Plasma ACTH and Cortisol Concentration of Coronary-Prone Subjects[1] (36530)

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In a number of studies (1–4) we have found that subjects presenting a particular overt behavior pattern which we have labeled Type A (characterized chiefly by excessive drive and conflict against time, other persons and/or various challenging situations) are significantly more prone to the future incidence of clinical coronary heart disease than subjects exhibiting a converse behavior pattern (Type B). Having identified the enhanced coronary-proneness of such subjects, we now are attempting to discover the possible biochemical and biophysical abnormalities of such individuals which might account for their apparent relative vulnerability to future clinical coronary artery disease.

Since emotional stress of almost any variety might be expected to involve the hypothalamo–pituitary–adrenal system, we have interested ourselves in the study of the integrity of this system in Type A subjects. In our first study (5) relevant to the components of this system, we found that the average daily excretion of 17-HOCS of the Type A subjects was the same as that of the Type B subjects. However, in our second study (6) we observed that when *fully developed* Type A subjects (*i.e.*, subjects who exhibit extreme competitive drive and experience constantly an overwhelming sense of time urgency) were challenged with large doses of corticotropin (ACTH), most of them excreted significantly less 17-HOCS than Type B subjects. This last suggested to us that these Type A subreactors might have a deficit in their "adrenal reserve." Such a postulated deficit in turn suggested the possibility that these individuals might be subject to a previous long standing as well as a possible contemporary excess discharge of ACTH. We, therefore, thought it would be useful to measure the plasma ACTH and cortisol levels of a group of *fully developed* Type A subjects and compare them with those of a group of *fully developed* Type B subjects (*i.e.*, subjects who exhibit no competitive drive, and are totally free of any sense of time urgency). The results of this study are reported below. They suggest that Type A subjects during their working hours do secrete more ACTH than Type B subjects.

Methods. Nine fully developed Type A and 10 fully developed Type B volunteer male subjects, who appeared to be in excellent health, cooperated in this study. Six heparinized blood samples (collected in ice-chilled tubes) were obtained from most of the volunteers during their waking hours (*i.e.*, 7:00 a.m., noon, 3:00, 5:00 and 9:00 p.m.). The blood samples obtained at 9:00 a.m., noon and 5:00 p.m. were drawn in our laboratory. Those obtained at 7:00 a.m. and 9:00 p.m. were drawn at the subjects' homes and that obtained at 3:00 p.m. at their place of work. The plasma of these samples was obtained as quickly as possible after the blood had been drawn, and was stored in the frozen state. Later, an aliquot of each plasma sample was sent in the frozen state to the laboratory of Drs. S. A. Berson and R. S. Yalow where the ACTH content of each plasma sample was measured according to their methodology (7). The remaining aliquot of each plasma sample was analyzed for its cortisol content according to the method of Stewart, Albert-Recht and Osman (8). Each 7:00 a.m. sample was also analyzed for its plasma cholesterol concentration (9).

Results. There was, as Table I illustrates,

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TABLE I. Plasma ACTH and Cortisol Values of Type A and Type B Subjects.

Case	Age	Ht	Wt	Plasma cholesterol (mg/100 ml)	7:00 a.m. ACTH (ng/100 ml)	7:00 a.m. Cortisol (μg/100 ml)	9:00 a.m. ACTH (ng/100 ml)	9:00 a.m. Cortisol (μg/100 ml)	Noon ACTH (ng/100 ml)	Noon Cortisol (μg/100 ml)	3:00 p.m. ACTH (ng/100 ml)	3:00 p.m. Cortisol (μg/100 ml)	5:00 p.m. ACTH (ng/100 ml)	5:00 p.m. Cortisol (μg/100 ml)	9:00 p.m. ACTH (ng/100 ml)	9:00 p.m. Cortisol (μg/100 ml)	Peak level ACTH (ng/100 ml)	Peak level Cortisol (μg/100 ml)
A Subjects																		
1	39	74	220	295	30	17.0	—	—	30	16.8	30	13.5	25	12.3	60	7.0	60	17.9
2	35	72	178	253	48	13.2	32	14.5	30	11.3	22	17.5	0	11.3	—	—	48.0	17.5
3	43	72	180	300	0	21.8	—	—	30	18.2	25	15.2	25	13.0	18	13.4	30.0	21.8
4	50	72	171	307	35	15.8	25	13.5	0	11.8	35	11.0	35	8.7	28	16.5	35.0	16.5
5	43	70	175	295	110	28.5	35	18.5	50	10.8	50	13.2	40	15.8	38	15.0	110.0	28.5
6	46	69	168	369	58	27.8	35	34.0	35	28.0	45	26.0	20	21.0	15	15.3	58.0	34.0
7	41	73	180	312	120	17.0	15	7.0	—	—	60	11.3	20	7.9	15	4.3	120.0	17.0
8	42	70	160	280	60	11.0	78	10.0	58	11.5	75	12.5	58	9.2	50	6.8	78.0	12.5
9	47	75	195	301	62	20.9	90	15.2	35	10.0	90	19.5	32	9.5	65	9.0	90.0	20.9
Av	43	72	181	301[a]	58.1	19.3	44.3	16.1	33.5	14.8	48	15.5	28.3	12.2	36.1	10.9	69.9[b]	20.7
SE M				±10.3	±12.6	±2.0	±10.7	±3.3	±6.0	±2.2	±7.8	±1.6	±5.3	±1.5	±7.2	±1.7	±10.6	±2.2
B Subjects																		
10	56	65	155	213	30	19.5	—	—	32	17.8	30	12.0	18	14.5	10	17.4	32	19.5
11	56	67	166	182	20	20.5	—	—	38	12.5	30	18.7	18	11.0	18	13.8	38	38.0
12	39	71	163	262	35	13.2	32	9.0	0	8.0	35	6.5	25	6.0	10	1.0	35	13.2
13	50	69	168	177	48	24.0	20	17.0	20	23.5	30	14.0	0	14.2	—	—	48	24.0
14	57	73	174	218	48	6.8	0	10.8	0	13.5	25	10.2	32	8.9	30	7.9	48	13.5
15	56	69	174	225	20	13.1	—	—	14	16.2	28	11.5	23	7.5	23	6.0	28	16.2
16	54	69	160	237	62	26.0	—	—	60	13.2	62	8.0	28	10.7	50	8.0	62	26.0
17	39	70	200	211	20	18.0	—	—	32	14.5	30	11.0	0	15.0	—	—	32	18.0
18	30	71	192	248	—	23.5	35	13.7	38	13.2	38	8.0	38	12.0	0	9.6	38	23.5
19	52	70	170	232	32	10.5	50	14.2	40	10.8	48	10.9	42	9.3	32	7.1	48	14.2
Av	48	69	172	221	35	17.5	27.4	12.9	27.5	14.3	35.6	11.1	22.4	10.9	21.6	8.9	40.9	18.9
SE M				±8.5	±5.0	±2.0	±8.4	±1.4	±6.0	±1.3	±3.6	±1.1	±4.5	±1.0	±5.6	±1.8	±3.3	±1.5

[a] Value significantly greater than corresponding value of Type B subjects: $p < .001$; [b] $p < .02$.

considerable variation in both the plasma cortisol and ACTH levels not only between individuals of each group but also in the same individual during the day.

The average plasma ACTH values of the Type A subjects, at each of the 6 time intervals were greater (see Table I) than those of the Type B subjects. Despite the fact that the differences in the respective means were not statistically significant by the T test (*i.e.*, $p < .1$), at any one of the 6 time intervals (ostensibly because of the great variation in the individual ACTH values of each group at such time intervals), nevertheless, according to the binomial distribution theorem (H_0: $p = .5$), the chances of observing 6 successive averages of Type A subjects to be greater than those of Type B subjects is of a very low probability ($p < .002$). This last fact strongly suggests that the type A subjects exhibited throughout their waking hours a significant increase in their plasma ACTH values. In further support of this conclusion, was the finding that the average maximal plasma ACTH value of the day (*i.e.*, the "peak" value) was also significantly ($p < .02$) greater in the Type A than in the Type B subjects.

The usual circadian change in plasma cortisol concentration was observed in both groups of subjects. Thus the average plasma cortisol level of the Type B subjects at 7:00 a.m. was 17.5 μg/100 ml, a value almost twice that (8.9 μg/100 ml) observed in these same patients 14 hr later at 9:00 p.m. Similarly the average plasma cortisol level of the Type A subjects was 19.3 μg/100 ml at 7:00 a.m. and 10.9 μg/100 ml at 9:00 p.m. On the other hand, at no time interval of the day was the average plasma cortisol of the Type A subjects significantly greater than that of the Type B subjects. Similarly the average "peak" or maximal plasma cortisol value of the Type A subject was not significantly different from that of the Type B subjects.

As has been observed repeatedly before (1, 10, 11), the average plasma cholesterol (301 mg/100 ml) of the Type A subjects was significantly greater ($p < .001$) than that (221 mg/100 ml) of the Type B subjects.

Discussion. As we have stated before (12), whatever the biochemical defects may turn out to be, which render Type A subjects relatively prone as a group to the early onset of clinical coronary heart disease, such defects, at any given instant in time, probably will be relatively subtle in degree. This is probably particularly the case when such subjects are studied years or even decades before they experience cardiac symptomatology. It is because of this difficulty in detection that we invariably choose for biochemical studies only those subjects who exhibit the extreme development of either behavior pattern.

In the past, we have been able to detect under the above described circumstances, alterations in the plasma cholesterol (1, 10, 11), triglyceride (10, 11) and lipoprotein spectra (13) of Type A subjects. In addition we have observed various hormonal changes in these subjects such as (a) increased day time urinary excretion of norepinephrine (6) (b) a postprandial hyperinsulinism (11) and (c) a diminished reserve of growth hormone (14). Finally we have observed (5) that the adrenal response to excess corticotropin was significantly reduced in the majority of fully developed Type A subjects.

The present results suggest that *fully developed* Type A subjects also differ from *fully developed* Type B subjects in that they appear to exhibit a higher level of plasma corticotropin throughout their waking hours. This apparent chronic hypersecretion of ACTH may be due to a compensatory reaction to some block in adrenal function in these subjects. On the other hand it might be due to excess hypothalamic secretion of corticotropin-releasing factor. In either event, this hypersecretion of ACTH may explain why the average adrenal responses of Type A subjects to an excess of exogenous ACTH were significantly less than those of the control Type B subjects.

All thse slight to moderate hormonal (and lipid) alterations which we have observed in most *fully developed* Type A subjects appear to us to suggest that these individuals harbor alterations (albeit only functional) in their hypothalamo–pituitary–adrenal system. This is not at all surprising when one consid-

ers the exquisite sensitivity of this same system to emotional stresses of various varieties—of which Type A behavior pattern one.

Summary. The plasma corticotropin and cortisol concentrations of 9 coronary-prone (Type A behavior pattern) and 10 coronary-resistant (Type B behavior pattern) subjects were studied at 6 time intervals during their waking hours. The average plasma corticotropin content of the 9 Type A subjects was significantly greater during the total period measured than that of the 10 Type B subjects. The average daily peak value of plasma corticotropin of the Type A subjects also was found to be significantly increased. No significant differences were found in either the average or peak plasma cortisol values between these 2 groups of subjects.

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