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Research Article

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In a second series of experiments the stop-flow pressure which is generated by sweat glands during secretion was measured. Values up to 500 mm Hg were found in both patients and normals. According to van't Hoff's law ($\Delta P = RT\Delta C$) hydrostatic pressure differences of this magnitude can be generated by the osmotic difference of 27 mOsm/kg of water observed between precursor sweat and plasma in the present experiments. With respect to the mechanism of sweat secretion this finding supports the hypothesis that active solute transport creates an osmotic gradient which causes osmotic water flux.

Micropuncture Studies of the Sweat Formation in Cystic Fibrosis Patients

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ABSTRACT In order to determine whether the precursor solution of sweat is abnormal in cystic fibrosis, osmolality and concentrations of sodium and chloride were measured in fluid obtained by micropuncture from the sweat gland coil of the nail fold of patients with this disease. Osmolality was 323 ±4.8 SE (mOsm/kg of water), sodium concentration was 151 ±1.1 SE (mEq/liter), and chloride concentration was 124 ±6.0 SE (mEq/liter). The sweat: plasma ratio for osmolality averaged 1.1 ±0.015 SE. These values are not significantly different from the corresponding ones obtained previously in normal individuals. It is concluded therefore that the disturbance of sweat gland function as far as electrolytes are concerned is restricted to the excretory ducts.

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INTRODUCTION

It is known that in patients with cystic fibrosis the NaCl concentration of sweat is higher at a given flow rate than in normal individuals (11–13). There are several possible explanations for this abnormality. The primary secretion might be hypertonic while NaCl reabsorption in the duct is normal; the NaCl reabsorption in the duct might be decreased; or the water permeability of the duct might be increased. Most of the evidence up to this time, although indirect, supports the second possibility, namely, that in cystic fibrosis sodium reabsorption in the sweat duct is impaired (1, 3, 16). To get direct proof of the localization and nature of the functional defect in patients with cystic fibrosis two methods were used: (*a*) micropuncture of the partially dissected sweat gland coil and microanalysis of the precursor fluid; (*b*) measurement of secretory pressure. The results indicate that the disturbance in sweat gland function as far as electrolytes are concerned must be limited to the excretory duct.

METHODS

The experiments were carried out on sweat glands of the nail fold of the fingers of patients with cystic fibrosis ranging in age from 10 to 23 yr and on normal individuals of the same age group. In addition to the chronic pulmonary disease and pancreatic deficiency, the diagnosis of cystic fibrosis was based on the sweat test (4). The sweat tests for diagnostic purposes were performed by the pilocarpine iontophoresis method (4) and the results listed in Table I.

The technique used for micropuncture was similar to that described in an earlier paper (14) and is only briefly outlined here. The hand was immobilized in a plaster cast or in a sand-filled glove under negative pressure. In order to visualize the sweat gland, colored mineral oil was injected through the gland orifice from the skin surface. To avoid contamination of the secretory part of the sweat gland with oil the injection was stopped as soon as the front of the oil column became invisible in the depth of the tissue. In some experiments methylene blue was used instead of oil.

It was flushed out from the gland rapidly but left the duct walls stained. The duct was dissected free and followed up to the coil which could easily be identified by its surrounding fat tissue. Bleeding was prevented by placing a tourniquet on the finger and by cooling the arm with an ice bag only for a few minutes during dissection. The micropuncture was started 30 min or even longer after the blood supply of the gland was normalized. Rarely it was necessary to anesthetize with Xylocaine, and usually it took only a few minutes to expose the coil. Visualization of the tubules which form the sweat coil was improved by transillumination with a quartz rod. Single secretory tubules which can easily be distinguished from excretory tubules by their larger diameter were punctured with micropipettes, and samples of 0.1–1.0 ml were withdrawn for microanalysis. In some experiments sweating was induced by local application of a 5% solution of acetylcholine before samples were obtained. There was no difference in the results obtained from stimulated or unstimulated glands.

For sodium determination, the helium-glow photometer of Vurek and Bowman (17) was used; chloride and osmolality were determined with the micromethods of Ramsay, Brown, and Croghan (9, 10). The plasma values were determined by the same methods and corrected for Donnan equilibrium and plasma water by multiplying the plasma concentration by the factor 1.01 for sodium and 1.12 for chloride.

For measurements of the secretory pressure a micropipette with a tip of 30 μ in diameter, filled with colored mineral oil, was introduced about 500 μ into the duct, so that the sweat gland opening was occluded (Fig. 1). The sweat, which entered the pipette and pushed the oil backwards, was stopped from flowing by compensating pressure applied to the micropipette. This pressure was read on a mercury manometer and taken to be equal to the secretory pressure of the gland. To obtain highest sweat flow rates and secretory pressures, the measurements were made after

TABLE I

Na^+, K^+, and Cl^- Concentrations in the Final Sweat of Cystic Fibrosis Patients

Name	Sex	Age	Sweat tests		
			Na	K	Cl
		yr		*mEq/liter*	
G. N.	F	17	96.5	16	85.2
C. P.	F	10	115.3	10.3	116.2
M. P.	F	17			110.0
T. M.	M	21	80.5	18.6	80.0
W. P.	F	15	96.0	20.2	59.9
T. H.	M	15	128.9	19.3	QNS
C. A.	F	14	108.6	15.06	115.3
K. C.	F	23	121.2	13.59	125.5
R. M.	M	13	124.2	6.82	99.8
R. F.	M	13	121.0	11.0	128.2
N. M.	F	22	119.3	10.0	102.0
J. D.	M	12	136.8	11.29	109.4

Patients were subjects for micropuncture of the sweat glands. The initials are the same as on Table II. Normal values (9): Sweat $Cl^- < 60$ mEq/liter, mean 18 mEq/liter; sweat $Na^+ < 70$ mEq/liter, mean 22 mEq/liter.

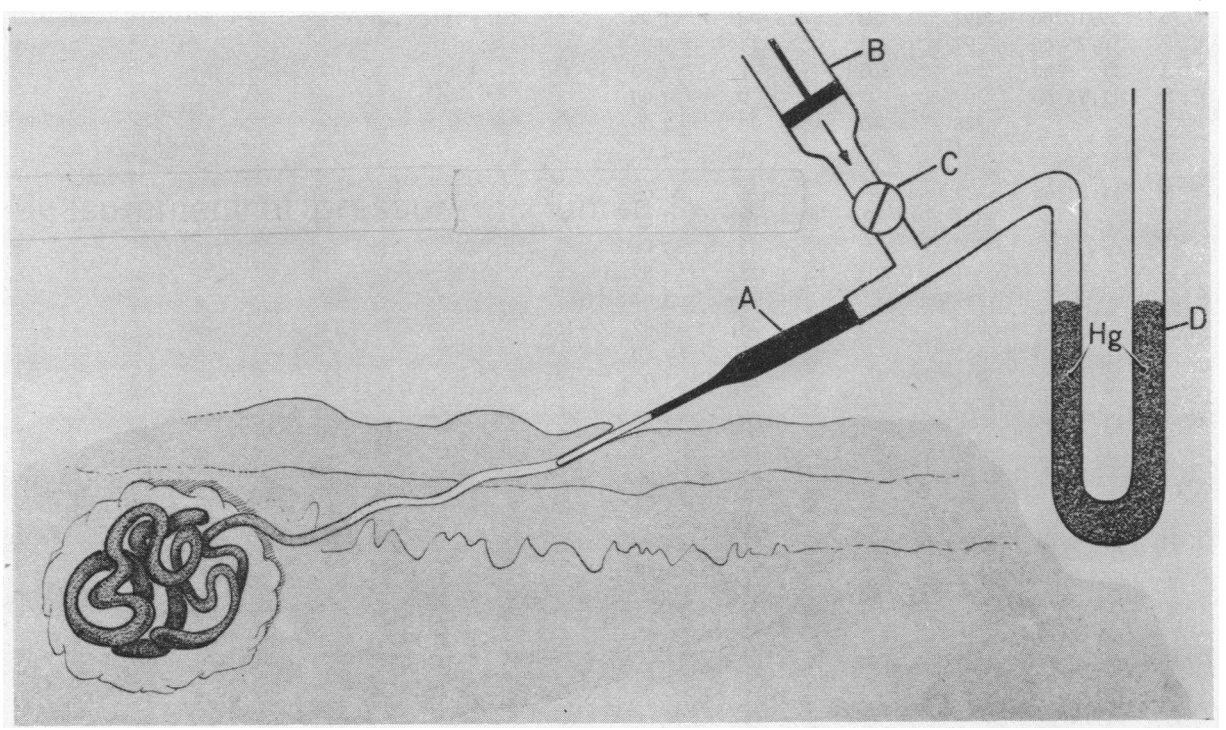

FIGURE 1 Apparatus to measure the secretory pressure in sweat glands. *A*, oil-filled micropipette inserted into the sweat pore; *B*, syringe to apply counter pressure; *C*, stopcock; *D*, mercury manometer.

stimulation with pilocarpine iontophoresis. Immediately after the pressure of a sweat gland had been determined the corresponding sweat flow rate was measured in the same gland. If the sweat flow was too small to allow accurate determination of the volume delivered by a single gland, sweat from several adjacent glands was collected and the volume divided by their number to obtain the flow rate per gland.

RESULTS

The data for osmolality, Na^+ and Cl^- concentrations of the sweat obtained by micropuncture from the sweat gland coil of 12 patients are shown in Table II and in Figs. 2 and 3. The mean values for osmolality from 40 measurements in 12 patients with cystic fibrosis was 323 ±4.8 SE (mOsm/kg of water). The mean Na^+ concentration from 11 measurements in five patients was 151 ±1.1 SE (mEq/liter) and the mean Cl^- concentration from 13 measurements of five patients was 124 ±6.0 SE (mEq/liter). For comparison the corresponding values from normal individuals obtained in a previous study by the present investigator and with the same technique (14) are listed in Figs. 2 and 3. It can be seen that the mean values from normals and patients do not deviate from each other. The average sweat: plasma (S/P) osmolality ratio was 1.10 ±0.015 SE (Table II and Fig. 4) which is significantly different from 1.0 ($P < 0.001$). The precursor sweat secretion, therefore, was slightly hypertonic.

The results of the pressure measurements are represented in Table III and Fig. 5. 17 measurements on nine normal subjects are compared with 23 measurements on 11 patients with cystic fibrosis. The stop-flow pressure increases with an increasing rate of flow of sweat up to 500 mm Hg in the highest flow rates in both groups. Apparently there was no difference between the secretory

TABLE II

Osmolality and Sodium and Chloride Concentrations in the Primary Secretion of Sweat Glands and in the Plasma of Cystic Fibrosis Patients

		Osmolality				Sodium concentration			Chloride concentration		
Patient	Date	Coil sweat	Plasma	S−P	S/P	Coil sweat	Plasma water	S/P	Coil sweat	Plasma water	S/P
		mOsm/liter				*mEq/liter plasma water*			*mEq/liter plasma water*		
G. N.	9/16/66	291	294	− 3	0.99						
C. P.	10/26/66	297	311	− 14	0.95						
M. P.	11/ 3/66	304	305	− 1	1.00	150	138	1.09			
C. P.	11/15/66	302		0	1.00						
		328	302	+ 26	1.09						
		301		− 1	1.00						
T. M.	11/23/66	329		+ 24	1.08						
		323		+ 18	1.06						
		307		+ 2	1.01						
		331	305	+ 26	1.09		136				
		327		+ 22	1.07						
		333		+ 28	1.09	155		1.14			
		365		+ 60	1.20						
		327		+ 22	1.07	155		1.14			
W. P.	12/ 5/66	360		+ 80	1.29						
		296	280	+ 16	1.06						
		296		+ 16	1.06						
		285		+ 5	1.02						
T. H.	12/ 7/66	345		+ 55	1.19						
		372		+ 82	1.28						
		378	290	+ 88	1.30						
		371		+ 81	1.28						
		392		+102	1.35						
		377		+ 87	1.30						
C. A.	1/14/67	322		+ 32	1.11	160	140	1.14			
		287		− 3	0.99						
		301		+ 11	1.04						

TABLE II—(*Continued*)

Patient	Date	Osmolality				Sodium concentration			Chloride concentration		
		Coil sweat	Plasma	S−P	S/P	Coil sweat	Plasma water	S/P	Coil sweat	Plasma water	S/P
		mOsm/liter				*mEq/liter plasma water*			*mEq/liter plasma water*		
T. M.	1/25/67	328		+ 33	1.11				100	114	0.83
		344		+ 49	1.17				125		1.10
K. C.	2/ 3/67	315		+ 26	1.09						
									125		1.10
		338	289	+ 49	1.17				130	114	1.14
		321		+ 32	1.11						
		309		+ 20	1.07						
K. M.	2/ 7/67	296		+ 6	1.02				110		1.00
		274	290	− 16	0.94				100	110	0.91
		296		+ 6	1.02				125		1.14
		312		+ 22	1.08						
R. F.	2/15/67	318		+ 22	1.07				160		1.44
		328	296	+ 32	1.11				150	111	1.35
		306		+ 10	1.03				160		1.44
									103		0.93
N. V.	2/22/67					140	140	1.00			
						142		1.01			
J. D.	3/14/67					156		1.10			
						144		1.01	116		1.04
						150	142	1.06		112	
						157		1.11			
						150		1.06	110		0.90
Mean		323	296		1.10	151	139	1.08	124	112	1.11
SE		±4.8	±2.5		±0.015	±1.1	±4.7	±0.008	±6.0	±2.5	±0.1

pressure of patients with cystic fibrosis and the normal subjects.

DISCUSSION

The present data for the concentration of Na^+ and for osmolality in the percursor solution obtained directly from the sweat gland coil of patients with cystic fibrosis are not significantly different from those obtained previously in normal subjects (14). The large scatter of Cl^- concentrations in the precursor sweat of cystic fibrosis patients suggests that the concentrations of other anions, i.e. lactate and bicarbonate, are also more variable as compared with normals. However, in order to confirm this assumption the concentrations of bicarbonate and lactate would have to be measured directly in the precursor sweat.

It is not possible to study the Na^+ and Cl^- concentrations and the osmolality of the precursor solution in the coil of the sweat gland and compare them with the respective values in the final sweat at the skin surface in the same sweat gland, because of the microdissection and mobilization of the sweat gland duct which make it impossible to obtain secretion from the duct itself. It was only possible to compare the mean values in the precursor solution in the coil in both normal subjects and patients with cystic fibrosis with those obtained by iontophoresis from a relatively large number of sweat glands simultaneously.

Since the mean values for Na^+, Cl^- concentration, and osmolality in the precursor solution in the coil are similar in normal subjects and patients with cystic fibrosis, it was concluded that the reason for the striking difference in these parameters in the final sweat secretion on the skin surface must be due to abnormal reabsorption in the excretory duct of the sweat glands of the fibrocystic patients.

To prove this directly, microperfusion experiments on the duct are needed so as to study the transport characteristics of the duct separately from the coil, but they are technically difficult to perform. On the other hand, some insight into the functional defect of the duct could be expected from the measurement of the electrical po-

tential difference, which we have performed in a subsequent series (15).

It was found that the electrical potential difference, which is generated by the reabsorptive sodium transport mechanism in the duct (14), was no different in cystic fibrosis patients as compared with normal subjects. This finding was the more surprising because the net NaCl reabsorption from the duct of the cystic fibrosis patient is reduced by 50–70% (3). To explain these apparent discrepancies it was hypothesized that in cystic fibrosis the smaller net transport of sodium may be accompanied by a decreased permeability for the passively moving chloride ions. An attractive speculation seems to be that an increase in negatively fixed charges is the cause for a decreased passive permeability to chloride and also for an increased passive-leak permeability to sodium. The latter would result in a diminished net sodium transport because actively transported sodium ions would leak back through the passive shunt pathways.

The data of Emrich et al. (3) indicate strongly that an increased water permeability of the duct is not responsible for the high sodium concentration in sweat of cystic fibrosis patients. Emrich has shown that at a given sweat flow rate the urea S/P and the lactic acid S/P is lower in cystic fibrosis patients than in normals. If the water permeability were higher, the opposite finding would be expected.

The observation of hypertonicity in the precursor solution of sweat is of some interest with respect to the possible mechanisms of sweat secretion. In the previous experiments in normals the osmolality of the plasma was not measured and the mean osmolality of the precursor sweat solution (318 mOsm/kg ±2.83 SE) was assumed to be isotonic. Since, however, the osmolality of the precursor solution of normals and patients with cystic fibrosis is not different, it is likely that the primary sweat secretion is slightly hypertonic in normals too. A hypertonic precursor fluid in glands is not unusual. Holzgreve, Martinez, and Vogel (5) for instance found in micropuncture experiments of the submaxillary gland in young rats a hypertonicity in the precursor fluid of 46 mOsm/kg of H_2O. Hypertonicity of primary secretions could suggest that fluid transport is achieved by simple osmosis. The mechanism would require active solute transport

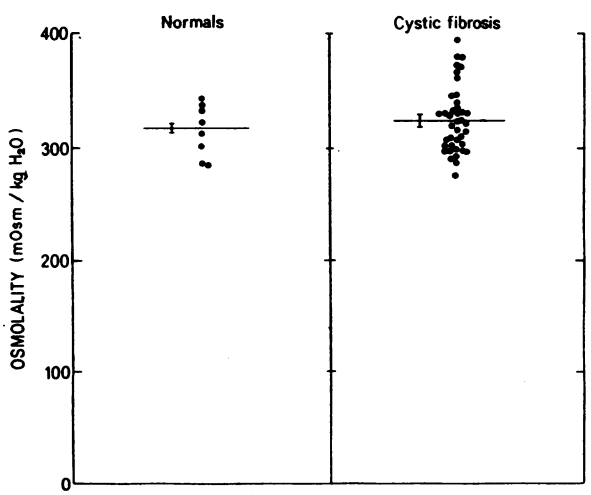

FIGURE 2 Osmolality of precursor solution in human sweat gland coil. The horizontal line indicates the mean value and the vertical bars the SE of the mean. The values for normal subjects are taken from a previous publication (9).

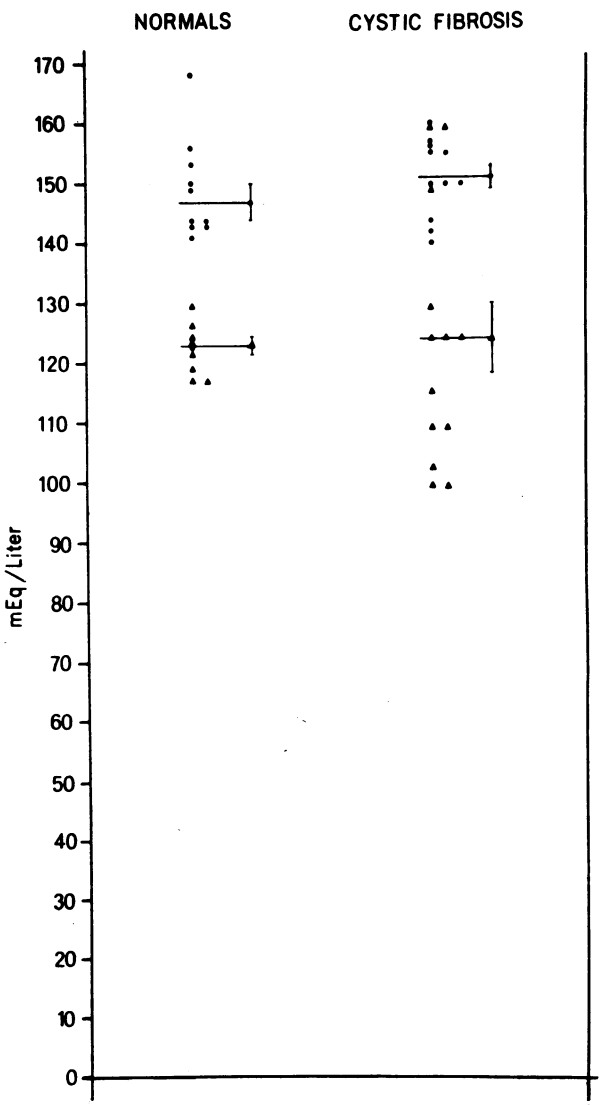

Figure 3 Sodium (●) and chloride (▲) concentration of the precursor solution in human sweat gland coil. The horizontol lines indicate the mean values and the vertical bars the SE of the mean.

into the glandular lumen to generate the hypertonicity which in turn causes water influx.

The following equation permits calculation of transepithelial water flux (J_v) (6):

$$J_v = Lp(\Delta P + \sigma RT\,\Delta C) + J_v \text{ active} \qquad (1)$$

where L_p = hydraulic conductivity;
ΔP = hydrostatic pressure difference;
σ = reflection coefficient of the substance of which the concentration difference ΔC is responsible for the osmotic pressure difference;
RT = gas constant × absolute temperature;
J_v active = active transport or volume flux when ΔP and ΔC are zero.

The hypertonicity of the precursor fluid found in our micropuncture experiments correponds to ΔC under free-flow conditions. In our stop-flow experiments J_v was zero and ΔP was measured. If we assume that an active water transport does not exist equation 1 becomes

$$\Delta P = \sigma RT\,\Delta C \qquad (2)$$

To test equation 2 and to calculate σ it would be desirable to correlate the stop-flow pressures ΔP and osmolal differences between precursor fluid and plasma measured under stop-flow conditions ΔC at the same gland. This however is impossible at the present time from the technical aspect, but even not knowing ΔC under stop-flow conditions we can take the following approach. If the low interstitial tissue pressure is neglected, ΔP could be considered equal to the stop-flow pressure, i.e., a mean of 400 mm Hg during maximal stimulation of the gland. The mean osmolality of the precursor fluid during free-flow studies was independent of the stimulatory state and resulted in a RT ΔC corresponding to a pressure of 515 mm Hg. Since ΔC under free-flow conditions will always be smaller than under stop-flow conditions—the secreted fluid tends to diminish ΔC — the σ value calculated from ΔP stop flow, and RT ΔC free flow will be a maximal value.

$$\frac{\Delta P \text{ (stop flow)}}{RT\,\Delta C \text{ (stop flow)}} = \sigma \leqq \frac{\Delta P \text{ (stop flow)}}{RT\,\Delta C \text{ (free flow)}} = 0.78$$

Concerning our finding that the osmolal difference between precursor fluid and plasma did not change during stimulation we refer to the following statement of Diamond and Bassert (2). "It has been puzzling that in those organs which do form hypertonic secretions, the transported fluid is still hypertonic at the lowest transport rates, when one would expect osmotic equilibration to be most nearly complete." This behavior could be explained if σ in equation 1 would change in proportion to the state of stimulation, i.e., if the osmotic efficiency of the substances which induce water flux would increase during stimulation and would be low in the unstimulated gland.

To our knowledge the only other data available on secretory pressure of sweat glands are those of Kittsteiner (7) in 1913 who reports that he could not stop sweating by applying counter pressures up to 250 mm Hg.

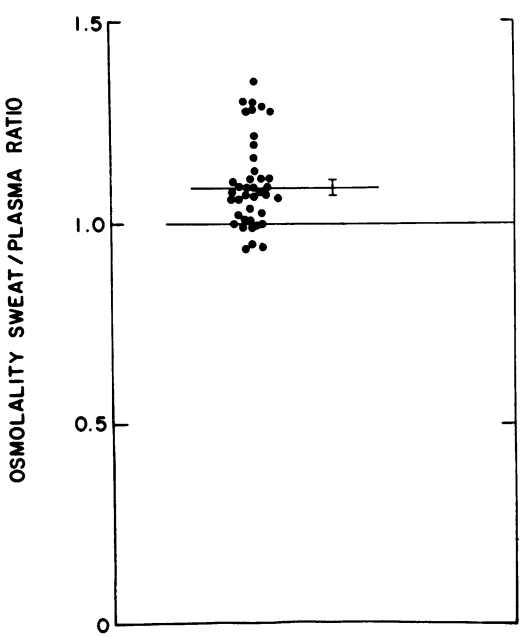

FIGURE 4 Sweat: plasma ratios for osmolality of the precursor sweat secretion of patients with cystic fibrosis. The horizontal line indicates the mean value and the vertical bars the SE of the mean.

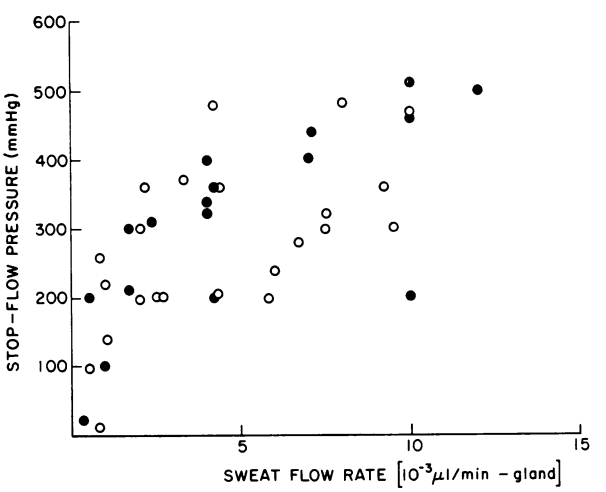

FIGURE 5 Stop-flow pressure in the sweat glands of normal individuals (closed circles) and of patients with cystic fibrosis (open circles) plotted against postocclusion sweat flow rate.

TABLE III

Stop-Flow Pressure and Secretory Rate of Sweat Glands in Normals and Cystic Fibrosis Patients

Pressure measurements in normal controls				Pressure measurements in cystic fibrosis patients			
Name	Date	Pressure	Sweat flow rate	Name	Date	Pressure	Sweat flow rate
		mm Hg	*μl/min*			*mm Hg*	*μl/min*
E. G.	10/ 5/66	200	10.0	G. N.	10/27/66	260	0.8
St. F.	10/ 6/66	300	1.7	M. P.	11/ 2/66	480	8.0
J. F.	11/10/66	310	2.4	M. P.	11/ 7/66	200	2.0
		320	4.0		11/10/66	100	0.5
						200	4.2
St. F.	11/11/66	400	7.0				
		220	1.7	Ch. P.	11/10/66	200	5.8
		340	4.0			480	4.2
						300	9.5
J. F.	11/11/66	400	4.0			360	2.2
		100	1.0				
		20	0.3	W. P.	12/ 8/66	10	0.8
					12/13/66	300	7.5
E. G.	11/ 4/66	200	0.5			200	2.5
B. D.	11/15/66	200	4.2	R. C.	1/13/67	360	4.3
						140	1.0
J. F.	11/22/66	360	4.2				
				T. M.	1/28/67	300	2.0
G. R.	1/ 5/67	440	7.1				
		520	10.0	R. F.	2/ 2/67	240	6.0
		460	10.0				
		500	12.0	K. C.	2/ 3/67	370	3.3
				M. F.	3/ 3/67	470	10.0
						320	7.5
						360	9.2
						220	1.0
						200	2.7
						280	6.7

The question as to which substance is actively transported into the lumen of the secretory tubules during secretion cannot be answered at present. Although in salivary glands an active chloride transport has been postulated (8) as the first step in secretion, and although in our experiments for chloride a mean sweat over plasma ratio > 1.0 has been found, this does not prove active chloride secretion as long as the electrical potential profile across the secretory coil is unknown. Our own attempts to measure it with Ling-Gerard microelectrodes in the exposed coil *in situ* have not been successful enough to yield conclusive results.

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