STUDIES OF pH OF SWEAT PRODUCED BY DIFFERENT FORMS OF STIMULATION*

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During the past two years we examined the pH of the sweat, as well as the pH on the skin surface after stimulation of sweating by drugs, such as pilocarpine, acetylcholine, or adrenaline and compared the results with those obtained after stimulation by heat or muscular exercise.

About twenty-five years ago Brill (1), Marchionini (2), and Herrmann and Fuerst (3) observed a lower degree of acidity in sweat evoked by systemic administration of pilocarpine than in thermal sweat. A possible explanation of the higher pH in response to pilocarpine was seen in a relatively stronger stimulation of the apocrine glands.

The influence of an admixture of apocrine sweat appeared possible, since at that time the pH was usually tested in sweat samples collected from rather extensive skin areas; and the apocrine glands were known to be located not only in the axillae, but also around the mamillae, and in other skin areas. It has never been proven, however, that augmented apocrine sweating is responsible for the higher pH of pilocarpine sweat, and this explanation has never been quite convincing.

For this reason and in view of the more recent reports of Shelley and Hurley that the apocrine glands are not susceptible to cholinergic stimulation (4–6) and—last, but not least—in view of the established concept that heat sweating is cholinergic in nature (7), we have extensively studied the pH of both sweat and skin surface after the different forms of sweat stimulation.

I. METHOD OF pH MEASUREMENT

Most of our tests were performed potentiometrically by means of the Beckman pH meter "Model G", connected with a "fiber type reference" (calomel) electrode, Beckman No. 1170, and a special glass electrode, Beckman No. 1190-42†, which—with its hemisphere of only 5 mm in diameter—has been devised for the examination of minute traces of aqueous material on small surface areas. Prior to each application of the electrodes, the area on which the examination was carried out was moistened with a quantity of a saturated KCl solution in water, just sufficient to secure and maintain a "bridge of contact" between the electrodes. Our technique of testing was similar to the procedures employed by Blank (8a), Draize (8b), and Arbenz (8c) in pH examinations on the skin surface, although these investigators used somewhat different equipment, and saline solution to sustain the "bridge of contact".

We used the combination of Beckman's glass electrode No. 1190-42 with "reference" electrode No. 1170 for measurements on the skin surface, as well as for those in vitro tests for which it was impossible to collect sweat volumes in excess of 0.035 ml. The available

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traces of sweat were carefully drawn up in glass capillary tubes and gathered on a flat watch-glass.

When larger sweat volumes were available for testing in vitro, we usually employed Beckman's "one drop" glass electrode No. 289-82, in conjunction with "reference" electrode No. 270.

In addition, parallel tests were performed regularly with an indicator method which we developed several years ago for pH estimation on the skin (9, 10)—utilizing a special universal indicator* and glass capillaries. In the present study, this method was employed both for examinations on the skin surface and for testing in vitro. The proportions of sweat and indicator drawn up in a capillary were roughly 0.015 ml and 0.03 ml, respectively.

II. EXPERIMENTS

A. Testing of pH *in vitro*

1. Outline of Procedure

Sixteen healthy male and three healthy female volunteers, 21 to 37 years of age, were subjected to the experiments. In all, 183 test series comprising a total of 6,757 single tests were performed.

The use of soap was not permitted for a period of at least 24 hours prior to each examination. When special preparations, such as creams, deodorants, etc., had been in use, any remnants were removed, and their use was avoided for an adequate period of time before the examinations were initiated.

The investigations were carried out during all seasons of the year (climate of New York City), in an air-conditioned room.

Thermal stimulation of sweating. The subjects were seated between two reflector-type sweat boxes and exposed to dry heat (about 108° F.) in the manner outlined in our previous reports (11, 12). The exposure was discontinued as soon as sweat droplets were distinctly visible to the naked eye in the temporal and scapular areas, as well as the axillary vaults, which were used as standard test areas. At this stage—in male subjects usually 10 to 15 minutes, in females about twice as long after the heating was started—the sweat was carefully drawn up in capillaries from the areas under test.

Whereas we used and designated this procedure as our *"standard method" of thermal sweat stimulation*, the exposure to dry heat was prolonged to 60 or 70 minutes in additional experiments.

Stimulation of sweating by muscular exercise

Sweating was evoked by frequent knee-bending. In some instances, this exercise was continued for as long as one hour beyond the time of the first appearance of discrete sweat droplets and the first pH-determination.

Stimulation of sweating by drugs

Pilocarpine. To induce *"local"* sweating, 0.1 to 0.3 ml of a 1% solution of pilocarpine hydrochloride in sterile physiologic saline solution were injected intradermally. In another group of experiments sweating was provoked *systemically* by subcutaneous or intramuscular injection of 1 ml of the same solution.

About 10 to 20 minutes after administration of the drug—when sweating had reached its maximum—samples of sweat were collected to test the pH. After intracutaneous injection, the samples were obtained from the injected site and, when possible, also from other areas; after systemic administration, the samples were gathered from the forehead (temporal area), as well as from other test areas, when sufficient quantities were present.

* Stanscien Indicator (Standard Scientific Supply Corp., New York, N. Y.) containing 0.1 gm. of powdered Parstains Universal Indicator in 75 ml of methanol (41%) and dist. water (59%), with sufficient *n* sodium hydroxide added to effect solution and a dark green color.

Acetylcholine. Intradermal injections of the chloride were employed in the concentration and manner described for pilocarpine hydrochloride; but in some experiments the volume was increased to 0.5 ml, in order to facilitate the collection of sweat.

Mecholyl chloride (acetyl-beta-methylcholine chloride). 20 mgm of this substance, dissolved in 1 ml of saline solution, were administered by intramuscular or subcutaneous injection in a few additional experiments designed to evoke sweating systemically.

pH of the Drug Solutions Employed. The values obtained by means of our "one drop" glass electrode were as follows:

			(pH)
Plain saline solution			6.0
Pilocarpine hydrochloride	1:100	in saline	5.2
Pilocarpine hydrochloride	1:1000	in saline	5.7
Pilocarpine hydrochloride	1:10,000	in saline	6.0
Acetylcholine chloride	1:100	in saline	5.0
Acetylcholine chloride	1:1000	in saline	6.0
Acetylcholine chloride	1:10,000	in saline	6.0
Acetylcholine chloride	1:20,000	in saline	6.0
Adrenaline chloride	1:100,000	in saline	6.0
Adrenaline chloride	1:1,000,000	in saline	6.0
Nicotine sulfate	1:100,000	in saline	5.9
Atropine sulfate	1:1000	in saline	6.6
Mecholyl chloride	1:50	in saline	5.9

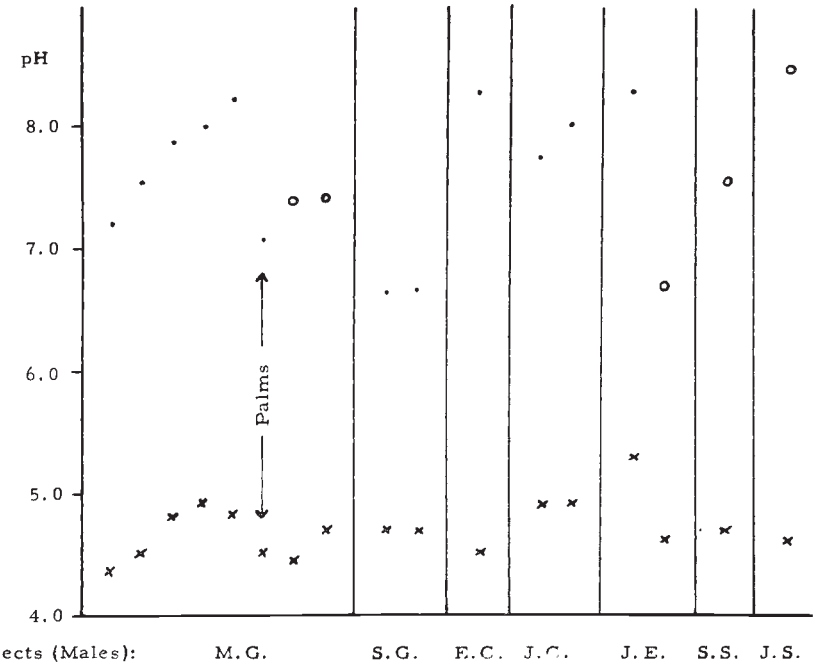
Sequence of different forms of stimulation. As a rule, adequate periods of time were allowed to elapse between different forms of sweat stimulation in one and the same subject, e.g., between thermal and pharmacodynamic stimulation, in order to avoid possible influences of one stimulus on the effect of another.

A number of experiments, however, were designed to study the influence of exposure to heat on the pH of sweat produced by pharmacodynamic stimulation—and, vice versa, to observe the effect of pharmacodynamic stimulation on the pH obtained upon exposure to heat. In these experiments, therefore, localized sweating was induced by intradermal injection of pilocarpine or acetylcholine, and after pH examination, additional sweating was evoked by heat; further samples of sweat were gathered from the injected, the symmetrically situated site and from other areas—and the pH was tested again. In similar experiments, sweating was induced first by exposure to heat, and during the exposure additional outpouring was elicited by intracutaneous injection of one of the two cholinergic solutions. In order to obtain comparable pH values for the sweat evoked by exposure to heat alone, sweat was collected from the contralateral control site—or from the same skin area of these subjects during the corresponding phase of purely thermal sweating.

pH examination after boiling of sweat. Since it has been established that the CO_2 contents of the sweat influences its pH (8, 13), 14), we utilized a very crude procedure, employed by Szakall (13) for a similar purpose, to obtain some preliminary indication of variations in the concentration of CO_2 in our samples: when sufficient sweat quantities were available, the pH was determined prior to and after brief *boiling* of the sample.

2. Results

a) *pH of sweat evoked by topical stimulation.* Graph I shows the pH values of sweat collected after local stimulation by pilocarpine or acetylcholine and the corresponding values obtained in seven male subjects after stimulation by our standard exposure to heat. The difference is apparent. Whereas—in five of the volunteers—the values obtained at the height of thermal sweating averaged 4.9



GRAPH I. pH values of sweat collected from test areas (lateral upper back).
• afterintradermal injection of pilocarpine (1%, 0.1 ml).
○ after intradermal injection of acetyl choline (1%, 0.1 ml).
× after "standard" thermal stimulation (within 24 hours prior to or after injection)

(4.6–5.4, 11 examinations*) in specimens from the lateral upper back†, the corresponding figures after intradermal injection of pilocarpine averaged 7.8 (6.7–8.3, 11 examinations). In an analogous experiment performed in the palms, a similar pH difference was found in sweat produced by the two forms of stimulation (Graph I).

Graph I also shows that the effect of intradermally injected acetylcholine (5 experiments, 4 subjects) was about the same as that of pilocarpine.

In two of the subjects in whom the intradermal injection of pilocarpine (upper back) induced sweating not only locally, but also in distant areas, the pH of sweat from such a distant area (temporal region) was tested and found not to exceed, but to equal in range the pH of thermal sweat: the values were 4.6 and 5.5.

* Unless specific mention is made to the contrary, all pH values here presented are those determined potentiometrically—and not those obtained with the indicator.

By and large, the values found with the indicator paralleled the results obtained potentiometrically. When the values differed, the indicator readings usually deviated—by about about 0.5 to 0.8 units—toward the acid side. Any experimentally induced changes of the values observed in successive tests with the indicator tended to be more drastic, but to be noticeable for shorter periods of time than when determined potentiometrically.

† The average pH obtained in thermal sweat from this site throughout our investigations was 4.9 in male subjects (range: 4.2–6.6; 13 subjects; 38 examinations). The values in our three female volunteers were 6.2, 6.2, and 7.5, respectively.

TABLE I

pH of sweat produced by local pharmacodynamic stimulation (upper back) prior to, or during thermal sweating

Subject	a) in Sweat Obtained from Site of Intradermal Injection of Drug				b) in Thermogenic Sweat	
	Prior to thermal sweating		During thermal sweating		Prior to application of drug (site of injection)	After application of drug (control area)
	Pilocarpine	Acetylcholine	Pilocarpine	Acetylcholine		
M. G.	7.8	—	7.8	—	4.8	—
M. G.	7.55	—	7.25	—	—	4.5
M. G.	8.25	—	6.9	—	—	4.8
M. G.	*	—	7.2	—	—	4.65
M. G.	7.35	—	7.6	—	—	—
M. G.	—	7.4	—	7.05	—	4.5
M. G.	—	*	—	7.4	—	4.7
St. Gr.	*	—	6.65	—	—	4.7
St. Gr.	*	—	6.7	—	—	4.7
J. C.	*	—	7.75	—	—	5.4
J. E.	8.1	—	8.3	—	5.3	—

* Introduction of drug during exposure to heat and thermal sweating.

b) *pH of sweat evoked by intradermal injection of cholinergic drugs in combination with thermal stimulation.* The following table (Table I) shows that the pH of sweat locally produced by the application of a cholinergic drug remained high during superimposed sweating induced by our standard exposure to heat. Similarly, a high pH was instantly observed in sweat produced in a site of pharmacodynamic stimulation when the drug was applied during exposure to heat and the ensuing generalized eruption of sweat.

c) *pH of sweat produced by different forms of systemic stimulation.* In sweat collected from the temporal area of 9 male subjects (27 experiments), the maximum* pH after standard exposure to heat averaged 5 (range 4.15–6.2); after muscular exercise—4.8 (range 4.1–5.3); after subcutaneous injection of pilocarpine—5.1 (range 4.6–6.4), and after intramuscular injection of pilocarpine—6.1 (range 4.8–7).

Mecholyl chloride (20 mgm in saline) was injected intramuscularly in two of the same subjects, and subcutaneously in one. The pH of sweat collected thereafter from the forehead was 6.4, 5.4, and 4.7, respectively.

The results presented were obtained in specimens from the forehead, since it was here rather than in other skin areas† (back), that sufficient quantities of sweat could be collected after each of the different forms of systemic stimulation.

* When it was possible to collect several consecutive sweat samples after a given stimulus, and whenever different pH values were found in these samples, the highest figure obtained was used for the calculation of our average values.

† It appears noteworthy that the *palms* sometimes showed distinct sweating—though insufficient in amount for pH tests in vitro—in response to systemic administration of pilocarpine.

Apparently, the pH of sweat evoked by subcutaneous injection of pilocarpine was similar to—though in several instances slightly higher than that of the sweat produced by our standard form of thermal stimulation, whereas the pH of sweat delivered upon intramuscular injection of pilocarpine (or Mecholyl chloride) was, as a rule, moderately, though distinctly higher. Even after intramuscular injection, however, the values remained far below the pH of the sweat locally produced by intradermal injection of the drug.

It must be added that in the few experiments in which sweat was sampled during *prolonged exposure to heat, a progressive rise in pH* was noted, approaching or even exceeding the highest values encountered after intramuscular pilocarpine (or Mecholyl chloride) injection (Table VI). In the pilocarpine experiments, however, the elevated values were obtained from the onset of sweating.

As is apparent from the previous average figures, a pH similar to that observed in "standard" thermal sweating was found in sweat generated by muscular exercise. The values obtained during exercise at no time exceeded the pH observed in the same subjects after "standard" exposure to heat.

d) *pH of sweat after boiling.* Only seven of 20 samples of sweat collected after thermal or local pharmacodynamic stimulation showed a change in pH—i.e., a slight to moderate increase or decrease—after boiling; and this change was erratic in relation to either of the two forms of sweat stimulation.

B. Testing of pH on skin surface

1. Outline of procedure

The test subjects and preparatory instructions were the same as specified under 'A'.

Successive testing. Prior to any stimulation of sweating, the pH was determined on the surface of all test areas, and after stimulation the tests were repeated at 10-minute intervals for as long a period of time as feasible. In a considerable number of experiments we were able to combine pH examination of sweat collected from our test areas with determinations on the surface of the same sites.

Sweat stimulation and drugs employed. The methods and materials used to induce sweating were identical with those described previously (under 'A'), except for additional intradermal tests with pilocarpine and acetylcholine in higher dilutions; and for intradermal injections of 0.1–0.3 ml of a solution of *adrenaline chloride*, $1:10^3$ to $1:10^6$ in saline, which were employed in order to attain "adrenergic" outpouring of sweat (15–18).

In all experiments in which a sudorific drug was injected intracutaneously, the pH of the skin surface was determined not only on the site of the drug injection, but also on a symmetrically situated area in which the same volume of *plain saline solution* was injected intradermally, and on several untreated sites (see below). In the injected areas the pH was tested in the center of the wheal, as well as in its immediate surroundings.

For the tests in skin regions generally having no apocrine glands, nearly all intradermal injections were given in the lateral parts of the upper back. In another group of experiments, the skin of the *axillary* vaults was the site of injection.

In order to ascertain the actual importance of *sweating* for the values found on the skin surface, several experiments were performed in which the pH was investigated on an area (upper back) intradermally injected first with 0.3 ml of an *atropine* solution 1:1000 in saline, and immediately thereafter with 0.1 ml of a 1% pilocarpine-, or acetylcholine solution. Parallel tests were carried out on the surface of areas injected with the pertinent cholinergic drug solution alone, with 0.3 ml of the atropine solution alone, and with saline alone, as well as on an unprepared control site.

In an attempt to determine whether or not stimulation of sweating directly at the end

TABLE II

pH on skin surface after different forms of sweat stimulation

Experiment	Test Site*	No. of Ex-p'mts.	No. of sub-jects	Sex	Av. (Average) or Individual (Initials)	Before (or at) Beginn. of Exp.	After Beginning of Experiment								
							10′	20′	30′	40′	50′	60′	70′	80′	90′
No stimulation or injection ("blank" control)	T	21	7	M	Av.	5.2	5.1	5.1	5.2	5.1	5.3	5.1			‡
					(Range:)		4.3–5.9	4.4–6.0	4.3–5.8	4.6–6.1	4.3–6.2	4.7–6.0	4.4–6.0		
	B	10	7	M	Av.	4.8	4.8	4.8	4.8	4.8	4.8	4.8			
					(Range:)		4.3–5.5	4.4–5.4	4.4–5.4	4.3–5.4	4.5–5.3	4.5–5.4	4.5–5.4		
	A.V.	15	7	M	Av.	6.9	6.9	6.9	6.9	6.8	6.8	6.7	6.8		
					(Range:)		6.4–7.7	6.1–7.6	6.2–7.7	6.1–7.5	6.1–7.6	6.1–7.3	6.1–7.3		
Intradermal inj. of phys. saline sol. (0.1–0.5 ml) in test site (saline control)	B	32	10	M	Av.	5.0	5.1	5.1	5.1	5.1	5.1	5.1	5.2	5.2	§
					(Range:)		4.3–6.1	4.3–6.3	4.3–6.7	4.3–7.0	4.3–6.7	4.3–6.3	4.3–6.1	4.3–6.2	4.3–6.1	
"Standard" exposure to dry heat	T	19	9	M	Av.	4.9	5.1	5.0	4.9	5.1	5.1	5.1	5.3		‖
					(Range:)		4.4–6.3	4.5–6.3	4.6–6.0	4.6–6.0	4.7–5.9	4.9–6.0	4.9–6.1	5.2–6.2	
	B	24	9	M	Av.	4.8	5.0	4.9	4.9	5.1	5.2	5.2	5.3		
					(Range:)		4.3–6.4	4.4–6.4	4.5–6.4	4.7–6.3	4.7–6.3	4.8–6.3	4.7–6.2	4.7–6.2	
	A.V.	6	6	M	Av.	7.1	7.3	7.3	7.2	7.1	7.0	7.0	7.1		
					(Range:)		6.3–7.4	6.4–7.8	6.5–7.6	6.4–7.6	6.3–7.6	6.3–7.3	6.3–7.5	6.3–7.4	
"Standard" exposure to dry heat	T	3	3	F	Av.	5.8	−†	6.6	6.0	6.0	6.0	6.2	6.1		
					(Range:)		5.6–6.2		6.1–7.0	5.6–6.2	5.8–6.2	5.6–6.2	6.1–6.3	6.1–6.2	
	B	3	3	F	Av.	5.5	−†	6.8	6.1	6.0	5.9	6.1	6.1		
					(Range:)		5.3–5.7		6.4–7.3	5.6–6.4	5.6–6.3	5.5–6.3	6.0–6.3	6.0–6.1	
Intradermal inj. of pilocarpine HCl 1% in saline (0.1 ml) in test site	B	6	6	M	Av.	5.2	7.1	7.7	7.8	7.7	7.4	7.1	6.9	6.9	(7.3)§
					(Range:)		4.6–6.0	6.4–7.9	7.2–8.2	7.4–8.3	6.9–8.2	6.9–8.0	6.5–8.0	6.2–7.8	6.0–7.7	(6.9–7.7)
	B	1	1	F	M.B.		6.1	6.8	7.3	7.3	7.2	7.6	7.3			
Same with 0.1% pilocarpine HCl	B	6	6	M	Av.	5.2	6.5	7.2	7.3	7.1	6.8	6.4	5.6		
					(Range:)		4.4–6.1	5.6–7.7	6.8–7.6	6.7–8.1	6.4–8.0	6.2–7.8	6.2–7.4	4.9–6.2		
Same with 0.01% pilocarpine HCl	B	3	3	M	Av.	5.1	6.3	6.8	6.6	5.9	5.7	(6.0)	(6.1)		
					(Range:)		4.8–5.6	6.0–6.8	6.1–7.9	5.7–8.1	5.6–6.2	5.4–5.9	(5.4–6.6)	(5.6–6.6)		
Same with 0.1% pilocarpine HCl	A.V.	3	3	M	Av.	6.7	7.4	7.4	7.5	7.0	6.9	6.8	6.7	6.8	§
					(Range:)		6.4–7.0	6.7–7.9	6.7–8.1	6.4–8.4	6.3–7.8	6.5–7.5	6.4–7.4	6.4–7.3	6.7–7.0	
Intradermal inj. of acetylcholine chloride 1% in saline (0.1 ml) in test site	B	6	5	M	Av.	4.9	7.3	7.7	7.3	6.8	6.6	6.2	6.3	(6.3)	§
					(Range:)		4.6–5.4	6.7–8.0	7.0–8.0	6.0–8.0	5.5–7.5	5.8–7.2	5.4–7.0	6.0–6.9	(5.7–6.7)	
	B	1	1	F	F. H.		5.3	6.9	7.6	7.8	7.2	6.9	6.8			
Same with acetylcholine chloride 0.01%	B	5	3	M	Av.	5.1	6.3	6.0	6.3	6.0	5.9	(6.0)			
					(Range:)		4.4–5.6	4.8–7.0	4.6–6.5	6.0–.66	5.9–6.1	5.8–6.0	(6.0)			

* *T*—temporal region; B.—lateral upper back; A.V.—axillary vaults.

† Sweating still minute.

‡ After 1st measurement.
§ After injection.
‖ After beginning of thermal stimulation.

organ and stimulation via axon-reflex, following the procedure of Rothman and Coon (19), produce different effects upon the pH, *nicotine sulfate* (1:100,000 in saline) was injected intracutaneously; and in a few other trials, acetylcholine (1:20,000) was injected in a site previously infiltrated with *procaine hydrochloride*, 1:50,000, while a control area was treated with acetylcholine, omitting the procaine injection. For technical reasons, the indicator was superior to the electrodes for assaying the pH on the two pertinent concentric fields in these test areas.

In a group of somewhat similar experiments, the pH on sites injected intradermally with adrenaline (1:100,000)—or with plain saline solution was compared with the pH on sites treated with the same solutions after previous infiltration with procaine chloride, 1:50,000 and 1:100 in saline.

Test areas. When sweating was evoked by systemic stimulation, the temporal areas, the scapular region and the axillary vaults were our regular test sites; depending on the special purpose of some of the experiments, the pH was determined also in additional regions—e.g., on chest, forearms, etc.

In all experiments in which *local* sweating was induced (by intradermal injection), the pH was determined not only on the surface of the injected area and of the control sites in the corresponding region (see above), but also on skin areas *distant* from the injected site; whenever, for example, the drug had been injected in the upper back, the pH was invariably examined in the temporal areas and axillary vaults, too, since it was conceivable that changes in pH might be produced systemically even under these conditions.

2. Results

a) *Results of control experiments and of thermal stimulation.* Table II shows the mean pH values obtained at 10-minute intervals under different experimental conditions. Evidently, there is very little difference between the average results obtained without preparatory treatment, after intradermal injection (of 0.1 to 0.5 ml*) of physiologic saline solution in a test area (back), and after our standard form of thermal sweat stimulation—when the latter was employed in male test subjects.

Whereas these *average* values at most show a minute rise after our standard exposure to heat, and a still weaker rise after the intradermal injection of saline, a more distinct, though usually only moderate rise in pH was observed in a number of *individual* experiments. In none of these experiments did the pH ever show a tendency to decline.

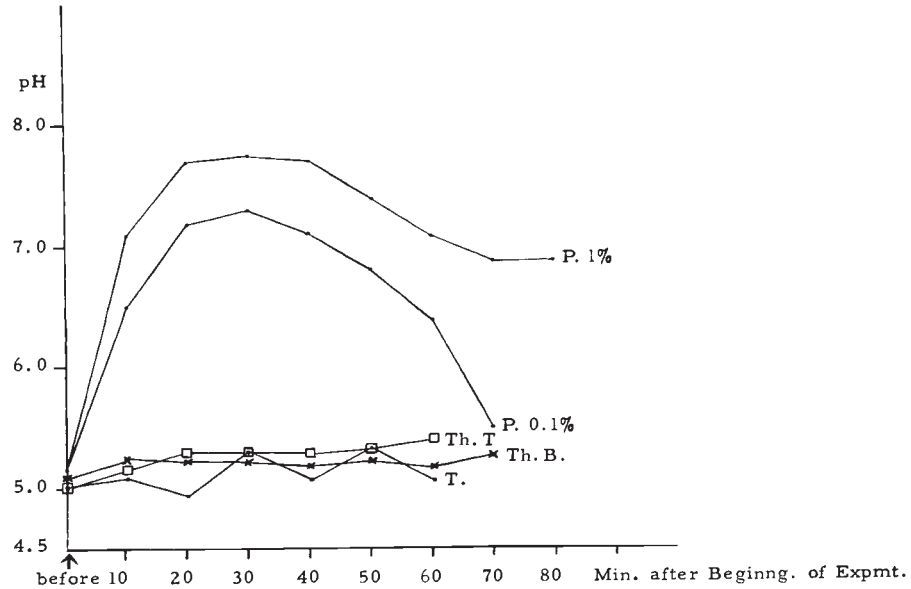
As is apparent from Table II, our few female volunteers showed a more distinct rise in pH after "standard" thermal stimulation than did the male subjects. In the females, however, sweating appeared after a distinctly longer exposure to heat.

Unlike the values obtained after our standard exposure to heat, the pH showed a significant and steady rise in *both* sexes during *continued* exposure, though the rise again was much higher in the (two) females subjected to this procedure than in the male volunteers (see Table VI). In both sexes, this progressive rise was paralleled by a similar, but generally lesser elevation of the pH in sweat samples collected during the prolonged stimulation.

b) *Effect of topical sweat stimulation by drugs on pH of skin surface*
Stimulation by cholinergic drugs.

Site of stimulation: lateral upper back. Table II, as well as Graphs II and III demonstrate the average pH found in successive determinations on an area of

* 0.1 ml was injected in 22 of the 32 experiments.



GRAPH II. pH on skin surface after local stimulation of sweating by intradermal pilocarpine injection. Each curve presents average results of 6 experiments performed in same (6) subjects.

P. 1% = pH on surface of area (lat. upper back) injected intradermally with pilocarpine 1% in phys. saline.

× P. 0.1% = pH on surface of area (lat. upper back) injected intradermally with pilocarpine 0.1% in phys. saline.

•—• T = pH on surface of temporal region after the intradermal injection of pilocarpine 1% in area of back.

□—□ ThT = pH on surface of temporal region after "standard" thermal stimulation.

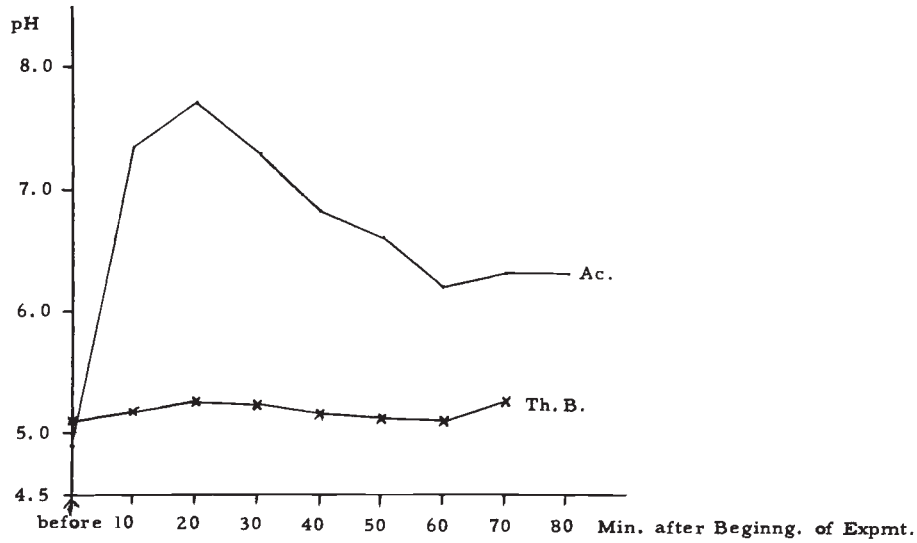
×—× ThB = pH on surface of lateral upper back (test area) after "standard" thermal stimulation.

the lateral upper back, in which pilocarpine or acetylcholine in saline solution (concentrations as specified) had been introduced by intradermal injection. Graph II, moreover, shows the mean values concomitantly obtained on a site (temporal region) *distant* from the injected area, and the average values obtained on the back and the temporal area of the same males after "standard" stimulation of thermal sweating.

Evidently, the topical pharmacodynamic stimulation of cholinergic sweating was followed by a significant local rise in pH, in which the values greatly—by 2 to 2½ units—exceeded the range observed after "standard" thermal stimulation. This rise and its course were very similar in each of 31 pertinent experiments. As could be anticipated, the similarity in the response of different subjects was most pronounced in the experiments in which the same drug and the same concentration were employed.

As shown on Graph II, the pH increase obtained with the 1% pilocarpine solution differed relatively little from that obtained with the 0.1% solution, but the elevation tended to persist longer after use of the higher concentration.

In addition, Graph II shows that the values obtained during the experiments



GRAPH III. pH on skin surface after local stimulation of sweating by intradermal injection of acetylcholine.

Ac = Average pH values obtained in 5 subjects (5 experiments) on skin surface of area (lateral upper back) intradermally injected with acetylcholine—1% in phys. saline.

Th.B. = Average pH values obtained in same subjects on same area after "standard" thermal stimulation.

in the temporal region, i.e., in an area distant from the injected site, were similar in range to the pH observed after thermal stimulation. No elevation in pH was apparent in the temporal region, even when there was a "distant" sweating response in this area.

One experiment, in which pilocarpine (1%) was injected intradermally in a female subject and another, in which acetylcholine (1%) was injected in another female showed an increase in pH similar to that observed in the male subjects, except for perhaps a more gradual and later appearance of the maximum in the females (Table II).

The pH obtained in the immediate surroundings of an injected test site, as well as that on the saline-injected control areas did not differ from the pH encountered on completely untreated skin of the same region (upper back).

Whereas on further dilution of pilocarpine or acetylcholine both the rise in pH and the sweating response became gradually weaker and more and more fleeting, extreme dilutions still sufficient to evoke (minute) sweating failed to produce a rise in pH. The threshold concentrations varied considerably in different subjects, and to some extent even in different examinations of one and the same subject, but the extreme dilution producing an increase in pH invariably paralleled the minimum concentration capable to elicit sweating.

The highest dilution at which pilocarpine produced a distinct rise in pH was $1:2 \times 10^6$ (0.1 ml)—observed in one of six subjects tested with serial dilutions,

while the minimum concentration inducing a sweating response was $1:7 \times 10^6$ (observed in the same subject). The corresponding threshold concentrations of acetylcholine were $1:4 \times 10^6$ and $1:6 \times 10^6$, respectively.

Effect of axon-reflex sweating. After intradermal injection of *nicotine sulfate* (1:100,000) in saline, *no* change in pH was noted on the surface of the injected site and its surroundings (3 experiments), although "peripheral" sweating appeared immediately after the injection.

Similarly, when sweating was induced by intradermal injection of acetylcholine (1:20,000) in saline, the rise in pH was confined to the surface of the whealed area, while no elevation whatsoever was noticeable in the surrounding zone in which some degree of sweating was apparent (3 experiments).

After the intradermal introduction of acetylcholine (1:20,000) in a site impregnated with Procaine (1:50,000), a rise in pH was demonstrable on an area equal to the symmetrically situated "control" area where the corresponding rise in pH was produced without preparatory treatment with Procaine.

Site of stimulation: palms. In three subjects, one of whom received 0.1 ml of pilocarpine (1%) in saline by intradermal injection, while the other two were injected in the same area with 0.1 ml of (1%) acetylcholine in saline, the pH* on the injected site rose from 4.5 to 6.7, 8.0, and 8.5, respectively.

Subsequent painting of the area with our indicator solution revealed that this shift toward alkalinity was limited to the surface of the injected site, while the color shade in the immediate surroundings was characteristic of the marked acidity which existed all over the control area of the other palm—and which, prior to the injection had been present all over the test area as well.

Site of stimulation: axillary vaults. Our three experiments in which pilocarpine (0.1%) was injected intradermally in the axillary vaults showed a rise in pH resembling the results obtained in the corresponding experiments on the back. The elevation in the axillary vaults, however, was smaller and more transitory.

Injection of cholinergic drugs in atropinized areas

In two experiments, intradermal injection of *atropine sulfate* (0.1% in saline, 0.3 ml), prior to intradermal injection of pilocarpine (1% in saline, 0.1 ml) in the same site, and in two other experiments prior to injection of acetylcholine (1%, 0.1 ml), completely or almost completely abolished the rise in pH produced by the respective cholinergic drug in the absence of atropinization. The extent of this rise was evident from the values obtained on a control area injected with the pertinent cholinergic drug alone. Table III shows the result of one experiment as representative of the results obtained in all four of these experiments.

Stimulation of sweating by adrenaline

Site: upper back. In 20 experiments, adrenaline chloride in saline (1:100,000 or 1:1,000,000; 0.2 ml) was injected intradermally in the scapular area of 11

* These figures are not included in our tabulation, because they were obtained with the universal indicator.

TABLE III

Effect of local atropinization on pH of skin surface in area subjected to intradermal injection of pilocarpine

Site No.	Intradermal Injection of Test Site with	Before	Minutes after Injection							
			10′	20′	30′	40′	50′	60′	70′	80′
1	Physiol. saline sol. 0.4 ml*	4.3	4.3	4.3	4.3	4.25	4.3	4.3	4.3	4.3
2	Pilocarpine hydrochl. 1% in phys. saline sol., 0.1 ml†, preceded by saline sol., 0.3 ml	4.3	6.4	6.4	6.8	5.65	5.1	4.9	4.7	
3	Atropine sulf. 0.1% in phys. saline sol., 0.3 ml; followed immediately by pilocarpine hydrochl. 1% in phys. saline sol., 0.1 ml	4.3	4.3	4.5	4.35	4.4	4.3	4.4		
4	Atropine sulf. 0.1% in phys. saline sol., 0.3 ml	4.3	4.35	4.5	4.45	4.45	4.35	4.4		

pH values (in subject R. D.) on different test sites of upper back during course of experiment.

* Injected 20 min. prior to injections in sites 3 and 4.

† Injected 10 min. prior to injections in sites 3 and 4.

volunteers. Only seven of the subjects (in 13 of the 20 experiments) responded with local sweating. The average pH values determined on the surface of the test areas in 11 of these experiments* are shown on Table IV. A moderate rise is apparent in the pH obtained on the adrenaline sites; an almost equal rise, however, was observed on the control areas injected with 0.2 ml of saline alone. In six of the seven subjects who showed sweating in response to adrenaline, local sweating appeared in response to saline, too—though to a lesser degree. In several of these experiments, the injections provoked complaints of great pain.

No pH elevation whatsoever was observed in the seven experiments in which adrenaline failed to elicit sweating.

Site of stimulation: axillary vaults. The results obtained in three subjects in whom adrenaline was injected intradermally in one axillary vault, and plain saline in the other, showed a moderate pH increase in both axillae (Table IV); also a sweating response was apparent on both sites, on the adrenaline site more so than on the saline site.

Procaine infiltration of test sites. Whereas a slight to marked decline of the pH values was noticeable in four of five experiments in which impregnation with Procaine hydrochloride (1:50,000 as well as 1:100) preceded the intradermal injection of adrenaline or that of saline, the results are still indefinite.

c) *pH on skin surface after systemic sweat stimulation.* As is shown on Table V, practically no rise in pH was observed on the surface of the test areas—temporal

* The remaining results are not shown on the table, because these experiments were carried out after submission of the manuscript.

TABLE IV

Average of pH values obtained on skin surface of areas intradermally injected with adrenaline (or with plain physiol. saline)

Experiment	Test Site*	No. of Expmts.	No. of Subjects	Sex	Prior to Injec.	Minutes After Injection								
						10′	20′	30′	40′	50′	60′	70′	80′	90′
No treatment ("blank" control area)	B	11	7	M	5.2	5.2	5.2	5.2	5.2	5.2	5.3	5.3	—	—
				(Range:)	4.8–5.4	4.7–5.4	4.7–5.4	4.8–5.4	4.7–5.4	4.7–5.4	5.3–5.4	5.2–5.4		
Intradermal injection of adrenaline chloride 1:10^6 or 1:10^5 in phys. saline (0.2 ml)	B	11	7	M	5.0	5.8	5.8	5.6	5.6	5.6	5.6	5.4	5.4	(5.2)
				(Range:)	4.6–5.4	4.9–6.4	5.3–7.1	5.3–6.5	5.2–6.7	5.3–6.5	5.2–6.5	5.1–5.7	5.1–5.9	(5.2)
Intradermal injection of phys. saline (0.2 ml; saline control area)	B	8	7	M	5.0	5.6	5.7	5.8	5.6	5.5	5.5	5.3	5.3	(5.1)
				(Range:)	4.6–5.3	4.9–6.3	5.0–6.7	4.9–7.0	5.0–6.7	4.9–6.3	4.8–6.0	4.9–5.7	4.9–6.0	(5.1)
Intradermal injection of adrenaline chloride (as above) in phys. saline (0.2 ml)	A.V.	3	3	M	6.6	7.2	6.7	6.7	6.7	6.6	6.6	6.6	—	—
				(Range:)	6.3–6.9	6.9–7.4	6.6–6.9	6.5–6.9	6.5–7.0	6.4–6.7	6.5–6.7	6.5–6.7		
Intradermal injection of phys. saline (0.2 ml; saline control)	A.V.	3	3	M	6.8	7.3	7.0	6.8	6.7	6.7	6.7	6.5	—	—
				(Range:)	6.5–7.0	7.3–7.4	6.9–7.2	6.5–7.0	6.5–6.9	6.5–6.9	6.5–6.9	6.5–6.6		

* B—lateral upper back; A.V.—axillary vaults.

TABLE V

pH on skin surface after different forms of systemic sweat stimulation

Experiment	Test Site*	No. of Exp'mts.	No. of Subjects	Sex	Av. (Average) or Individ. (Initial)	Before Beginn. of Exp'mt.	Minutes After Beginning of Exp'mt.								
							10′	20′	30′	40′	50′	60′	70′	80′	90′
Muscular exercise	T	5	5	M	Av.	4.6	4.7	4.8	4.8	(4.9)	(4.8)				
					(Range:)	4.5–4.9	4.2–5.1	4.8–4.9	4.7–5.0	(4.9)	(4.8)				
	B	5	5	M	Av.	4.6	4.6	4.5	4.6	(4.9)	(4.5)				
					(Range:)	4.5–4.7	4.5–4.7	4.4–4.7	4.5–4.8	(4.9)	(4.5)				
Subcutan. inj. of pilocarpine HCl, 1% in phys. saline sol. (1 ml)	T	5	5	M	Av.	4.9	5.4	5.6	5.7	5.7	5.6	5.5	5.6	5.5	
					(Range:)	4.6–5.5	4.7–6.1	5.0–6.5	4.8–6.7	4.8 5.7	4.7–6.3	4.7–6.1	5.0–6.0	4.9–5.9	
	B	5	5	M	Av.	4.8	5.0	5.0	5.0	5.0	4.9	4.9	5.0	5.0	
					(Range:)	4.5–4.9	4.7–5.5	4.7–5.2	4.6–5.5	4.6–5.5	4.5–5.5	4.5–5.5	4.5–5.4	4.5–5.5	
	A.V.	5	5	M	Av.	6.9	7.0	6.8	6.8	6.9	6.9	6.9	6.8	6.8	
					(Range:)	6.2–7.5	6.2–7.4	5.9–7.3	6.1–7.3	6.3–7.3	6.4–7.2	6.3–7.3	6.3–7.3	6.4–7.1	
Intramusc. inj. of pilocarpine HCl 1% in phys. saline sol. (1 ml)	T	10	8	M	Av.	4.9	5.6	5.9	6.0	5.9	5.8	5.8	5.8	5.7	5.4
					(Range:)	4.4–5.9	4.5–7.3	4.5–7.3	5.3–7.1	5.1–7.1	4.8–7.0	4.8–7.1	5.1–7.0	5.0–6.2	5.0–6.3
	B	10	8	M	Av.	5.0	5.2	5.2	5.2	5.1	5.1	5.1	5.2	5.3	5.0
					(Range:)	4.5–5.5	4.5–6.0	4.6–6.0	4.6–6.0	4.5–5.8	4.5–5.9	4.5–5.8	4.7–5.9	4.7–5.7	4.1–5.6
	A.V.	10	8	M	Av.	6.5	6.9	6.6	6.7	6.7	6.7	6.6	6.7	6.6	6.8
					(Range:)	4.3–7.7	5.9–7.9	5.5–7.7	5.5–7.5	5.5–7.6	5.5–7.4	5.5–7.3	5.8–7.2	5.9–7.3	5.8–7.2
Subcutan. inj. of mecholyl chloride 2% in phys. saline sol. (1 ml)	T	1	1	M	J. E.	4.4	4.9	5.2	5.2	5.0	4.9	4.6	4.7	4.8	4.8
	B	1	1	M	J. E.	4.5	4.6	4.6	4.8	4.7	4.6	4.7	4.7	4.7	4.7
	A.V.	1	1	M	J. E.	7.4	7.4	7.5	7.4	7.0	7.0	7.0	7.0	6.9	6.8
Intramusc. inj. of mecholyl chloride 2% in phys. saline (1 ml)	T	1	1	M	S. S.	5.1	6.6	6.0	5.9	6.0	5.9	5.9	5.7	5.7	
	B	1	1	M	S. S.	5.3	6.1	5.7	5.7	5.7	5.6	5.5	5.6	5.6	
	A.V.	1	1	M	S. S.	7.2	7.5	7.3	7.6	7.3	7.1	7.5	7.2	7.1	
	T	1	1	M	R. S.	5.0	5.7	5.6	5.6	5.5	5.7	5.5	5.5	5.5	
	B	1	1	M	R. S.	4.7	4.9	4.9	4.9	4.9	4.9	5.0	5.1		
	A.V.	1	1	M	R. S.	6.6	7.0	7.1	7.3	7.1	7.0	6.9	6.9	6.8	

* T—temporal areas; B—back; A.V.—axillary vaults.

TABLE VI

pH on skin surface (and in sweat) during prolonged exposure to dry heat

Subject	Sex	Site*	Before S.S.†	Minutes After Beginning Of Exposure To Heat													
				10′		20′		30′		40′		50′		60′		70′	
				Sw.‡	S.S.	Sw.	S.S.	Sw.	S.S.	Sw.	S.S	Sw.	S.S.	Sw.	S.S.	Sw.	S.S.
J. E.	M	T	4.6		4.5		4.6		4.7		4.7		4.9		5.1		5.1
		B	4.6		4.7		5.0		5.1		5.1		5.3		5.7		5.4
		A.V.	7.1		7.6		7.6		7.5		7.5		7.5		7.5		7.5
D. H.	M	T	6.0		6.2		6.2		6.2		7.0		7.0		7.0		7.1
		B	5.7		5.9		5.8		6.1		6.6		7.0		7.0		7.2
		A.V.	7.7		7.9		7.9		8.0		7.9		7.9		8.0		8.0
W. C.	M	T	4.4	4.2	4.5	4.6	5.1	4.9	5.0	6.0	5.9	6.1	6.3	6.3	6.8	6.3	6.8
		B	4.8	4.6	4.8	4.7	4.8	4.9	5.1	5.1	5.2	5.0	5.2	5.5	5.4	5.6	5.6
		A.V.	6.8	5.7	6.8	5.7	6.8	5.7	6.7	5.2	6.7	5.4	7.0	5.4	6.8	5.4	6.8
T. S.	M	T	4.8	4.8	5.1	5.5	6.2	6.1	6.6	6.6	6.7	6.5	6.9	6.6	7.0	6.3	7.2
		B	4.7	4.5	4.8	4.8	5.3	4.9	5.4	5.1	5.7	5.4	6.0	5.9	6.1	5.8	6.0
		A.V.	6.9	6.0	6.9	6.0	7.2	6.3	7.2	6.4	7.2	6.0	7.3	6.6	7.3	6.0	7.5
Averages	(M)	T	4.9		5.1		5.5		5.6		6.1		6.3		6.5		6.6
		B	4.9		5.0		5.2		5.4		5.6		5.9		6.0		6.0
		A.V.	7.1		7.3		7.4		7.4		7.3		7.4		7.4		7.4
F. H.	F	T	6.1	—	—	6.8	7.1	7.1	7.5	7.2	7.7	7.4	8.1	7.5	8.1	—	—
		B	5.6	—	—	7.3	7.1	7.7	7.9	7.8	8.2	7.9	8.3	8.1	8.4	—	—
M. B.	F	T	6.4	—	—	7.0	7.2	7.2	7.9	7.3	8.1	7.9	8.4	7.7	8.2	—	—
		B	6.2	—	—	7.5	7.6	7.8	7.8	7.2	7.8	7.8	8.6	8.0	8.6	—	—

* T—temporal areas; B—lateral upper back; A.V.—axillary vaults.

† S.S.—Skin surface.

‡ Sw.—Sweat.

region, lateral upper back, and axillary vaults—after stimulation of sweating by *muscular exercise.*

Systemic sweating evoked by *intramuscular* administration of pilocarpine or Mecholyl chloride was followed by an increase in pH—which was most apparent in the temporal region, to a lesser degree in the axillae, and least apparent on the back (Table V). The amount of sweat delivered to the skin surface in any phase of these experiments was exceeded by that observed at the end of our "standard exposure" to heat.

After *subcutaneous* injection of the cholinergic drugs, a moderate pH elevation, below that observed after intramuscular injection, was noted in the temporal areas, whereas no distinct increase in pH (or sweating!) was apparent on the skin of the axillae or the back.

It was the prolonged *exposure to dry heat* which, of all our forms of systemic sweat stimulation produced the highest rise in pH (on temporal areas and back—Table VI).

III. DISCUSSION

pH increase after stimulation of sweating by cholinergic drugs

The observation of previous investigators (1–3) that sweat produced by systemic administration of pilocarpine shows a higher pH than thermal sweat

is confirmed by our results, inasmuch as in a given subject the pH of sweat evoked by our intramuscular injection of pilocarpine exceeded that of thermogenic sweat—provided that the thermal stimulation was discontinued soon after the appearance of sweat in a quantity sufficient for collection in vitro, i.e., after our "standard exposure" to heat.

The greatest pH rise in the sweat was obtained after local stimulation of sweating by intradermal injection of pilocarpine or acetylcholine, while the pH increase was less pronounced after intramuscular injection of pilocarpine or Mecholyl chloride, and no significant change was noted after subcutaneous injection of these drugs. By and large, the pH changes observed in vitro were paralleled by the values obtained directly on the skin surface, although the latter showed a greater tendency to elevation.

In agreement with earlier interpretations (2, 3), there was evidence that the variations in pH observed on the skin surface in this study were largely due to pH changes in the sweat. Whereas there was no direct correlation between pH increase on the skin and the amount of sweat delivered to the skin surface in response to different forms of sweat stimulation, upon intramuscular injection of the cholinergic drugs the pH rose as sweating appeared in the different areas under test: the rise was highest in the temporal region, less pronounced in the axillae, and hardly noticeable on the back.

As a rule, when a difference in time was noted, there was a lag between the pH rise in the sweat and the pH rise on the skin—which further substantiates the observation that the skin surface pH was essentially determined by the pH of the sweat.

Final evidence of this effect was afforded by our experiments in which atropinization prevented the pH increase on the surface of an area intradermally injected with pilocarpine or acetylcholine.

pH observed after intradermal injection of adrenaline

The moderate local rise in pH observed on skin areas in which sweating appeared after the intracutaneous introduction of adrenaline can not be interpreted as an outright consequence of adrenergic sweating, since a similar, though weaker sweating response and virtually the same rise in pH were demonstrable on the control sites impregnated with the corresponding volume of plain saline solution. In fact, our observations to date and several data reported by others suggest that an oddly evoked axon reflex sweating might in part be responsible. Sodium chloride alone may apparently be effective in the same direction.

Physiologic saline solution was employed as the diluent of adrenaline also by previous investigators who studied its effect on sweating (15, 20, 18, 16, 21, 22). Wada and collab. demonstrated axon reflex sweating upon intradermal injection of sodium chloride in hypertonic (3% to 8%) concentration, whereas the isotonic solution "was usually without stimulating effect on the sweat secretion" (20).

Sonnenschein observed a "slight to marked inhibition" of local adrenaline sweating by infiltration of the area with procaine 1:100 (18). Chalmers and Keele, on the other hand, obtained distinct palmar sweating at the site of adrenaline injection after proximal procaine block of the median nerve (21). These findings, together with our preliminary observation of the reduction of both sweating and pH through preceding procaine infiltration (1:100 and 1:50,000) of the adrenaline—and the saline sites, indicate that axon reflex sweating may

be at play. Further investigations are necessary to clarify the mechanism of the sweating response in these experiments.

Problem of difference in pH after pharmacodynamic and "natural" stimulation of sweating

Factors which are not responsible. Whereas we are unable to offer any definite explanation for the described difference in pH after pharmacodynamic stimulation of sweating and after stimulation by our "standard exposure" to heat or by muscular exercise, certain factors can be ruled out.

1) The pH of the solutions injected could *not* have caused the rise in pH, as strongly acid solutions produced the highest rise, and the pH of all our solutions was below 6.8 (see IIA, 1).

2) Contrary to the earlier supposition concerning the effect of pilocarpine, the rise we observed after pharmacodynamic stimulation of sweating is *not* due to increased activity of the apocrine glands. This is apparent from the fact that the most outstanding pH elevations were produced by our drugs in areas where apocrine glands are absent, e.g., in the palms.

Local stimulation of sweating by pilocarpine seemed to affect the pH on the skin of the axillary vaults less than on areas with only (or almost exclusively) eccrine glands (Table II). The a priori higher pH of the apocrine sweat and its buffer capacity are presumably responsible for this difference.

The fact, moreover, that no difference was noticed between the pH response to intradermally injected adrenaline in the axillary vaults and that in our other test areas, is at variance with the hypothesis that increased apocrine sweating is the cause of the pharmacodynamically induced rise in pH. For it was shown in recent years by Shelley and Hurley (4) (5) (6), that adrenaline produces expulsion of apocrine sweat, and a higher elevation in pH would have to be expected in the axillae than in other skin areas upon the intradermal introduction of adrenaline. Briefly, the pH changes observed in this study are primarily attributable to the pH of eccrine sweat.

3) Increased environmental temperature as such, is *not* responsible for a decline in pH or an inhibition of the rise in pH. This is apparent from the observation that the pH in sweat obtained from the temporal areas after intradermal pilocarpine injection in the back was as low as that of sweat obtained in the same area after "standard" thermal stimulation.

Similarly, the pH rise observed during prolonged exposure to heat is at variance with a supposition that increased environmental temperature may lower the pH.

Direct evidence of the absence of a "specific" influence of heat on our pH values was afforded by the experiments in which the high pH in sweat evoked by pharmacodynamic stimulation was demonstrable in the area of stimulation when thermal sweating was superimposed after intradermal injection of the drug, as well as when the drug was injected during thermal sweating (Table I).

The possibility that thermogenic sweat carries more CO_2 than sweat produced by drugs was dismissed since the pH in our samples of thermal sweat failed to show a more pronounced tendency to increase after boiling than the pH of sweat produced by pharmacodynamic stimulation.

Factors which may be at play. It appears that in sweating evoked by cholinergic drugs, the pH of the sweat and the skin surface will not rise when only traces of the drug (if any at all) are present at the effector organ; and vice versa, that the pH rises in proportion to the amount of drug present at the effector organ.

The most pertinent instance of a missing rise is the result of our experiments in which local—though minute—sweating was induced by cholinergic drugs in extreme dilution.

Another example of nonappearance of a rise, already discussed previously, was observed in the temporal areas after intracutaneous injection of pilocarpine in the back (IIA, 2 and Graph II); a third instance is the absence of a rise in pH in the zone of axon reflex sweating (7, 19, 15) around the areas in which we injected nicotine sulfate 1:100,000 or acetylcholine 1:20,000 intracutaneously.

While the pH values obtained under these conditions did not exceed the values found after "standard" thermal stimulation or after muscular exercise, the rise observed by us under the direct influence of massive, experimentally introduced drug quantities upon the sweat organ was approached by the results of *continued* thermal stimulation. A steady rise during prolonged and intense heat was noted by us (3) and by Marchionini (2) also 25 years ago.

An apparently related finding is the striking elevation in pH noticed in our *female* test subjects after "*standard* exposure" to heat—which conforms with the sex difference in pH observed by Thurmon and Ottenstein in thermal sweat (23). As in our earlier investigations (11), a longer exposure to heat was required in the female, than in the male volunteers to induce visible sweating. And it is implied in the findings of Rothman and Kahn (24), as well as in those of Gibson and Shelley (25) that more acetylcholine is needed in females than in males, to evoke sweating. Thus, it would seem that the sweat's pH increases also in response to "natural" forms of stimulation, when larger quantities of acetylcholine are liberated.

The high pH observed by Szakall in the sweat of miners during hard and prolonged labor (13) quite possibly represents another instance of pH rise in response to "stress" on the effector apparatus.

In their aggregate, these findings indicate that the pH difference observed in sweating induced by "natural" forms of stimulation (moderate heat or muscular exercise) and in sweating evoked by drugs is related to the *amount* of chemical intermediator acting upon the effector organ. Whereas infinitesimal amounts of acetylcholine are liberated by the organism in response to various forms of physiologic stimulation—and utilized to initiate the energy transformations which result in sweating, the agents employed in our experiments for pharmacodynamic stimulation were of necessity introduced in unnaturally massive quantities. And acetylcholine mobilized in the tissues evidently is rendered inactive more rapidly (under the influence of cholinesterase) than is any one of the experimentally introduced drugs, including acetylcholine chloride. On the other hand, *the conditions of experimental sweat stimulation by cholinergic drugs seem to present some intensification of conditions which exist when the sweat organ is under "natural" stress.*

As to the biochemical process possibly underlying the pH increase observed

in sweating upon strong cholinergic stimulation or irritation, excessive formation of lactate might be at play, whenever the pH exceeds a level of about 5.3 (Bergeim and Cornbleet (26)), or once it has risen above this level under the influence of some trigger factor. This possibility is not precluded by Thurmon and Ottenstein's finding of a lower pH and higher lactic acid concentration in thermal sweat of males than in that of females (23). It appears quite possible that this difference in the concentration of lactate radical is reduced, as the stimulus of sweat gland function is intensified and lactic acid formation increased to an extent which at pH-ranges above 5.3 causes mobilization of acid binding elements in quantities producing a shift in pH toward alkalinity,* comparable with the effect of systemic lactate administration in diabetic acidosis, transfusion acidosis, etc. In fact, after subcutaneous injection of Mecholyl chloride, B. Ottenstein found in her own sweat (from forehead, trunk, and axillary fossae) a considerably higher pH—and at the same time two to three times more "lactic acid" (most of which was presumably lactate) than after thermal stimulation (27).

Based on Shelley and Mescon's (28) and Yuyama's (29) observation of glycogen depletion in the eccrine sweat coils during intense glandular activity, histochemical examinations were initiated in this Department by Dr. S. Morrill and the author. The preliminary results indicate that more glycogenolysis tends to occur in the acini during sweating after intradermal pilocarpine injection than after "standard" thermal stimulation—although the latter evokes a stronger outburst of sweating. This degrading glycogen most likely is an essential source of sweat lactate, though Weiner and van Heyningen could not afford direct and conclusive evidence supporting this assumption (30).

IV. SUMMARY AND INFERENCES

1) The pH of sweat samples and of the skin surface of 19 healthy subjects was examined electrometrically as well as and by means of an universal indicator after different forms of experimental sweat stimulation. The temporal region, the lateral upper back, and the axillary vaults served as standard test areas.

2) Any change in pH obtained on the skin surface in response to a stimulus was in the direction of an increase.

The highest values of pH in the sweat and/or the highest rise of pH on the skin surface were observed in areas in which local sweating was induced by intradermal injection of pilocarpine or acetylcholine (back, palms, and axillary vaults).

3) Sweat stimulation by exposure to dry heat for a limited period of time ("standard exposure") was in male test subjects followed by only a slight, or by no pH elevation on the skin. In all of three female test subjects, however, a distinct rise was noted. Prolonged thermal stimulation produced a gradual rise even in male subjects; and a strong rise in females.

4) No increase in pH was observed in the sweat or on the skin surface after muscular exercise (knee bending).

* We are indebted to Dr. R. C. Warner, Asst. Prof. of Chem., N. Y. Univ.-Bellevue Med. Center, and to Dr. S. Weisberg, Natl. Dairy Res. Labs., Oakdale, L. I., for corroborating these views.

5) The raised pH of sweat obtained from a site where sweating had been induced by intradermal injection of a cholinergic drug showed no significant decline in samples of sweat produced at this site upon superimposed thermal stimulation; similarly, the high pH was apparent immediately when the drug was injected during exposure to heat and during thermal sweating. (This was one of several findings precluding the possibility that the lower pH of thermal sweat is caused by elevated environmental temperature as such.)

6) The pH rise observed on the surface of sites intracutaneously injected with pilocarpine or acetylcholine was suppressed by previous atropinization of the area—thus again evidencing that the pH of the sweat is largely responsible for that found on the skin surface.

7) In 13 of 20 experiments on the back (7 of 11 subjects), and in all of three experiments in the axillary vaults (3 subjects), intradermal injection of adrenaline in saline was followed by a mild sweating response and a moderate pH increase on the surface of the injected site. However, a similar response was obtained in the same subjects on the control sites injected with plain saline solution. The mechanism of the sweating response in these experiments is now under study.

8) After systemic stimulation of sweating by intramuscular injection of pilocarpine or Mecholyl chloride, the pH of the sweat moderately exceeded that obtained after "standard" exposure to heat; whereas subcutaneous injection of these drugs produced sweat with a pH hardly above that produced by the "standard" thermal exposure. On the skin surface, the intramuscular injections effected a distinct rise in pH in the temporal region, a less pronounced elevation in the axillary vaults, and no apparent elevation on the back; a slight rise occurred in the temporal region after subcutaneous injection.

9) Whereas the cause of the observed pH changes is unknown, the following points came to light:

a) Contrary to earlier assumptions, increased activity of the *apocrine* glands can be ruled out as a cause of the pH increase resulting from sweat stimulation by cholinergic drugs. In fact, our findings afforded evidence that the pH changes observed were primarily attributable to the pH of *eccrine* sweat.

b) The high pH values obtained after pharmacodynamic stimulation of sweating with cholinergic drugs were reduced to the lower range observed in sweating induced by relatively moderate forms of "natural" stimulation whenever a minimum quantity of drug was presented at the sweat organ. On the other hand, the pH values obtained in pharmacodynamic and in thermal sweating again approached each other, as the pH of the thermal sweat rose under the influence of prolonged exposure to heat. *These findings point toward a correlation of the pH values with the concentration of cholinergic agent present at the effector organ—suggesting that in "physiologic" sweating acetylcholine is generally active in much smaller quantities and rendered inert much faster than is usual when cholinergic drugs are administered to elicit "pharmacodynamic" sweating; but that in sweating under increased "natural stress" on the sweat organ, the conditions come closer to those induced by experimental administration of the drugs in commonly employed doses.*

c) Preliminary histochemical studies suggest that more glycogen may break down in the sweat coils and more lactate may form after stimulation of sweating by pilocarpine, than after "standard" thermal stimulation—which might be related to the shift toward alkalinity in response to the drug.

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DISCUSSION

Dr. Theodore Cornbleet, *Chicago, Ill.:* We consistently found heat sweat contains more lactic acid than sweat produced by pharmacodynamic stimulation. Even the sweat stimulated by local radiant heat contains more than that from drugs. Pilocarpine sweat showed a slightly higher level than that of physostigmine. Axillary and "trunk" sweat have about the same amount of lactic acid, but women show a lower level of it than men.

Dr. Nicholas Nicolaides, *Chicago, Ill.:* I would like to ask about one point which was unclear to me, and that is, in what sense the presenter was using the concept of pH. In chemical terms an increase in pH means an increase in alkalinity. It seems paradoxical that an increase in pH was accompanied by an increase in lactic acid.

Dr. Stephen Rothman, *Chicago, Ill.:* I would like to reassure Dr. Nicolaides that pH means pH also among dermatologists. I agree that it was somewhat confusing to hear that the pH was increasing when apparently it was meant that the acidity was increasing. Maybe the collaborators of Dr. Herrmann could clarify this point.

Dr. Norman B. Kanof (in closing): Naturally, the term pH was employed in the usual sense.

As was pointed out in the presentation, the allusion that excessive formation of lactate (not lactic acid) might contribute to the observed increments in pH has been quite hypothetical. This intricate question is presently under investigation.

For more explicit data and comments I refer you to Dr. Herrmann's publication.