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Influence of Environmental and Skin Temperature on Threshold for Nicotine Axone Reflex Sweating in Humans.*† (23712)

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The major characteristics of axone reflex sweating and pilomotion, elicited by intradermally injected nicotinic drugs in the human, have been elucidated through the efforts of several workers(1,2). As yet no evidence exists either that these axone reflexes occur physiologically or, if they do, what role they might play. One possibility is that such a peripheral mechanism might serve to modify the response of the cutaneous effectors to their central nervous controls. Determination of effects of environmental and skin temperature changes on the characteristics of nicotine sweating appeared to offer an indirect test of this hypothesis. Measurement of threshold effects proved simpler and probably more accurate than measurement of changes in extent of suprathreshold responses, although some of the latter were essayed. The present study was restricted chiefly to the sweat response, although some corollary data on piloerection are also given. A very closely related investigation is that of Benjamin(3) who, studying the response of sweat glands to locally applied heat, showed an interaction between this stimulus on the one hand, and environmental temperature and locally injected acetylcholine on the other.

Methods. Healthy, white individuals, aged 20 to 34, were used as subjects; all but one experiment, noted below, were done on males. Injections of nicotine were made intradermally on the volar forearm with 26 gauge needles and 1 or ½ ml tuberculin syringes; in all cases, the volume injected was 0.05 ml. Solutions were made by diluting nicotine alkaloid to appropriate concentrations in sterile 0.9% NaCl; concentrations are expressed in terms of weight to volume. Sweating was detected by Randall's(4) iodine-starch paper method; the response was quantitated in terms of area and intensity on arbitrary scales. Piloerection was noted visually and, because of difficulty in quantization, noted only as

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TABLE I. Effect of Local Heating on Nicotine Sweat Threshold.

Subject 1					Subject 2			
Left arm		Right arm*		Room temp. (°C)	Left arm*		Right arm	
Skin temp. (°C)	Nicotine threshold	Skin temp. (°C)	Nicotine threshold		Skin temp. (°C)	Nicotine threshold	Skin temp. (°C)	Nicotine threshold
		34.5	$1:1.6 \times 10^6$	26	34	$1:1 \times 10^6$		
		31.0	$1:1.2 \times 10^6$	16	29	$>1:6 \times 10^5$		
				Heat on arm				
32.0	$1:1.2 \times 10^6$	36.5	$1:1.4 \times 10^6$	16	38	$1:1 \times 10^6$	29	$>1:6 \times 10^5$
				Heat off arm				
		29.0	$1:1 \times 10^6$	16	29	$>1:6 \times 10^5$		

* Heated arm.

present or absent.

Results. The threshold concentration of intradermal nicotine for producing the sweat response at room temperature (23°-26°C) varied from 1:800,000 to 1:2,000,000 among the individuals tested. Considerable variation was noted from day to day for any one subject. In 4 subjects, the magnitude of sweating was determined at a range of concentration from 1:50,000 to 1:1,000,000. Maximal sweating was observed between 1:400,000 and 1:800,000, with gradual diminution at increased and decreased concentrations outside this range. In the same subjects, axone reflex piloerection was observed at concentrations of 1:200,000 to 1:1,000,000, the maximum response appearing to coincide with the maximum sweating response.

The effects on threshold of altering the environmental temperature were studied on four males and one female. In each case the nicotine threshold was first determined at room temperature (26°-27°C); the subject was then placed in a room at 15° (in one case, 18°) for at least 30 minutes and retested; the subject was then returned to the previous environment for at least 30 minutes and threshold again determined. Skin temperature was monitored with a thermocouple or a mercury thermometer; the indicated temperatures of the 2 devices corresponded within 1°C. At each environmental temperature, skin temperature was allowed to stabilize before tests were made. In all subjects the threshold at 15° or 18° was at least 15% higher than it had been at 26°; on return to 26°, the threshold fell towards its original level. In each case, skin temperature fell from 34°-35° (room temperature of 26°) to 29°-32.5° (room temperature of 15°-18°).

To evaluate the role of local skin temperature in the sweating response to nicotine, a modification of the above experiment was performed in 2 subjects (Table I). The threshold was determined first on one forearm at room temperature. The subject was put in the cold room (16°) until skin temperature stabilized, whereupon threshold was again determined on that arm. This arm was then heated by an infra-red lamp until skin temperature reached 36.5°-38°, and nicotine threshold again determined on the heated arm, and on the opposite, unheated, arm as well. The heat lamp was then turned off and threshold retested on the previously heated arm after skin temperature had fallen again to 29°. As indicated in Table I, elevation of local temperature was adequate to cause a fall in nicotine threshold.

Discussion. Two major conclusions follow from these observations. 1) The dose-response characteristics of nicotine in producing axone reflex sweating are similar to those of its "nicotinic" action at autonomic ganglia: above a certain optimal concentration the response is self-inhibitory. This confirms the views of Coon and Rothman(1). 2) The threshold for nicotine sweating is a function of ambient temperature. This relationship is due in large part, if not entirely, to the effect of alterations in local skin temperature on sensitivity of the cutaneous components of the axone reflex mechanism. This is shown by the significant change wrought by isolated alteration of skin temperature. This result is parallel to Benjamin's(3) demonstration that

the sensitivity of sweat glands to acetylcholine is a function of local skin temperature.

The evidence suggests the possibility that the sudomotor axone reflex, should it occur physiologically, may serve to modify the response of the sweat glands to their central control. As indicated previously, however, the existence of such an axone reflex has not been demonstrated under physiological conditions.

Summary. The dose-response characteristics of nicotine axone reflex sweating are similar to those of the nicotine action on autonomic ganglia. The threshold for nicotine axone reflex sweating is raised with lowered environmental temperature. The effect appears to be due predominantly to alteration in local skin temperature.

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Effect of Preweanling Administration of Lactose on Subsequent Caries Susceptibility.* (23713)

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Previous work(1) showed that administration of a 20% sucrose solution 3 times a day to suckling white rats during calcification of their molars produced a highly significant increase in the subsequent caries score as compared with unsupplemented litter mates. This technic which measures only the systemic effect of supplements apart from local effects thus appeared useful in studying the systemic effect that other carbohydrates may have on subsequent caries.† The present study was designed to determine if lactose given under these conditions would also produce a significant change in caries.

Method. Fifty-eight animals from 7 litters were divided into 2 groups. One group of 30 animals was given 20% lactose solution orally 3 times a day, from the 3rd day following birth through the 21st day. The amount administered was approximately 1:1000 of body weight. In addition all animals received dam's milk *ad libitum*. Litter mates totaling 28 animals were used as controls and were given nothing in addition to dam's milk throughout the suckling period. When weaned at 21 days of age, all animals were placed on a cariogenic diet of the following composition: casein 24, sucrose 65, salts USP XIV 4, corn oil 5, dehydrated whole liver 4, vitamin mix 2(2), choline 0.2 part. Animals were sacrificed at the end of 13 weeks, and the molars were examined under a 20-power dissecting microscope after grinding successive planes parallel to the occlusal surface. Individual charts which showed the relationship of enamel, dentin, and pulp of each molar were used to record the carious lesions. The lesions were scored by the method of Shaw(3). Table I shows these results.

Results. The 10% difference in caries score between experimental and control animals was not significant. This is in marked contrast to results obtained when a 20% sucrose solution was administered in equal dosage to

TABLE I. Administration of 20% Lactose and Resulting Caries Score 13 Weeks Later.

Supplement	No. animals	Caries score (± S.E.)	t value
Lactose	30	20.4 ± 2.87	.53
Control	28	18.2 ± 2.88	

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