Adrenal Response to Excess Corticotropin in Coronary-Prone Men* (34093)

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Subjects presenting a particular overt behavior pattern which we have labeled Type A (characterized by excessive drive and conflict against time, other persons, and/or challenging situations) have been found by us (1, 2) to be far more prone to the future incidence of clinical coronary heart disease then subjects exhibiting a converse behavior pattern (Type B).

Since emotional stress of almost any kind might be expected to involve the pituitary–adrenal axis, it was thought of interest to determine and compare the urinary excretion of 17-hydroxycorticosteroids (17-HOCS) of both types of subjects under basal conditions and again after the administration of a relatively large amount of corticotropin. The results of this study are reported below.

Methods. Eighteen apparently well and active men (average age, 40 years) whom we had assessed as exhibiting the fully developed Type A behavior pattern (1, 2) were selected for this study. Twenty similarly well and active men (average age, 44 years) whom we had assessed as exhibiting the converse type of behavior pattern (Type B) also were selected. The men of both groups consisted of salesmen, physicians, corporate executives, and fire fighters. Their exercise and dietary habits as determined by questionnaire were similar.

Each subject received 100 units of corticotropin (Armour Acthar gel) by intramuscular injection at 5:00 PM. This very large dose (approximately twice the amount needed to effect maximal discharge of the adrenal hormone, cortisol) was employed in order to ensure (despite possible individual variabilities in absorption) maximal adrenal stimulation in each subject. A freshly voided urine sample was obtained immediately before the corticotropin injection. Then at 7:00 AM or 14 hr later, each subject emptied his bladder completely of nocturnally secreted urine and we collected a freshly voided sample at 8:00 AM and a second at 12:00 noon (*i.e.*, 15 and 19 hr respectively after the ACTH had been given). The three samples were analyzed for creatinine (3) and 17-HOCS (4) by a modified Porter-Silber procedure (5). In view of the fact that freshly voided urine samples rather than total urine collections over a given period of time were obtained, the urinary concentration of steroid was expressed in terms of milligrams of 17-HOCS per gram of creatinine. Since the steroid contents of the 15- and 19-hr urine samples were closely similar, the average of the two values was used. The average value of these two urine samples that were obtained in the 20 Type B subjects was considered as the average normal value because such subjects at least in regard to coronary heart disease appear to be relatively immune to its early occurrence (6). Accordingly any subject who exhibited an urinary value of 17-HOCS that lay in the range of this average value (plus or minus 2 $\times$ S D) was considered a "normoreactor." Subjects exhibiting urinary values above and below this range were labeled "hyperreactors" and "hyporeactors" respectively.

After all the subjects had been tested in this manner, six of the Type A subjects who appeared to "hyporeact" to ACTH administration and nine of the subjects (three Type A and six Type B) who appeared to be "normoreactors" were later retested to determine whether the initial results obtained on these "hyporeactors" were due to some artifact connected with the absorption of ACTH or with the voiding and collection of urine samples. The retesting procedure consisted of (1) an exact replication of the initial test employing corticotropin and (2) the oral ad-

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TABLE I. Urinary 17-HOCS and THS Excretion after ACTH and Metyrapone in Subjects with Type A and B Behavior Pattern.

				Urinary 17-HOCS excretion[a]				Urinary THS excretion[a]	
				First test		Repeat test			
No. of subjects	Av age (yr)	Av ht (in.)	Av wt (lb)	Before ACTH	15 & 19 hr after ACTH	Before ACTH	15 & 19 hr after ACTH	Before metyrapone	After metyrapone
A. Subjects with behavior pattern B									
20	44	70	180	5.8	35.7				
Range	(33–58)	(67–74)	(160–250)	(3.5–10.4)	(23.9–46.9)				
SEM	± 1.2	± 0.4	± 4.2	± 0.4	± 1.05 (SD ± 5.8)				
B. Subjects with behavior pattern A									
18	40	71	185	5.4	24.6				
Range	(30–52)	(68–74)	(160–225)	(2.4–7.0)	(5.0–48.9)				
SEM	± 1.3	± 0.3	± 4.1	± 0.3	± 3.2				
C. Hyporeactor subjects (type A) given repeat ACTH and metyrapone tests									
6	40	71	186	5.2	12.5	5.0	15.7	0.4	18.1
Range	(35–46)	(68–74)	(165–225)	(2.4–7.0)	(5.1–20.3)	(3.0–6.8)	(10.5–21.7)	(0.0–0.8)	(13.7–20.2)
SEM				± 0.5	± 1.93	± 0.4	± 1.85	± 0.13	± 0.9
D. Normoreactor subjects (type A and B) given repeat ACTH and metyrapone tests									
9	44	70	189	5.2	35.9	5.6	34.1	0.8	30.0
Range	(30–52)	(67–74)	(160–250)	(3.0–10.8)	(27.9–43.9)	(3.2–8.0)	(23.5–40.2)	(0.0–1.3)	(22.7–37.1)
SEM				± 0.3	± 1.8	± 0.3	± 2.8	± 0.14	± 1.6

[a] Milligrams of 17-HOCS or THS/g of creatinine.

ministration of metyrapone (750 mg q 4 hr for a total of 6 doses) after which a urine sample was obtained (4 hr after the last oral dose) and analyzed for tetrahydrodesoxycortisol (THS) by the 17-HOCS analytic procedure (4, 5) as above but substituting carbon tetrachloride extraction after the method of Henke *et al.* (7).

Results. As Table I illustrates, the basal urinary excretion of 17-HOCS was essentially the same in both groups of subjects. However, a considerable difference was observed between the two groups in the urinary excretion of this same corticosteroid 15–19 hr after the administration of ACTH. Thus the average excretion of the Type B subjects increased (See Table I) from the basal value of 5.8 mg to 35.7 mg/g of creatinine after the administration of ACTH, an increase of approximately 515% whereas the average excretion of the Type A subjects only increased from 5.4 to 24.6 mg/g of creatinine, an approximate increase of 356%. This difference in excretion after ACTH was found to be significant ($p<.01$) by the Student t test). It was of interest that the post-ACTH urine samples of 14 of the 18 Type A subjects (78%) contained quantities of 17-HOCS outside the range of expected values (*i.e.*, values more or less than 2 $\times$ SD) of the average urinary 17-HOCS content of the 20 Type B subjects. Thus the majority of the 18 (61%) Type A subjects excreted abnormally low quantities of 17-HOCS after ACTH administration. Indeed three of these 11 "hyporeactors" failed to exhibit any significant increase of 17-HOCS excretion after ACTH. Three of the 18 (17%) Type A subjects excreted abnormally high quantities of 17-HOCS after ACTH administration.

When the ACTH test was given again and also the oral administration of metyrapone to six of the Type A "hyporeactors" and to nine "normoreactors," it was observed (See Table I) that once again the 17-HOCS excretion in the six "hyporeactors" increased far less (200%) than that (510%) observed in the nine "normoreactors" after ACTH administration. Also the average THS concentration (18.1 mg/g of creatinine) of the urines of these same six "hyporeactors" was significantly less ($p<.001$) than that (30.0 mg/g of creatinine) of the urines of the nine "normoreactors" after the oral administration of the metyrapone.

These results suggest that the majority of subjects possessing a behavior pattern that has been found to be intimately associated both contemporaneously (1) and prospectively (2) with increased incidence of clinical coronary heart disease, also exhibit a difference in their adrenal response to excess ACTH whether the latter is exogenously administered or caused to be secreted by oral administration of metyrapone. The cause of this relative adrenal "unresponsiveness" (as compared with that present in Type B subjects) in most subjects with this type of behavior pattern is not clear but it is possible that this apparent loss in "adrenal reserve" may be the result of a previous long standing as well as a possible contemporary excess discharge of corticotropin. Determination of and comparison of circulating plasma ACTH of Type A subjects with that of Type B subjects might give information concerning this latter possibility.

Summary. The adrenal response to excess corticotropin (achieved either by its administration or by metyrapone-induced excess endogenous secretion) was found to be significantly reduced in the majority of individuals assessed as relatively prone to future incidence of clinical coronary heart disease when compared with the adrenal response of subjects believed to be relatively immune to the occurrence of the same disorder.

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