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## STUDIES ON TASTE THRESHOLDS IN NORMAL MAN AND IN PATIENTS WITH ADRENAL CORTICAL INSUFFICIENCY: THE ROLE OF ADRENAL CORTICAL STEROIDS AND OF SERUM SODIUM CONCENTRATION

By ROBERT I. HENKIN, JOHN R. GILL, JR., AND FREDERIC C. BARTTER

(From the Laboratory of Clinical Science, the National Institute of Mental Health, and the Clinical Endocrinology Branch, the National Heart Institute, Bethesda, Md.)

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Patients with adrenal cortical insufficiency exhibit an increased taste sensitivity for sodium chloride (NaCl) (1). Treatment with carbohydrate-active steroids returns the abnormal threshold to normal levels (1). In a variety of acute and chronic debilitating diseases, a number of them exhibiting major abnormalities of water and electrolyte metabolism, taste threshold for NaCl is comparable to that observed in healthy subjects (1). Taste thresholds for all modalities are decreased in cystic fibrosis, but they do not change after treatment with steroids (2).

The present study was designed to examine in detail taste thresholds in adrenal insufficiency and to explore the effect of adrenal cortical hormones on taste.

### METHODS

The subjects of this study were 13 normal volunteers, aged 6 to 35, two patients with anterior pituitary insufficiency, aged 21 and 36, and seven patients with Addison's disease, aged 25 to 65. All patients with Addison's disease had clinical features of this disease, urinary 17-hydroxycorticosteroids that were below 2 mg per 24 hours and did not increase with adrenocorticotropin (ACTH), 40 U given intravenously over 8 hours, each day for 5 days. Both patients with anterior pituitary insufficiency had hypothyroidism, hypogonadism, and adrenal insufficiency, with urinary 17-hydroxycorticosteroids in J.M. and S.P. of 1.1 and 2.2 mg per day, respectively, rising to 27 and 10.9 mg per day, respectively, with ACTH. All patients remained on an air-conditioned metabolic ward and ate a normal diet, which was well tolerated even when they were not receiving treatment. Sodium intake was 100 to 200 mEq per day. Body weight, determined with metabolic scales daily on arising, was used to provide a gross estimate of changes in the volume of body fluids. The patients were studied under each of three conditions: *a*) untreated for 4 or more days, *b*) treated with desoxycorticosterone acetate (DOCA), 20 mg per day for 1 to 7 days, and *c*) treated with prednisolone ( $\Delta_1F$ ), 20 mg per day for 2 to 5 days.

In addition, detection thresholds for the taste of NaCl

were measured between 7 and 8 a.m. in three normal Caucasian males, aged 18 to 20, before and during treatment with Pitressin. The two levels of sodium intake during Pitressin were 9 mEq and 150 mEq per day.

Taste was evaluated by measuring the detection threshold. A detection threshold is defined as the lowest concentration of test solution that can be consistently distinguished from distilled water. Thresholds were measured by one observer in the early morning hours in the normal subjects and in the morning or evening hours, or both, in the patients with adrenal insufficiency. Occasional retesting of the patient by another observer gave comparable results on each occasion. At the time of testing, the patients had not smoked or eaten for at least 1 hour. After the mouth was rinsed with distilled water, the solutions of test substance or glass-distilled water were administered as single drops and placed on alternate sides of the anterior one-third of the tongue.

Each test solution was presented to the patient together with two solutions of distilled water. The patient was requested to state which of the three solutions tasted different from the other two. The test solutions ranged from concentrated solutions, which taste different from water to all subjects, to dilute solutions which cannot be distinguished from water by normal subjects. When responses changed from consistently correct to incorrect, retests were made at and around the transition point. Threshold is defined as the lowest concentration of test substance to which the subject gave two successive correct responses while giving two consecutive incorrect responses at the next lower concentration. Thirteen different concentrations of test solution were each presented at least twice, and the order of presentation was varied. The probability that a threshold is determined by chance under these conditions is 1 in 2,500.<sup>1</sup> In this manner, thresholds were determined for representatives of each of the four basic taste modalities: NaCl, potassium chloride (KCl), and sodium bicarbonate ( $\text{NaHCO}_3$ ) for salt; sucrose for sweet; urea for bitter; and hydrochloric acid (HCl) for sour. All solutions were made in glass-distilled water with reagent grade chemicals. All solu-

<sup>1</sup>Statistical analysis of the method required that a model of the experimental design be made. Based on this model, all possible combinations of patient response were evaluated. The probability determination given above is the result of these calculations.

TABLE I  
Detection thresholds for taste in normal subjects

Subject	NaCl	KCl	NaHCO <sub>3</sub>	Sucrose	Urea	HCl
	<i>mmoles/L</i>	<i>mmoles/L</i>	<i>mmoles/L</i>	<i>mmoles/L</i>	<i>mmoles/L</i>	<i>mmoles/L</i>
RH	12	12	12	12	120	.8
AP	6	12	6	12	120	.8
JG	12	30	12	6	120	3
JP	30	30	30	12	120	6
PW	60	60	60	30	150	6
DH	12	30	12	12	150	3
JB	12	6	12	30	150	6
PM	12	12	12	12	120	3
EC	30	12	30	12	120	.8
DR	30	30	12	12	120	.8
MR	12	30	12	12	90	3
KP	30	12	12	30	150	6
JH	30	12	30	30	90	.8
Median	12	21	12	12	120	3
Range	6-60	6-60	6-60	6-30	90-150	.8-6

tions were administered from 60-ml medicine dropper bottles of similar shape and color. All solutions were kept at room temperature, approximately 22° C.

#### RESULTS

*Taste thresholds in normal subjects.* The detection threshold for each substance in each normal subject is presented in Table I. The medians of the detection thresholds for all normal subjects for the substances tested are as follows: NaCl, NaHCO<sub>3</sub>, and sucrose, 12 mmoles per L; KCl, 21 mmoles per L; urea, 120 mmoles per L; and HCl, 3 mmoles per L (Tables I). These medians are similar to those compiled from the

literature by Pfaffmann (3) (Figure 1). The values obtained for NaCl, KCl, NaHCO<sub>3</sub>, and sucrose are similar to one another, while those for HCl and urea differ appreciably from them.

*Taste threshold in adrenal insufficiency.* The detection threshold for each substance in each patient with untreated adrenal insufficiency is presented in Table II. The medians of the detection thresholds for the patients are as follows: NaCl, KCl, NaHCO<sub>3</sub>, and sucrose, 0.1 mmole per L; urea, 0.6 mmole per L; and HCl, 0.006 mmole per L (Table II). As in the normal subjects, the median detection thresholds for NaCl, KCl, NaHCO<sub>3</sub>, and sucrose are similar, while those values for HCl

TABLE II  
Detection thresholds for taste in adrenal insufficiency

Patient	Weight <i>kg</i>	Serum Na <i>mEq/L</i>	Serum K <i>mEq/L</i>	Detection threshold					
				NaCl <i>mmoles/L</i>	KCl <i>mmoles/L</i>	NaHCO <sub>3</sub> <i>mmoles/L</i>	Sucrose <i>mmoles/L</i>	Urea <i>mmoles/L</i>	HCl <i>mmoles/L</i>
A. Addison's disease									
GB	41.0	125	5.8	.001	.001	.001	.001	.008	.00006
MT	53.0	133	5.4	.3			.8	.6	.01
EM	52.8	132	4.9	.1			.1	.8	.006
JD	66.8	136	5.0	.01	.01	.01	.01	.8	.0006
HT	71.9	131	5.6	.5	.8	.8	.1	.3	.03
AB	58.7	136	4.5	.1	.3	.1	.1	.8	.006
RP	61.1	139	5.3	.01			.01	.8	.00006
B. Panhypopituitarism									
SP	31.3	138	4.7	.1			.01	.08	.0006
JM	72.9	140	4.9	.3	.1	.1	.3	.6	.03
Median				.1	.1	.1	.1	.6	.006
Range				.001-.5	.001-.8	.001-.8	.001-.8	.008-.3	.00006-.03

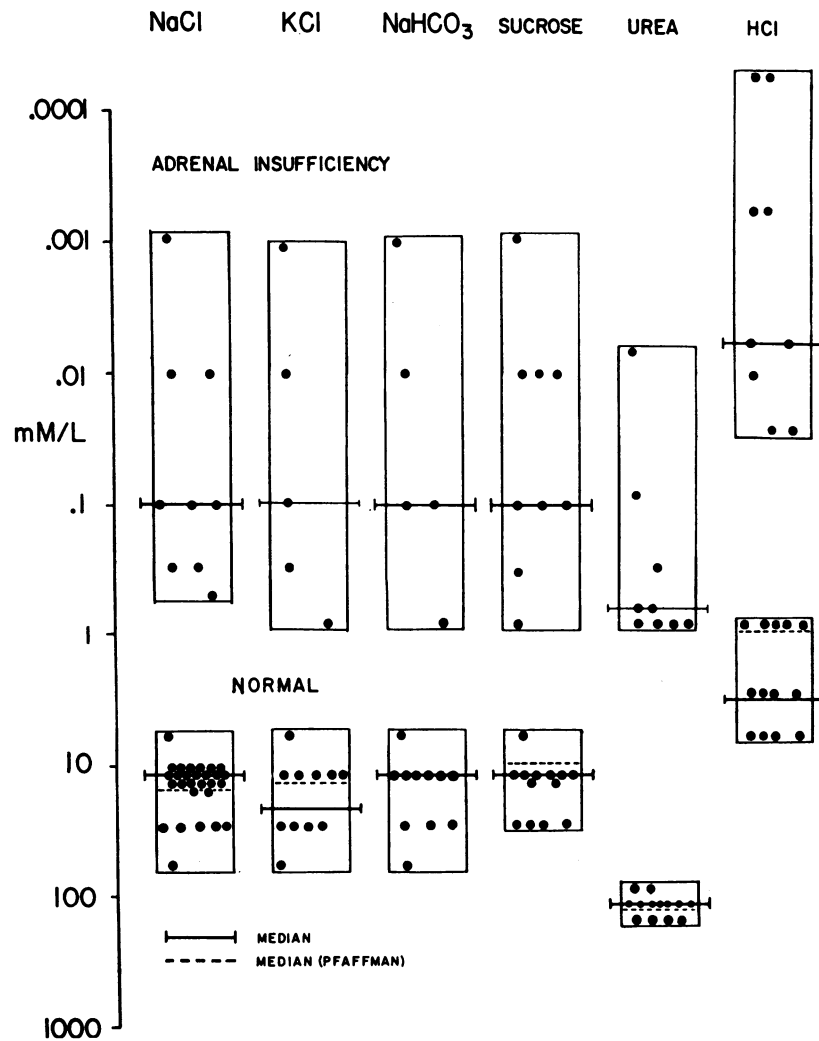


FIG. 1. THE MEDIAN AND RANGE OF THE DETECTION THRESHOLD FOR NaCl, KCl, NaHCO<sub>3</sub>, UREA, AND HCl IN ADRENAL INSUFFICIENCY AND IN NORMAL VOLUNTEERS. Note that the median detection thresholds in the normal subjects are similar to those found in the literature (dotted lines). There is no overlap between the thresholds of the patients and those of the normal subjects. The figure illustrates taste thresholds for NaCl in 15 normal volunteers not included in Table I.

and urea differ appreciably from them. All patients with adrenal insufficiency showed a markedly increased ability to detect all substances tested. They could detect minimal concentrations at least 8 times more dilute than those detected by the most sensitive normal subjects and, at most, 60,000 times more dilute than those detected by the least sensitive normal subjects. In no case did the range of the thresholds observed for a substance in the patients with adrenal insufficiency overlap

the range observed for that substance in the normal subjects (Figure 1).

The detection threshold for each substance in each patient with adrenal insufficiency treated with DOCA alone is presented in Table III. The medians of the detection thresholds for the patients are as follows: NaCl, NaHCO<sub>3</sub>, and sucrose, 0.01 mmole per L; KCl, 0.2 mmole per L; urea, 0.4 mmole per L; and HCl, 0.006 mmole per L (Table III). These values for median detection

TABLE III  
*Detection thresholds for taste in adrenal insufficiency treated with desoxycorticosterone acetate*

Patient	Weight	Serum Na	Serum K	Detection threshold					
				NaCl	KCl	NaHCO <sub>3</sub>	Sucrose	Urea	HCl
	kg	mEq/L	mEq/L	mmoles/L	mmoles/L	mmoles/L	mmoles/L	mmoles/L	mmoles/L
A. Addison's disease									
GB	44.2	137	4.0	.001	.001	.001	.001	.008	.00006
MT	54.1	138	3.6	.3			.8	.6	.01
EM	53.4	138	4.7	.1					
JD	68.5	142	4.1	.01	.01	.01	.01	.8	.0006
HT	77.1	138	4.1	.5	.8	.8	.01	.3	.006
AB	61.0	142	4.3	.1	.3	.3	.1	.8	.006
RP	62.7	145	4.5	.1			.5	.08	.01
B. Panhypopituitarism									
SP	32.5			.01			.01	.08	.0006
JM	73.2	144	5.0	.1	.01	.01	.01	.08	.006
Median				.1	.2	.2	.01	.4	.006
Range				.001-.5	.001-.8	.001-.8	.001-.8	.008-.8	.00006-.01

thresholds are virtually the same as those observed during the periods without treatment (Table II) despite a return of serum sodium and potassium concentrations toward normal levels and a gain in body weight (Table III).

The detection threshold for each substance in

each patient with adrenal insufficiency treated only with prednisolone, 20 mg per day, is presented in Table IV. The medians of the detection thresholds for the patients are as follows: NaCl, KCl, NaHCO<sub>3</sub>, and sucrose, 12 mmoles per L; urea, 120 mmoles per L; and HCl, 0.8 mmoles per

TABLE IV  
*Detection thresholds for taste in adrenal insufficiency treated with prednisolone*

Patient	Weight	Serum Na	Serum K	Detection threshold					
				NaCl	KCl	NaHCO <sub>3</sub>	Sucrose	Urea	HCl
	kg	mEq/L	mEq/L	mmoles/L	mmoles/L	mmoles/L	mmoles/L	mmoles/L	mmoles/L
A. Addison's disease									
GB	41.0	133	5.4	12	6	12	30	90	.8
MT	53.7	137	4.2	12	6	12	12	90	.8
EM	52.8	137	4.7	12	12	12	12	120	.8
JD	67.0	135	4.5	12	30	12	12	120	3
HT	74.4	135	4.1	6	12	6	6	120	.8
AB	60.0	140	4.8	12	30	12	12	120	30
RP	60.7	138	4.6	30				120	.8
B. Panhypopituitarism									
SP	31.3			12			12	90	3
JM	72.5	139	5.1	30	30	30	30	120	.8
SP*				6					
JM*				30					
JM†				.01					
JM‡				30					
Median§				12	12	12	12	120	.8
Range§				6-30	6-30	6-30	6-30	90-120	.8-30

\* These observations were obtained during treatment with ACTH.

† These observations were obtained during treatment with prednisolone, 2.5 mg per day.

‡ These observations were obtained during treatment with prednisolone, 5 mg per day.

§ Medians and ranges were calculated only from those values obtained during treatment with prednisolone, 20 mg per day.

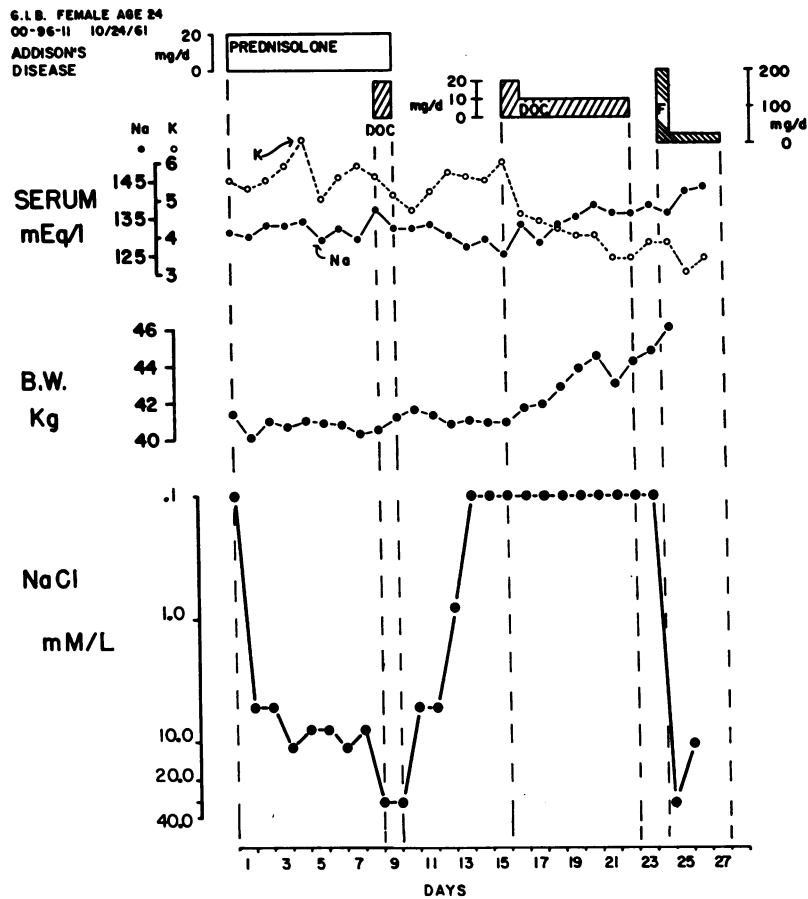


FIG. 2. EFFECT OF PREDNISOLONE, HYDROCORTISONE, AND DESOXYCORTICOSTERONE ACETATE ON SERUM Na AND K CONCENTRATIONS, BODY WEIGHT, AND TASTE THRESHOLD FOR NaCl. Threshold values for NaCl ranging from 6 to 60 mmoles per L are not considered significantly different.

L (Table IV). These values for median detection thresholds are virtually the same as those observed in normal subjects. In addition, detection thresholds determined in J.M. at a time when he was treated with prednisolone, 5 mg per day, were similar to those obtained during treatment with the higher dose of prednisolone. A lower dose of prednisolone, 2.5 mg per day, given for 2 days did not change the markedly lowered threshold values. It is clear that treatment with carbohydrate-active steroid returns taste threshold to normal levels in all patients with adrenal insufficiency studied.

#### DISCUSSION

Determination of threshold for a variety of substances representing the basic modalities of taste (salt, sweet, bitter, and sour) showed that the

threshold for all these substances was lowered in patients with untreated adrenal insufficiency, and indicated that taste is markedly altered in this disease state. The absolute thresholds were not the same for all substances tested, but the magnitude of the difference between values for the normal state and those for adrenal insufficiency was roughly the same for all substances. This difference is about 100 times with a range of 8 to 60,000 times. The magnitude of this difference may be in part attributable to the time of day selected for testing the normal subjects. While patients with adrenal insufficiency show no change in taste threshold throughout a 24-hour period, normal subjects exhibit a diurnal variation in taste threshold. In the afternoon, when sensitivity is greatest, this variation has been shown in a few subjects to overlap slightly the range of responses

of the least sensitive individuals among the patients with untreated adrenal insufficiency (4). All the normal subjects in the present study were tested in the early morning hours, when sensitivity is least.

The increase in taste sensitivity in patients with adrenal insufficiency was originally noted for NaCl (1). It has long been known that patients with adrenal insufficiency may have a craving for NaCl. Fifteen to 20% of the patients with adrenal insufficiency have been noted to exhibit this salt craving (5, 6). In our studies, all patients with this disease had an abnormally lowered taste threshold for NaCl. This difference in incidence suggests that the phenomenon of salt craving is different from that of increased taste sensitivity.

The thresholds observed for normal subjects in the present study are essentially the same as those reported in the literature (Figure 1), which have been obtained by various methods, most of which differ from that used here (3, 7-14). At the detection threshold, all of the test substances tasted bitter to the patients with adrenal insufficiency. In the five patients in whom it was measured, recognition or discrimination threshold, i.e., the lowest concentration of test substance recognized as that substance, was also lowered, although not to the same degree as the detection threshold.

Treatment with carbohydrate-active steroid returned the taste threshold for all test substances to normal in all patients with adrenal insufficiency. This change occurred usually within 1 day after treatment was initiated. This is in contrast to the much longer time, 3 to 4 days, required for the appearance of increased sensitivity after steroid therapy had been discontinued. Normal subjects similarly treated with prednisolone showed no change in taste threshold (15). Treatment with DOCA alone for as long as 7 days did not alter the abnormal taste threshold.

The relationship of serum electrolyte concentrations and body weight to taste threshold during treatment with carbohydrate-active steroid and DOCA is shown for one patient in Figure 2. In this patient, prednisolone alone returned taste to normal while hyponatremia and hyperkalemia were still present, whereas DOCA did not affect taste threshold, although it returned serum sodium and potassium to normal and produced a marked gain in body weight. This pattern of response was similar for all substances tested in all the patients with adrenal insufficiency (Tables II to IV).

In normal subjects made hyponatremic by treatment with Pitressin and water, taste threshold remained unchanged, even with concentrations of serum sodium as low as 112 mEq per L (Table V). In a number of subjects deprived of sodium

TABLE V  
*Detection thresholds for taste of NaCl in normal males before and during Pitressin and water*

Patient:	J.A.			M.S.			P.H.		
	Serum Na	Taste threshold NaCl	Body weight	Serum Na	Taste threshold NaCl	Body weight	Serum Na	Taste threshold NaCl	Body weight
	mEq/L	mmoles/L	kg	mEq/L	mmoles/L	kg	mEq/L	mmoles/L	kg
Untreated	137	60	58.0	141	60	78.3	143	60	59.7
Treated with	121*	60	60.6	135†	60	79.0	129†	60	61.6
Pitressin,	121*	60	60.9	132†	60	79.8	127†	60	62.4
4 pressor	119*	60	61.0	124†	60	80.4	123†	60	62.7
U in oil,	121†	60	61.3	123†	60	80.6	125†	60	62.7
im, per day	122†	60	61.5	120†‡	60	81.2	120†	60	62.4
	126†	60	61.2	121†	60	80.8	121†	60	62.1
	128†	60	60.9	120†	60	80.3	120†	60	62.0
	130†	60	60.9	113†	60	80.3	121*	60	61.6
	123†	60	60.4	115†	60	80.3	119*	60	61.3
	124†	60	60.1	115*	60	80.1	115*	60	61.0
	130†	60	60.0	115*	60	79.9	112*	12	60.8
	130†	60	60.1	113*	60	79.8	112*	60	60.6

\* Diet of 9 mEq Na.

† Diet of 150 mEq Na.

‡ Pitressin increased to 10 pressor U per day and each subsequent day. Thresholds determined daily, on subsequent days, during Pitressin.

(1) or treated with DOCA (15), taste thresholds also remained unchanged. A number of patients who had developed severe hyponatremia and contraction of extracellular volumes as a result of a variety of disease states showed no abnormality in taste threshold (1, 16). On the other hand, an increased taste sensitivity has been found in patients without alterations in total body water or sodium. In patients with cystic fibrosis, despite normal concentrations of sodium and potassium in the serum, taste thresholds were as low as those observed in patients with adrenal insufficiency. Despite treatment with DOCA or prednisolone, with accompanying changes in water and electrolyte metabolism, these thresholds remained unchanged. These observations suggest that the taste sensitivity is independent of the concentration of sodium or potassium in the serum and of changes in extracellular fluid volume.

Thus it is likely that the sodium retention and edema accompanying the uremic state in two patients given a diet low in sodium chloride were not the principal cause of the patients' abnormally low taste threshold for NaCl (1).

Yensen has reported that the taste threshold for NaCl is decreased with depletion of body sodium and increased with depletion of body water (17-19). These changes in threshold for NaCl were not accompanied by changes in threshold for any of the other modalities of taste, a phenomenon never observed in the present studies. Such a dissociation of threshold might be in part accounted for by a change in preference for NaCl brought on by the conditions of the test. Indeed, the method by which this recognition threshold was determined would include a large subjective component, e.g., changes in preference. The changes in threshold reported by Yensen are so small that subjective factors could perhaps account for them. This might explain a decrease in taste threshold in one subject with a decrease in the concentration of serum sodium of only 2 mEq per L (140 to 138 mEq per L). The accompanying decrease in body water was comparable to that observed during a study of water deprivation when taste threshold was noted to increase (19).

De Wardener and Herxheimer, using a method similar to the one used by Yensen, studied the recognition threshold for NaCl during forced water drinking. The water intake was not sufficient

to change serum sodium concentration (20). The thresholds reported during the period of water drinking were at times comparable to those observed during the control period, and varied over a range as great as the changes reported by Yensen.

The ability to restore taste threshold to normal is not limited to a single carbohydrate-active steroid. Furthermore, excessive amounts of steroid need not be given to restore taste to normal. At the time of admission, the patients with adrenal insufficiency had been taking only the following steroids or combination of steroids: cortisone acetate, 37.5 mg per day; or prednisolone, 5 mg per day; or dexamethasone, 0.75 mg per day, or 9  $\alpha$ -fluorohydrocortisone, 0.1 mg per day, or both. At this time, all taste thresholds were in the normal range and were comparable to those obtained during treatment with a dose of prednisolone, 20 mg per day, which is much greater than the usual dose for these patients.

Patient J.M. is a representative example (Table IV). On a maintenance dose of prednisolone, 5 mg per day, he showed threshold values comparable to those obtained with the larger dose of prednisolone, 20 mg per day. When carbohydrate-active steroid was administered in a dose lower than the usual maintenance dose, it had no effect on the abnormal threshold (Table IV). A dose of ACTH sufficient to return adrenal function to the normal range or above also returned taste threshold to the normal range (J.M. and S.P., Table IV).

The amount of carbohydrate-active steroid administered, however, does appear to influence the rate of return of taste threshold to normal. Whereas prednisolone corrected the abnormal taste response within 18 to 36 hours in all patients, a massive dose of hydrocortisone, 330 mg, given intravenously to one patient over a 6-hour period corrected the abnormal taste response within that period of time. A smaller but nonetheless pharmacological dose of hydrocortisone, 200 mg, given intravenously to this same patient over an 8-hour period was not effective until 18 hours had elapsed.

The abnormality of taste observed in adrenal insufficiency is not limited to this disease alone. Patients with cystic fibrosis also exhibit a comparably increased sensitivity of taste (12). How-



ever, this abnormality is unaffected by either DOCA or carbohydrate-active steroid. Preliminary observations suggest that a few normal subjects, including a family of both parents and two siblings, with normal adrenal function, have shown a persistently decreased taste threshold (16). Yet, in a large number of patients with a variety of acute and chronic debilitating illnesses not involving disease of the adrenal cortex, no significant alteration in taste could be found (1, 16). Studies on normal volunteers given large exogenous doses of prednisolone, 20 mg per day, for 5 days indicate that taste threshold does not change with this treatment (16).

In both the treated and untreated states, taste threshold does not depend upon ionization (compare NaCl with sucrose) or on the degree of dissociation of the ionized species (compare NaCl with  $\text{NaHCO}_3$ ), since the threshold for all three substances is the same. Since urea, a substance that readily passes through cellular membranes, could be tasted only in a concentration 10 times greater than that of the other five substances tested, simple membrane permeability is probably not a critical factor. This suggestion is further supported by the finding that the thresholds for NaCl and sucrose are the same despite differing molecular sizes and permeability characteristics.

The mechanism by which carbohydrate-active steroids alter taste threshold is not clear. Indeed, the neurophysiology of taste in general is not well understood. Carbohydrate-active steroids, however, have been shown to have an important effect on nerve function (21), and perhaps their effect on taste is mediated through an effect on nerve function.

Studies with three additional patients with Addison's disease, off treatment, have revealed that the median detection thresholds for the four basic modalities of taste are 10 to 1,000 times lower than the lowest thresholds reported in Table II (patient GB).

#### SUMMARY

1. Taste thresholds for salt (NaCl, KCl,  $\text{NaHCO}_3$ ), sweet (sucrose), bitter (urea), and sour (HCl) were determined in nine patients with adrenal insufficiency (seven with Addison's disease and two with panhypopituitarism) and com-

pared to those in normal volunteers. In adrenal insufficiency the taste sensitivity was roughly 100 times (range, 8 to 60,000 times) more acute than that in the normal subjects.

2. Treatment of the patients with desoxycorticosterone acetate (DOCA), 20 mg per day, returned serum sodium and potassium concentrations to normal and produced gains in body weight, but did not alter taste threshold. Taste threshold for all modalities was unchanged in a variety of conditions in which alterations in the concentration of serum sodium were produced or occurred naturally.

3. Treatment with prednisolone, 20 mg per day, returned taste threshold to normal in every patient, usually within the first day and frequently before any change in serum electrolyte concentrations or in body weight. When prednisolone was stopped, the increased taste sensitivity did not reappear for 3 to 4 days.

4. The nature of the effect of carbohydrate-active steroids on taste is obscure. It may be related to their effect on nerve function.

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