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THE ELECTROLYTE COMPOSITION OF PHARMACOLOGICALLY AND THERMALLY STIMULATED SWEAT: A COMPARATIVE STUDY*

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ABSTRACT

The sodium and potassium content of sweat induced by pilocarpine iontophoresis, and after the intracutaneous injection of pilocarpine, acetylcholine or methylcholine, were compared with thermal sweat. In most subjects, sodium concentrations were higher in pharmacologic sweat than in thermal sweat. An increase in potassium content in pharmacologic sweat was seen in all subjects.

Unphysiological exposure of the ductal portion, as well as the secretory portion of sweat gland to exogenous cholinergic drugs was assumed as a possible cause of the high sodium and potassium concentrations of pharmacologically-stimulated sweat.

Sweat glands stimulated by iontophoresis or by the intracutaneous injection of cholinergic drugs have frequently been used in physiologic studies and in the diagnosis of cystic fibrosis, but few comparative studies of pharmacologically and thermally stimulated sweat have been reported (1, 2). The sodium concentration of thermal sweat is a curvilinear function of sweat rate (3), whereas, in pharmacologically-stimulated sweat the relation between sodium concentration and sweat rate is uncertain (4).

The potassium concentration of pilocarpine-stimulated sweat, as reported by Schwachman and Mahmoodian (2) was considerably higher than we observed in thermal sweat (5). These discrepancies prompted us to compare the sodium and potassium content of sweat induced by each method.

METHODS

Fifteen normal young men, aged 22 to 25, were used as experimental subjects. In each subject, sweating was first induced pharmacologically on the volar surface of one forearm. Thermal sweat was induced immediately thereafter and sweat collected from the corresponding site of the other forearm.

1. *Pilocarpine iontophoresis.* In 8 subjects, 2″ × 2″ gauze pads soaked with 5 ml. of a 0.2% aqueous solution of pilocarpine HCl were applied to the volar surface of one forearm. An electrode was placed over the gauze pad, fastened with a rubber-band and connected to the positive pole of the iontophoretic instrument (Sweat Inducer, Buchler Instruments, Inc.). Another gauze pad, soaked with 0.2N sodium bicarbonate was applied to the extensor surface of the same forearm. A second electrode was placed over the pad and connected to the negative pole. During a 5 to 10 second period the current was slowly raised to two milliamperes and kept there for 5 minutes. After iontophoresis, the forearm was washed with distilled water and air dried. An aluminum chamber with an internal diameter of 2.5 cm was secured to the skin with Weldwood® contact cement. The test site within the chamber was again washed with deionized water and wiped carefully with dry electrolyte-free tissue papers. Two electrolyte-free filter papers with a diameter of 2.4 cm were placed within the chamber for three to four minutes and discarded at time zero. The entire procedure from the cessation of iontophoresis to time zero lasted about six to eight minutes. Five minute serial collections of sweat were obtained during the next 35 to 45 minutes. The amount of sweat collected was determined by weighing the filter papers in an air-tight, plastic bottle immediately before and after each sweat collection. Sweat was diluted with deionized water and was analyzed for its sodium and potassium content by flame photometry. Recovery studies which consisted of placing a few drops of known standard samples on the test site within the chamber and absorbing it again on filter paper proved the accuracy of the method with an error of ±5%.

2. *Intracutaneous injection of pilocarpine, methylcholine and acetylcholine.* In six subjects, pilocarpine HCl (0.1%); in one subject acetylcholine (0.3%) and in one subject both acetylcholine (0.3%) and methylcholine (0.1%); each in Ringer's solution were injected into the test sites of the forearm. In order to obtain a uniform sweating pattern 0.1 ml of each of the injection solutions was injected intracutaneously with a 30

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gauge needle into four different areas within the test site of 4.5 cm^2. Collection of sweat was begun six to eight minutes after injection, by which time bleeding or leakage of the injection solution, if any, had completely stopped. The treatment of the test site after injection and the method of sweat collection were the same as after pilocarpine iontophoresis.

3. *Thermal sweating.* In all 15 subjects, thermal sweating was induced in an environmental room (44° C initially, 47° C finally, RH = 80%) within 30 minutes after cessation of the pharmacological sweating procedure. The details of the method have already been described (3, 5). Initial sweat samples collected ten minutes after entering the environmental room were discarded in order to make the collection period comparable to that with pharmacological sweating.

4. *Injection of neostigmine.* In five subjects 0.025 mg of neostigmine methylsulfate in 0.5cc of Ringer's solution was injected into one side of the upper back and Ringer's solution alone to the contralateral site ten minutes before entering the environmental room. Sweat was collected in the same manner.

5. *Sweat pore patterns.* In seven subjects, the number of active sweat glands on the volar surface of the forearm was compared after thermal and pharmacologic stimulation. Sweat pore patterns were obtained on iodine-impregnated paper on one forearm ten minutes after iontophoresis and at about thirty minutes after the initiation of thermal sweating on the contralateral forearm. The method for counting the number of pores has been previously described (11).

RESULTS

In Figure 1, the sodium and potassium concentration of thermal and pilocarpine-iontophoresis

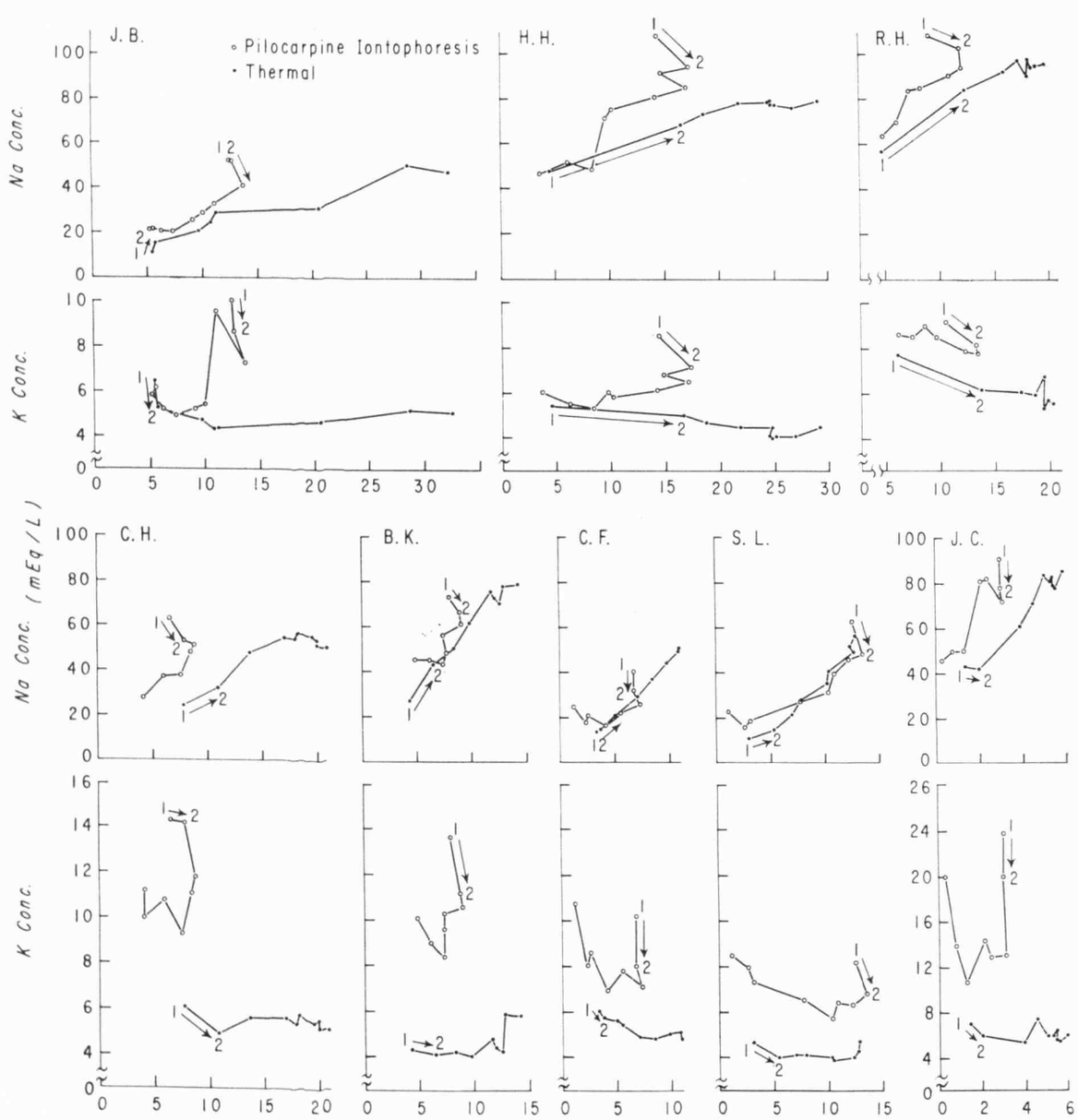

FIG. 1. Plots of sodium and potassium concentration vs. sweat rate for thermal sweat and pilocarpine iontophoresis-sweat. Figures indicate the first and second sweat samples. The arrows indicate the order of the serial sweat collections.

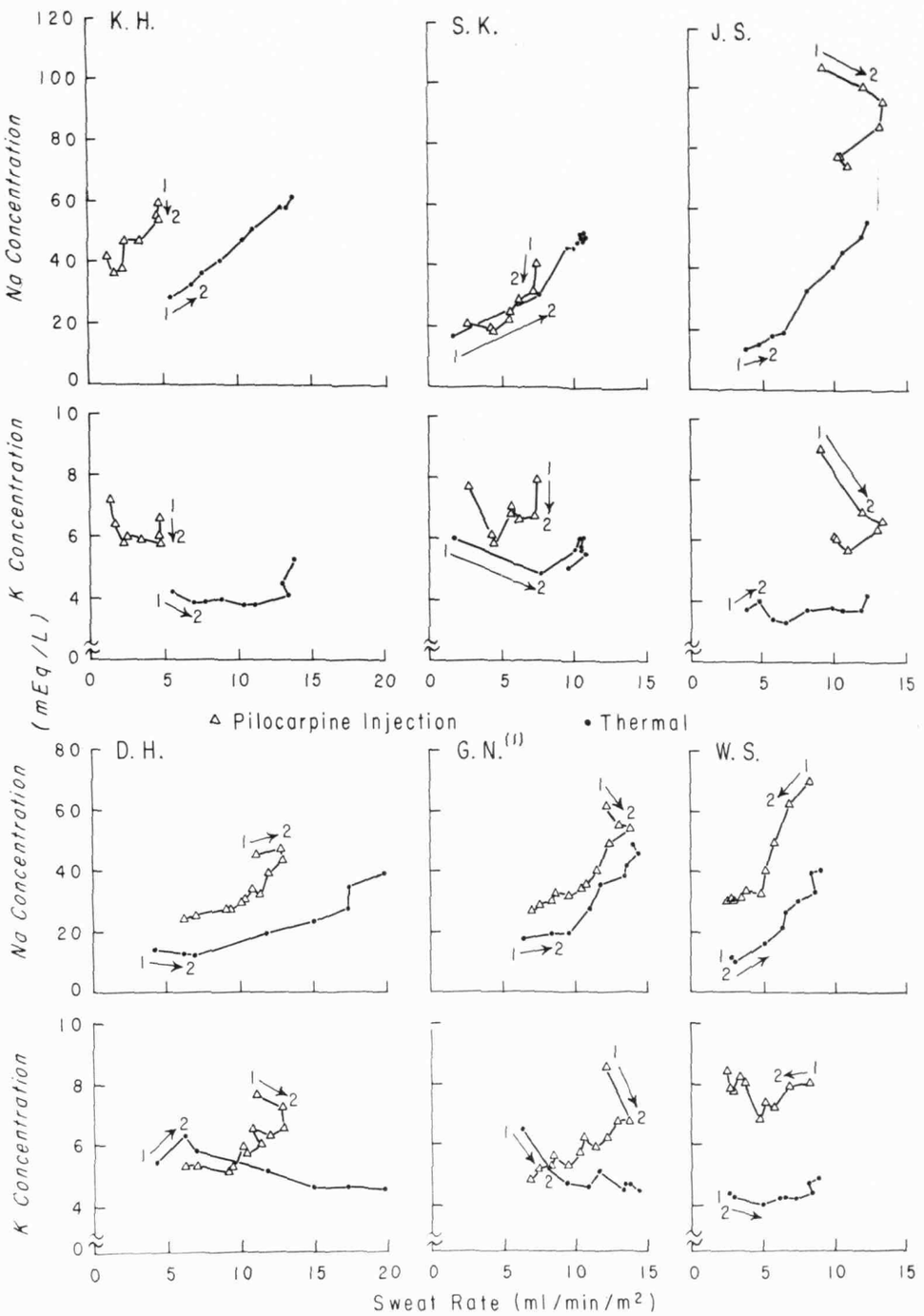

FIG. 2. Plots of sodium and potassium concentration vs. sweat rate for thermal sweat and sweat induced by pilocarpine injection.

sweat are compared. In all subjects, considerably higher potassium concentrations occurred at all sweat rates with pilocarpine. In thermal sweat, the first sweat sample tended to show the highest potassium concentration followed by a rather constant concentration of potassium ranging between four and six mEq/L. In pilocarpine sweat the first sample had a high potassium concentration which was followed by somewhat lower concentrations of potassium in the next few samples. Then potassium concentrations again rose.

In 5 of 8 subjects, the sodium concentration of the pilocarpine-induced sweat was consistently higher than that of the thermal sweat. The remaining subjects showed a high value only in the first few samples of pilocarpine sweat. Figure 2 compares thermal sweat and the sweat induced by pilocarpine injection. In 5 of 6 subjects, sodium concentrations were higher in the pilocarpine sweat and, in all subjects, potassium concentrations tended to be higher in the pilocarpine sweat, especially at high sweat rates.

The injection of methylcholine and acetylocholine produced the same results as the injection of pilocarpine (Fig. 3).

The Table lists the mean and the range of potassium concentrations in pharmacological sweat and thermal sweat in the 15 subjects. Mean

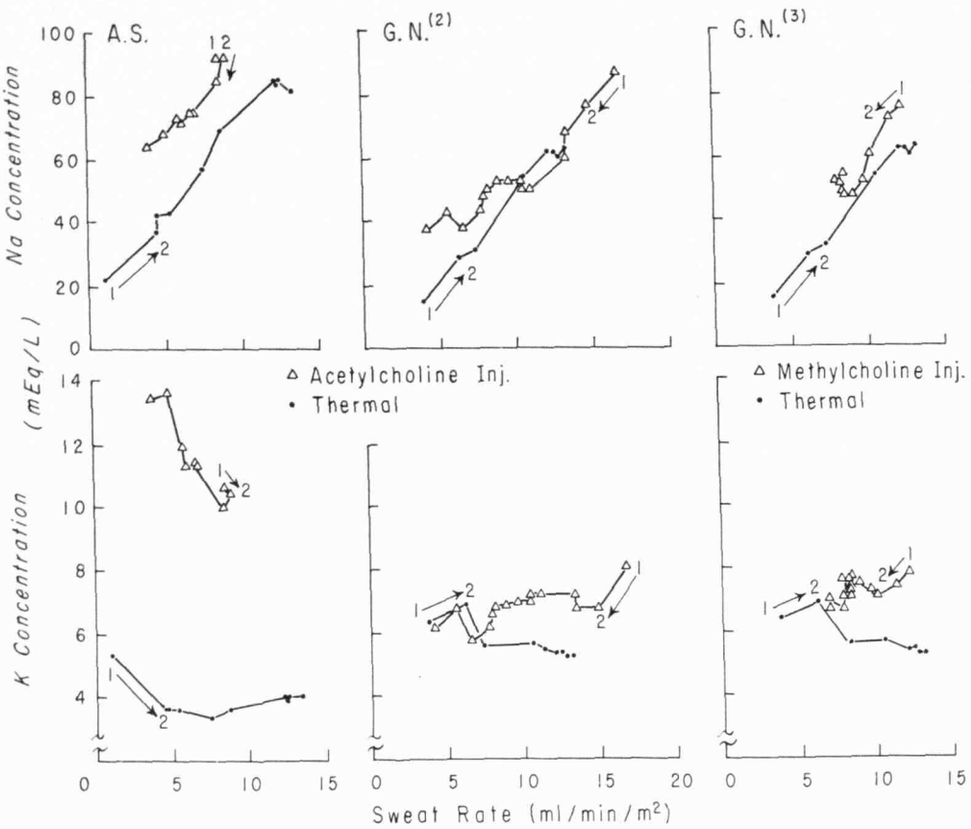

FIG. 3. Plots of sodium and potassium concentration vs. sweat rate for acetylcholine, methylcholine and thermal sweat.

TABLE

Potassium concentrations in thermal sweat and pharmacological sweat

Subject	Thermal sweat		Pharmacological sweat		
	Mean (mEq/L)	Range (mEq/L)	Mean (mEq/L)	Range (mEq/L)	
C. H.	5.4	6.1–4.9	11.7	14.3–9.3	Pilocarpine iontophoresis
S. L.	4.2	4.6–3.9	6.8	8.2–5.7	
J. C.	6.1	7.5–5.4	16.5	23.9–10.3	
C. F.	5.1	6.0–4.8	8.2	10.8–6.9	
B. K.	4.8	5.9–4.0	10.5	13.7–8.4	
R. H.	6.1	7.7–5.4	8.4	9.2–7.8	
H. H.	4.4	5.4–4.0	6.6	8.5–5.3	
J. B.	4.9	6.4–4.3	7.2	10.0–4.9	
S. K.	5.6	6.0–4.8	6.9	7.9–5.8	Pilocarpine injection
J. S.	3.8	4.2–3.3	6.6	9.0–5.7	
D. H.	4.8	6.3–4.5	6.2	7.6–5.1	
K. H.	4.3	5.3–3.8	6.1	7.2–5.8	
G. N.(1)	4.8	6.5–4.5	6.1	8.5–4.8	
W. S.	4.4	4.9–4.0	7.7	8.4–6.8	
G. N.(2)	5.6	6.4–5.3	7.0	8.1–5.8	Acetylcholine injection
A. S.	3.8	5.3–3.4	11.9	21.7–9.9	Acetylcholine injection
G. N.(3)	5.6	6.4–5.3	7.3	7.8–6.9	Methylcholine injection
Mean ± S.E.	4.9 ± 0.17		8.3 ± 0.66		$P < 0.001$

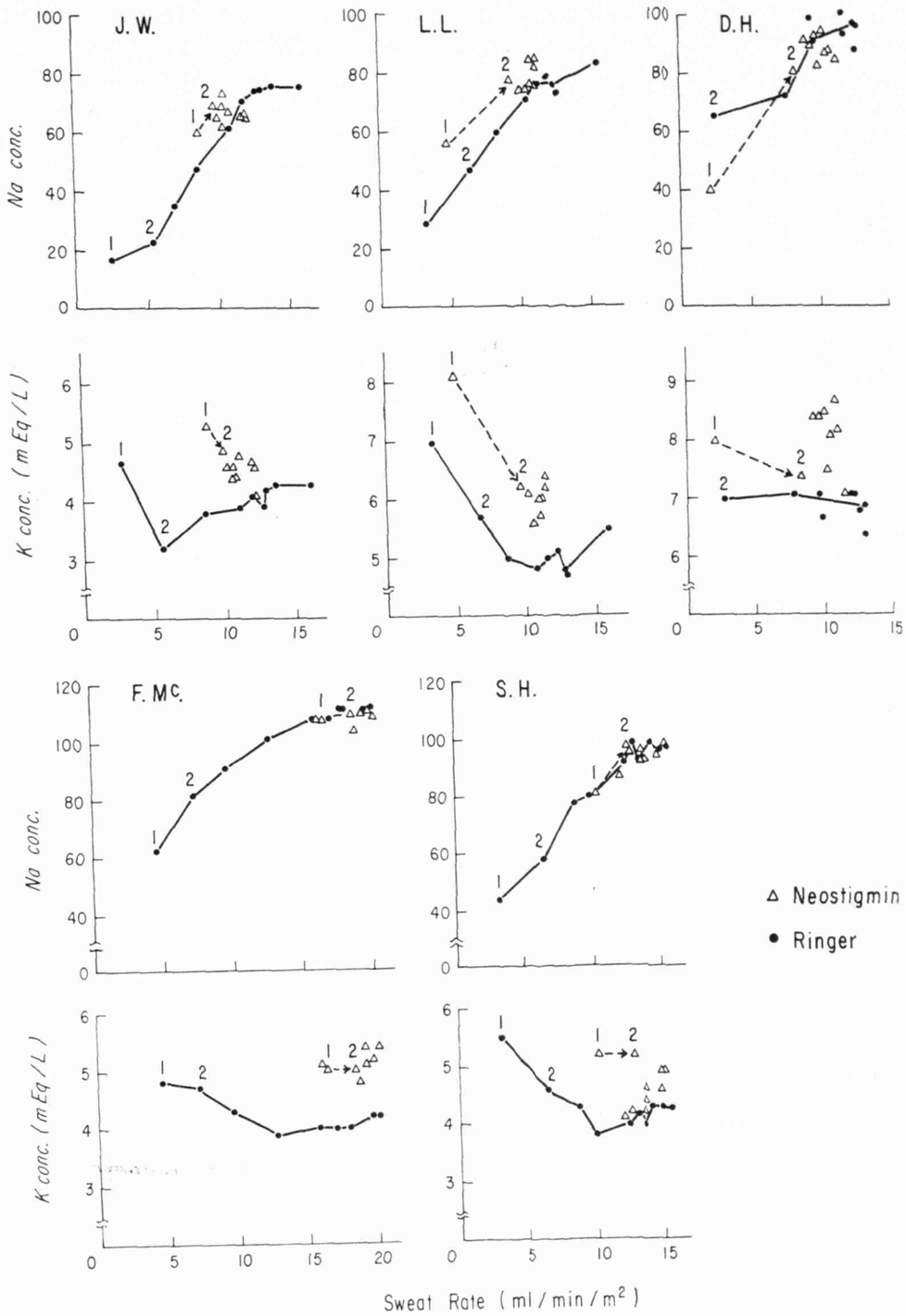

FIG. 4. The effect of neostigmine injection on sodium and potassium concentration of the thermal sweat. Figures indicate the first and second sweat samples.

potassium concentration was 4.9 ± 0.17 for thermal sweat and 8.3 ± 0.66 for pharmacological sweat. The local injection of neostigmine produced a high sweat rate with constantly higher potassium concentration (Fig. 4). The sodium concentration of the neostigmine sweat was comparable to that of the controls or slightly higher especially in the first few samples. (L.L. and D.M.) (Fig. 4). There was no significant difference in the number of active sweat glands after pharmacologic or thermal stimulation. The average number of pores was 132 ± 6.3 after iontophoresis and 134.7 ± 9.5 (S.E.) per cm² after thermal stimulation.

DISCUSSION

di Sant' Agnese observed no difference in the electrolyte composition of sweat obtained by thermal stimulation and that of pilocarpine-induced sweat (1, 6). Schwachman and Antonowicz (7) noted a lower sodium and chloride and a higher potassium concentration in pilocarpine-induced sweat than in "bag sweat" (thermal sweat induced without external heat and collected for one hour in an airtight bag).

In the present study, pharmacologically-induced sweat contained considerably higher concentrations of both sodium and potassium than

thermal sweat in most subjects. These differences were not caused by evaporation of water from the sweat samples during the process of collection since sweat was collected within an airtight aluminum chamber nor were these differences due to a variation in the number of active sweat glands. In man, the electrolyte content of sweat collected from the skin surface represents the difference between what is secreted by the secretory cells and what is reabsorbed by the ductal cells. The higher sodium concentrations seen occasionally in pharmacologic sweat can be due either to a hypertonic precursor fluid, a decreased reabsorption of sodium by the duct, or increased H_2O reabsorption by the duct. The first assumption may be possible since Slegers (13) observed a hypertonic precursor fluid in the cat sweat gland after mecholyl stimulation but not after direct electrical stimulation of the nerve. The second assumption, either a decrease in ductal sodium reabsorption or an increase in the back diffusion of water, or the combination of these two factors must also be considered since the possibility remains that the exogenous administration of cholinergic drugs in a dosage much higher than that of endogenous acetylcholine may affect the membrane or the function of ductal cells, whereas in thermal stimulation the minute amount of acetylcholine is localized only to the receptor site of the secretory cells (8).

The mechanism of excretion of potassium in sweat is poorly understood. It may be derived either from secretory cells or the ductal cells, in which a Na for K exchange transport is assumed to occur (9). However, a concomitant increase in both sodium and potassium concentration in pharmacologic sweat cannot be explained on the basis of facilitated Na for K exchange since under these circumstances sodium concentrations should be lower.

Cholinergic drugs have been shown to enhance the leakage *in vitro* of cellular potassium from slices of rat salivary gland (10) and from the frog cardiac muscle (12). Slegers observed the leakage *in vitro* of cellular potassium to the blood stream and the area surrounding the gland when the nerves supplying the cat sweat glands were stimulated electrically (13). If the decrease in ductal reabsorptive function and the increase in potassium secretion are related, then loss of cellular potassium from the ductal cells due to the administered cholinergic drugs with a resultant decrease in the functional integrity of the ductal cells could explain the whole process. However, after the injection of neostigmine (acetylcholinesterase inhibitor) in which more endogenous acetylcholine affects the secretory cells, the potassium increased significantly, which implies that the secretory cells might also contribute to the increase in sweat potassium concentration in pharmacologically-stimulated sweat.

REFERENCES

1. di Sant'Agnese, P. A. and Powell, G. F.: The eccrine sweat defect in cystic fibrosis of the pancreas. Ann. N. Y. Acad. Sci., *93:* 555, 1962.
2. Schwachman, H. and Mahmoodian, A.: Pilocarpine iontophoresis sweat testing. Result of several years' experience. Mod. Prob. Pediat., *10:* 158, 1967.
3. Cage, G. W. and Dobson, R. L.: Sodium secretion and reabsorption in the human eccrine sweat gland. J. Clin. Invest., *44:* 1270, 1965.
4. Grand, J. R., di Sant'Agnese, P. A., Talamo, R. C. and Pallavicini, J. C.: The effect of exogenous aldosterone on sweat electrolytes. J. Pediat., *70:* 346, 1967.
5. Sato, K. and Dobson, R. L.: The action of intracutaneously administered d-aldosterone and hydrocortisone on human sweat gland function. J. Invest. Derm., *54:* 450, 1970.
6. di Sant'Agnese, P. A.: Discussion remarks; p. 77, Proc. 3rd Int. Conf. Research on the Pathogenesis of Cystic Fibrosis, Bethesda, Md., 1964.
7. Schwachman, H. and Antonowicz, I.: The sweat test in cystic fibrosis. Ann. N. Y. Acad. Sci., *93:* 600, 1962.
8. Rothman, S.: *Physiology and Biochemistry of the Skin.* The University of Chicago Press, Chicago, 1954.
9. Slegers, J. F. G.: A mathematical approach to the two step reabsorption hypothesis. Mod. Prob. in Pediat., *10:* 74, 1967.
10. Schneyer, L. H.: Exchange of potassium in rat submaxillary gland, Secretory Mechanisms of Salivary Glands. Eds., Schneyer, L. H. *et al.* Academic Press, New York, 1967.
11. Sato, K. and Dobson, R. L.: The regional and individual variations in the function of human eccrine sweat gland. J. Invest. Derm., *54:* 443, 1970.
12. Harris, E. J. and Hutter, O. F. The action of acetylcholine on the movements of potassium ions in the sinus venosus of the heart. J. Physiol., *133:* 580, 1956.
13. Slegers, J. F. G.: Ionic secretion by epithelial membranes. Ciba Found. Study Group, *32:* 68, 1968.