few cases. The variation of the sensitivity to mecholyl seemed to be smaller than that to adrenaline or acetylcholine. In several cases, which occasionally showed doubtful or no response to both adrenaline and acetylcholine even in 10^{-3}, mecholyl was effective in producing sweat response, though of a slight intensity, at concentrations of 10^{-6} to 10^{-5}.

Intradermal pilocarpine in concentrations of 10^{-4} to 10^{-3} produced positive in 10, equivocal in 1 and negative responses in 2 out of 13 animals tested. Of the total of 45 tests, 32 gave positive responses. The threshold concentrations determined on the thorax and abdomen in 9 animals ranged from 10^{-7} to 10^{-5}. In contrast to the effects of the four agents described above, the sweating by this drug was apparently less intense. Even with high concentrations such as 10^{-4} to 10^{-3}, it began to appear gradually in 2 or 3 minutes after the injection, and the magnitude of sweating, which could be judged roughly by the number and size of sweat spots, were less remarkable than that produced with the 4 preceding drugs.

Effect of denervations on the sensitivity of the sweat glands

The extirpation of the lumbar sympathetic chain (L_2 to L_7) in 4 dogs, the section of the anterior and posterior spinal roots (D_{12} to L_3) in 3 dogs, and the section of the spinal roots (D_{12} to L_3) just distal to the union of anterior and posterior roots in 3 dogs were performed unilaterally under the morphine-ether narcosis. Threshold concentrations of intradermal adrenaline and acetylcholine were estimated on the denervated areas before and at various intervals during 2 to 4 months after the denervations, the corresponding areas of the contralateral side serving as control. Such operations often caused considerable decrease in the sensitivity to the both drugs equally on the normal as well as denervated sides, but it was usually transitory and was followed by a complete recovery within 1 to 2 weeks after operations. In none of these animals, however, was there any definite effect of the denervation itself on the sensitivity of the sweat glands to both adrenaline and acetylcholine during the whole course of observations.

Effect of blocking agents on the drug sweat responses

Unless otherwise stated, the two agents, sudorific and blocking, were mixed together at specified concentrations just before experiments and injected intradermally. Control tests were made by injecting stimulant drugs alone at the same concentrations into the corresponding areas on the opposite side.

Atropine sulphate (J. P.) in 10^{-5} was found to be sufficient to nullify almost completely the effects of 10^{-6} to 10^{-5} of acetylcholine, mecholyl and pilocarpine,

whereas it did not interfere with the effect of adrenaline at the same concentrations. However, a high concentration of atropine such as 10^{-3} weakened considerably the effects of adrenaline in 10^{-7} to 10^{-6}.

Dihydroergotamine (DHE 45, Sandoz) in concentration of 10^{-5}, which had been injected about 10 minutes previously, caused a complete inhibition of sweating by adrenaline in 10^{-7} to 10^{-6} at the same site of injection. When DHE was applied in mixture with adrenaline, it occasionally failed to suppress the effect of adrenaline completely. The sweating by acetylcholine was not affected by DHE applied previously or in mixture. However, DHE in 10^{-3}, infiltrated previously, partially inhibited the effect of a low concentration of acetylcholine such as 10^{-8}. It must be added that intradermal injection of atropine in 1 to 2% often elicited a slight localized sweating in the dog.

Effect of intradermal injection of nicotine

In several dogs, which showed a marked sweat response to intradermal injection of adrenaline or acetylcholine, 10^{-5} to 10^{-3} nicotine, which is sufficient to cause a typical axon reflex sweating in man (10), was injected intradermally in the frontal aspects of the thorax and abdomen or the ventral surface of the thigh. In none of these dogs was axon reflex sweating observed; higher concentrations of nicotine (10^{-3} to 10^{-2}) produced at most a very delayed appearance of a small number of sweat spots on the injection wheal, usually 5 to 10 minutes after the injection. In some dogs, however, sweating of axon reflex nature, though to a slight degree, was observed to occur only in the restricted areas where the spontaneous sweating could be produced as described above.

Recently Wada *et al.* found that high concentrations of NaCl also was effective in producing a definite axon reflex sweating in man, when applied intradermally (10). Accordingly, NaCl solution of 4% was tested, but no axon reflex sweating was produced, as characterized by a rapid and wide spread response; and a slight sweating, if any, was observed confined to the injection wheal. It should be added that acetylcholine in high concentrations such as 10^{-4} to 10^{-3} also failed to produce the axon reflex sweating in most hairy skin of the dog; the sweating generally spread along the lymphatic channels.

Refractory period after stimulation

After cessation of the sweating with a single intradermal injection of adrenaline, noradrenaline, acetylcholine or mecholyl, a direct radiant heat was applied to the same area by using a 60-watt electric bulb at a distance of about 8 cm above the skin surface. The sweat glands in the area of the previous injection failed to respond to the subsequent heat stimulation for a certain length of time, whereas those in the surrounding areas manifested a remarkable sweat response (Fig. 2). The stimulation with adrenaline resulted in a definite and long-lasting refractory period: it was more than 4 to 5 hours after 10^{-6} to 10^{-5} adrenaline and even 24 hours or longer after 10^{-4} to 10^{-3} adrenaline. The results were the same whether the commercial synthetic adrenaline solution or the solution of crystalline adrenaline was used. The stimulation with noradrenaline also led to a refractory state

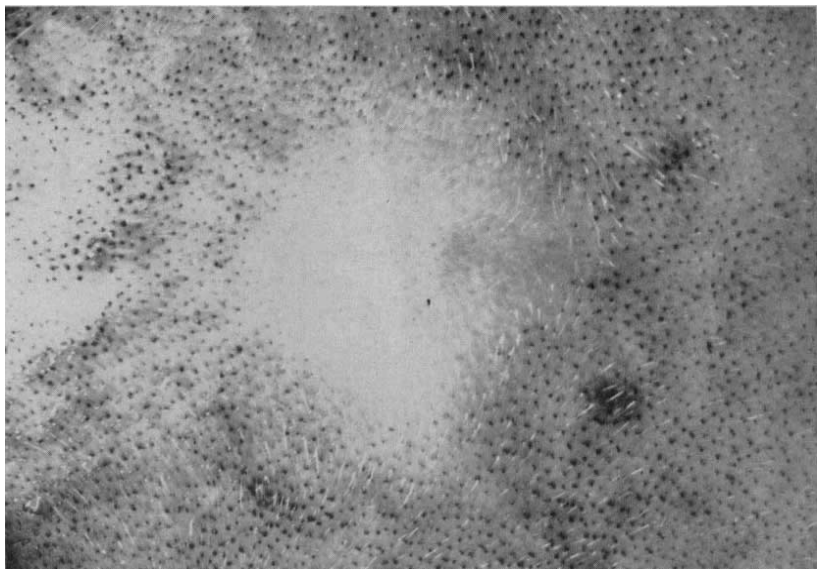

FIG. 2. Showing absence of sweat response to direct radiant heat in a skin area of chest, in which 10^{-4} adrenaline had been injected intradermally 24 hours previously. Photographed 20 minutes after heating.

which was almost comparable to that produced by adrenaline. In contrast, the refractoriness after acetylcholine and mecholyl was less intense and of shorter duration: a complete recovery from refractoriness usually occurred within 1 to 2 hours after the stimulation even with such high concentration as 10^{-4} or 10^{-3}. Control injection of normal saline solution proved to be without any inhibitory effect on the sweating by the subsequent heat stimulation.

Such a state of inactivity of the sweat glands was also seen after stimulation with direct radiant heat. A small area of about 15 mm in diameter was subjected to radiant heat for about 7 minutes in the same way as described above. Such areas showed lack or diminution of sweat response for a period of 1 to 2 hours to the subsequent heat stimulation.

Histologic evidence for the functional activity of the sweat glands

In 6 dogs, the skin biopsies were taken from the skin area in which the sweating had been induced 2 to 5 minutes previously by intradermal injection of adrenaline, acetylcholine, mecholyl and pilocarpine. These were compared with control specimens obtained from the non-sweating skin areas of the same animals.

The sweat glands in the hairy skin of the dog consists of a secretory portion, which is usually a loosely convoluted long tubule lined with a single layer of secretory epithelium (Fig. 3), occasionally with short branching, and a relatively short straight, or sometimes slightly winding duct, which is composed of two layers of small cuboidal, deeply basophilic epithelial cells. The whole of the secretory portion is invested in a well-developed myoepithelial cell layer, which runs along the long axis of the gland tubule. In the sections of unstimulated skin,

most of the glands were found to have low cuboidal or relatively flattened secretory cells, which lined a wide tubular lumina with a smooth luminar surface (Fig. 3, 4). In contrast, the glands stimulated by the sudorific drugs showed marked morphologic changes in the secretory epithelium, which might be associated with the secretory activity of apocrine type (Fig. 5, 6). Nearly all of the

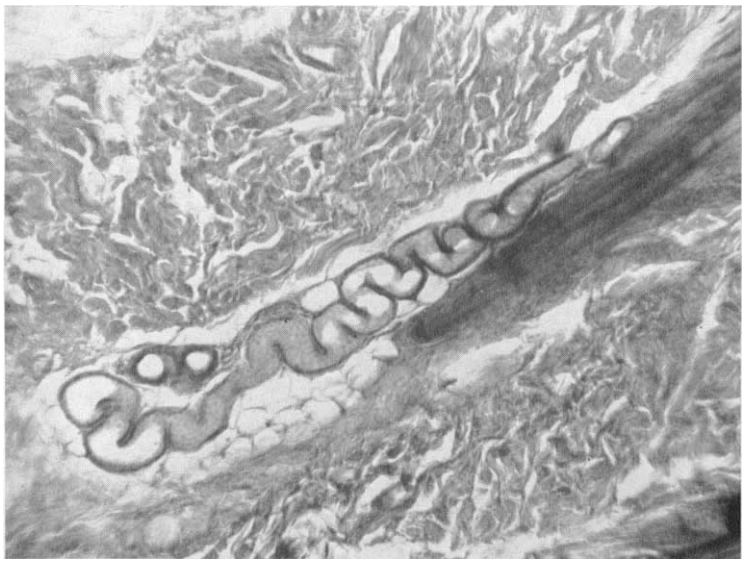

FIG. 3. Showing a loosely winding secretory portion of unstimulated sweat gland in skin of abdomen. (×75)

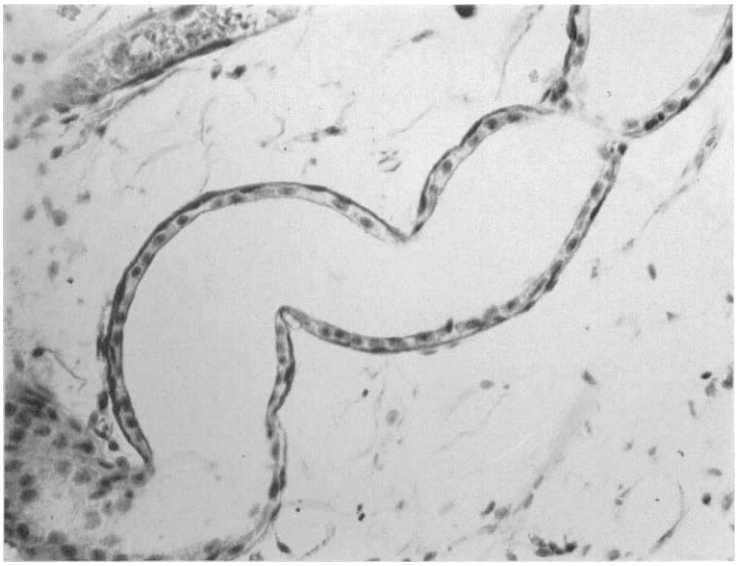

FIG. 4. High power view of secretory portion of unstimulated sweat gland in skin of abdomen. (×300)

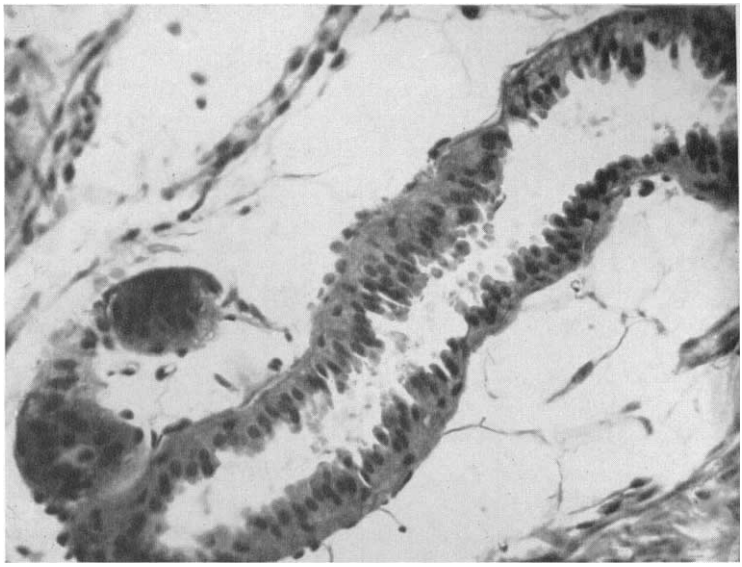

FIG. 5. Secretory portion of sweat gland in active stage following intradermal injection of 10^{-5} adrenaline. Biopsy was taken from chest 3 minutes after injection. (×300)

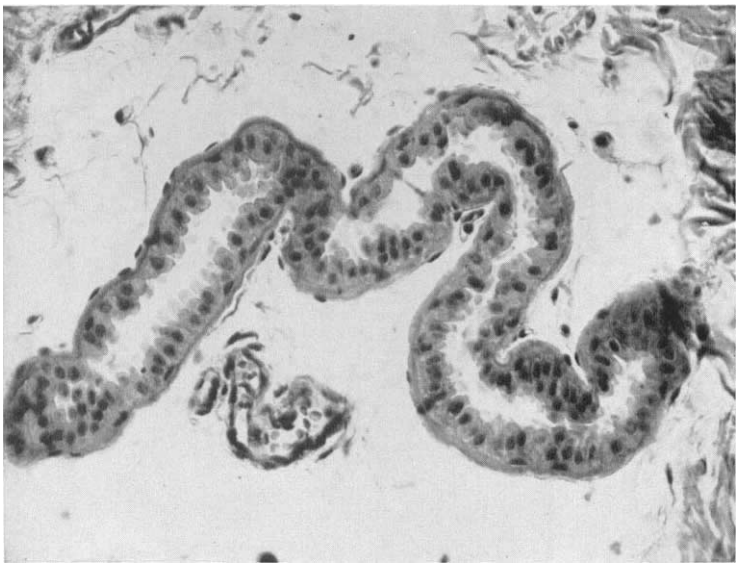

FIG. 6. Secretory portion of sweat gland from chest skin, showing its active state following intradermal injection of 10^{-5} acetylcholine. Biopsy was obtained 3 minutes after injection. (×300)

glandular cells assumed tall columnar shapes and protruded a cytoplasmic knob into the lumen, giving the luminar surface an irregular appearance. Their nuclei also changed from a flattened shape to a round or an elliptical one, which elongated following the long axis of the cylindrical cells.

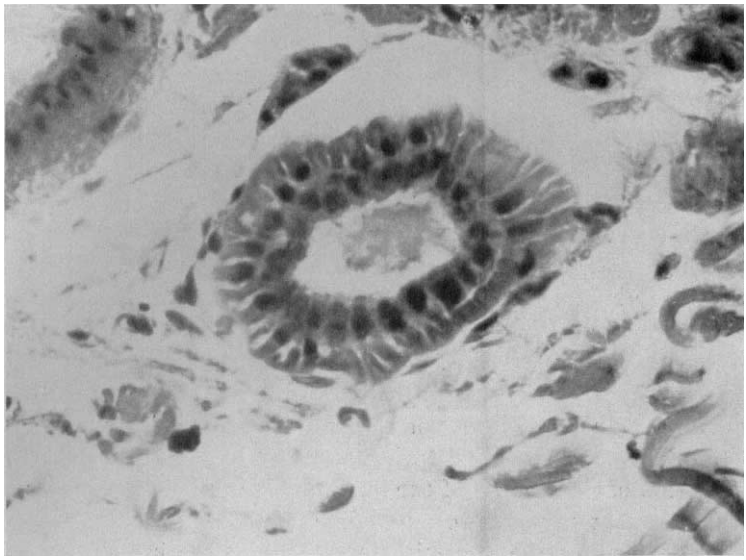

FIG. 7. Cross section of secretory portion of sweat gland stimulated by intradermal adrenaline in 10^{-4}. Note a remarkable thickening of myoepithelial layer associated with secretory activity of gland. Biopsy was taken from thigh 25 minutes after injection. (×550)

Another outstanding feature of sweating was the change in the myoepithelium. In the unstimulated glands, the myoepithelial layer was very thin and it could be identified with difficulty in routine hematoxylin-eosin preparations. In contrast, the glands stimulated by the sudorific agents showed a marked thickening of myoepithelium, with its nuclei situated closely beneath the base of the secretory epithelium (Fig. 5, 6, 7).

DISCUSSION

The presence of the sweat glands over the general hairy skin of the dog was first described by Gurlt as long ago as 1835 (11). His finding was confirmed later by a number of histologists and the literature was comprehensively reviewed by Claushen (12) and Bau (13). Very recently, the similar finding was also obtained by Nielsen (14) and Roy (15). The majority of them agreed in that the sweat glands in the hairy skin of the dog are of apocrine nature and their ducts share a common opening with hair follicles, though some of the early investigators, including Gurlt (11), were of the opinion that they open directly onto the skin surface, independent of the hair follicles. In the present study, the black spots, which designate the sweat response, were seen to appear almost always at the sites corresponding to the follicular orifices (Fig. 1, 2).

That the sweat responses to the intradermal sudorific drugs in the dog were produced by the true secretory activity of the glands was verified from the histological study. As described above, the secretory epithelium of the sweat glands before and during sweating revealed quite a different morphology, which is quite compatible with the general view that the apocrine gland cells of low cuboidal type present the resting state and those in high columnar type the

active state. Roy's finding that the resting sweat glands in dog's skin had glandular epithelium in columnar type cannot be reconciled with this consideration. Another possibility that the intradermal injection *per se* of fluid may expell mechanically the sweat which had been already formed and pooled in the tubular lumina can be ruled out by the ineffectiveness of intradermal injection of the saline alone in the majority of the tests.

The morphologic change in the myoepithelium during sweating seems to be suggestive of its functional ability. It has long been believed that the myoepithelium of the sweat glands possesses the contractile function and subserve the evacuation of the luminar content, though not confirmed so far. In the present experiments with dog's skin, the active glands were found to be associated with a marked thickening of the myoepithelial layer, which might indicate its contraction. This suggests that the myoepithelium of the apocrine sweat glands in the dog plays an important role in the process of sweating, possibly in the expulsion of the formed sweat. Recently, Hurley and Shelley (16) observed directly a wave-like motion of the tubules of the human axillary apocrine glands in association with the sweat response to adrenaline, but they failed to discern histologically any changes in the myoepithelium during sweating.

The sweat glands in dog's hairy skin responded well to both sympathomimetic and parasympathomimetic drugs, and the response to the former was selectively inhibited by DHE and the latter by atropine. This may suggest that they are under the control of both sympathetic and parasympathetic nervous system. However, the spontaneous sweating, whether emotional or thermal, could not be produced on the general hairy skin, in spite of the fact that the sweat glands there were as sensitive to the both kinds of sudorific drugs as were the human sweat glands. Moreover, it should be emphasized that the axon reflex sweating, which depends on the integrity of peripheral sudomotor fibers (17, 18, 19, 20), could not be elicited in the dog, except in the restricted areas where spontaneous sweating, probably through the nervous mechanism, was produced. On the basis of these findings, it seems justifiable to consider that most of the hairy skin of the dog are lacking in the sudomotor innervation, though the anatomical proof is unavailable. In addition, the denervation of the skin did not alter significantly the sensitivity of the sweat glands to adrenaline and other chemical stimulants. These facts show that it is hazardous to anticipate the existence and nature of innervation of the sweat glands from mere pharmacological observations.

The dog's sweat glands showed a definite refractory period after sweating. Various explanations for this may be offered. It is very difficult to attribute this refractoriness to a mechanical obstruction of the sweat duct by the fluid injected, since intradermal injection of the saline alone was without any effect on the subsequent stimulation. One might expect that adrenaline and noradrenaline would possess some inhibitory action on the sweat glands. The inhibitory effect of adrenaline on the sweat glands has long been a matter of controversy since the report of Elliott in 1905 (21). Recently, it has been shown that a single intradermal injection of adrenaline in man caused a long-lasting refractory state both in the eccrine glands of the forearm (22) and in the apocrine glands of the axilla

(23). The possibility that acetylcholine and mecholyl also possess any inhibitory effect on the sweat glands cannot be ruled out entirely. The depressive action of acetylcholine on the sweat glands was described by Langley and Uyeno (24). Recently, Sonnenschein *et al.* (22) reported the absence of spontaneous sweating in the area of injection of acetylcholine (1:500 and 1:5000) in man for 24 hours or longer, though not so clear-cut as that produced by adrenaline. In the present experiments the stimulation with direct heating of the skin also resulted in a refractory state for 1 to 2 hours, which was roughly comparable with that after acetylcholine or mecholyl. It may be possible that some local metabolic end-products produced by heating of the skin is responsible for the inactivity of the sweat glands. However, it seems also likely that such refractoriness after stimulation of the sweat glands in the dog is at least partly due to the secretory process characteristic of the apocrine sweat glands, which might be associated with a considerable loss of cellular constituents through the separation of cytoplasmic knobs. The long-lasting refractoriness after adrenaline and noradrenaline may be explained by assuming that the recovery of the glandular cells from such loss is delayed also by vasoconstriction. Crucial elucidation of the mechanism of the refractoriness is a problem to be further investigated.

SUMMARY

1. Functional activity of the apocrine sweat glands in the hairy skin of the dog was investigated.

2. The sweat glands were found to be highly sensitive to the sudomotor action of intradermal adrenaline, noradrenaline, acetylcholine, mecholyl and pilocarpine, in spite of the fact that spontaneous sweating of nervous mechanism was scarcely observed to occur.

3. The sudorific effect of adrenaline was selectively inhibited or abolished by dihydroergotamine, and that of acetylcholine, mecholyl and pilocarpine by atropine.

4. The denervation of the skin could not materially affect the sensitivity of the sweat glands.

5. Nicotine could not produce axon reflex sweating except in the restricted areas in some dogs, where a spontaneous, though slight, sweating was elicited. NaCl and acetylcholine were also found to be ineffective in producing axon reflex sweating in the general hairy skin.

6. The sweat glands which had responded to chemical as well as thermal stimuli showed refractoriness for a certain length of time, which differed according to the kind and intensity of the initial stimulations.

7. The secretory activity of the sweat glands under the pharmacologic stimulations was histologically confirmed.

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