

Relationship between Cortisol and Cholesterol in Men with Coronary Artery Disease and Type A Behavior

Harvey A. Schwertner, Raymond G. Troxler, Gregory S. Uhl, and William G. Jackson

To further understand the hormonal mechanisms linking behavior pattern and coronary artery disease (CAD), we investigated the relationship between 0930-hour plasma cortisol and cholesterol in relatively young males who had undergone coronary angiography and in a subgroup of individuals who had undergone the structured interview for classification of behavior pattern. A statistically significant association ($p < 0.05$) was found between cortisol and cholesterol for individuals who had either minimal CAD (20% to 49% narrowing) or significant CAD ($\geq 50\%$ narrowing), but not for subjects without CAD. An association between cortisol and cholesterol was also found to be significant for the subgroup of individuals with Type A-1 behavior pattern, but not for those with Type A-2, X, or B behavior patterns. The findings suggest that hormonal mechanisms involving cortisol and cholesterol metabolism may be operative in individuals with CAD as well as in individuals with Type A-1 behavior. (*Arteriosclerosis* 4:59-64, January/February 1984)

Since serum cholesterol is one of the most important risk factors for coronary heart disease, numerous studies have been made to identify factors that control its levels in blood. Extensive evidence now indicates that cholesterol metabolism is controlled by a complex system involving genetics, sex, diet, and age. Some evidence also indicates that behavior pattern may have an influence on cholesterol concentrations. Individuals with Type A behavior, for instance, have higher serum cholesterol concentrations and have more severe and extensive coronary atherosclerosis than do Type B individuals.¹⁻⁴ Behavior modification,⁵ on the other hand, has been shown to result in decreased cholesterol concentrations. Stress is yet another factor that results in increased cholesterol levels⁶⁻¹² and, as with behavior modification, relaxation training^{13, 14} tends to reverse the elevated cholesterol levels.

The mechanism by which behavior or stress influences cholesterol metabolism is not known; however, neurogenic pathways are thought to be involved.⁶⁻¹⁵ Since corticosteroids are lipogenic in

nature¹⁶⁻²² and since they are increased in Type A individuals under certain situations²³ and in individuals exposed to stress or other environmental challenges,^{24, 25} it is possible that much of the elevated cholesterol associated with coronary heart disease, Type A behavior, and stress could be the result of increased corticosteroids or increased responsiveness to corticosteroids.

We recently demonstrated an association between plasma cortisol and cholesterol in individuals who had undergone cardiac catheterization;²⁶ however, distinctions were not made with regard to the presence or absence of coronary artery disease (CAD). In this study, we specifically examined the association between cortisol and cholesterol in patients with minimal and significant CAD and in two groups of patients without CAD. In addition, we studied the relationship between the two steroids in individuals with different behavior patterns as determined by the structured interview.

Methods

Patient Population

United States Air Force (USAF) aircrew members involved in this study were referred to the USAF School of Aerospace Medicine for evaluations of

Address for reprints: Dr. Harvey A. Schwertner, Clinical Sciences Division, USAF School of Aerospace Medicine, Brooks AFB, Texas 78235.

Received December 27, 1982; revision accepted August 16, 1983.

medical conditions that could preclude the performance of flying duties. Nearly 60% of the patients referred were suspected of having cardiovascular disease, with most patients referred for electrocardiographic abnormalities at rest (usually S-T or T-wave abnormalities as a serial change) or during exercise testing. The remainder were referred for ophthalmologic, otolaryngologic, psychiatric, or neurologic evaluations.

In this study, 4.9% of the individuals in the negative cath group, 11.1% of the individuals in the minimal disease group (20% to 49% narrowing), and 20.0% of the individuals in the significant disease group ($\geq 50\%$ narrowing) had suspected or definite angina.

Exercise Test Procedures and Coronary Angiography

Each patient in the study group underwent a complete cardiovascular screen as well as an evaluation of the primary complaint. The cardiovascular screen included a chest radiograph, an electrocardiogram at rest, at least 16 hours of ambulatory electrocardiographic monitoring, an exercise tolerance test, and a thorough history and physical examination.

The symptom-limited exercise tests were performed at a constant treadmill speed of 3.3 miles per hour, with an incline increase of 5° every 3 minutes.²⁷ Electrocardiographic monitoring was performed from the standard bipolar X, CM₅, Y, and Z leads during the exercise period and for an 8-minute recovery period. Recordings were also made while the patient was in supine and standing positions. All patients were encouraged to exercise to exhaustion, leg fatigue, or chest pain. The stress electrocardiogram was considered abnormal if a horizontal or downsloping ST segment depression of 0.1 mv, or more, occurred for at least 80 msec from the J point.

Subjects who had abnormal exercise tests, significant arrhythmia, valvular disease, or left bundle branch block were offered the option of undergoing cardiac catheterization. The catheterizations were performed with the Judkins technique. Left ventriculograms were obtained in the 30° right anterior oblique projection and selective coronary angiograms were performed in multiple projections. All angiographic data were reviewed independently by two cardiologists and interpreted without knowledge of laboratory test results or behavior type. Discrepancies between the two cardiologists reviewing the angiograms were resolved by consensus or by a third cardiologist.

Cholesterol and Cortisol Analysis

Blood samples were obtained for cholesterol, high density lipoprotein cholesterol, and cortisol analysis after a 10- to 20-hour overnight fast on the day after admission but before treadmill testing. High density lipoproteins were obtained after precipitation of low- and very low-density lipoproteins from serum with

phosphotungstate-magnesium reagent.²⁸ Low density lipoprotein cholesterol (LDL-cholesterol) constituted both the low density and very low density lipoprotein fractions and was determined by subtracting the HDL-cholesterol concentration from the total serum cholesterol concentration. Both serum cholesterol and HDL-cholesterol were analyzed on an ABA-100 bichromatic analyzer (Abbott Laboratories, North Chicago, Illinois) with BMC Autoflor cholesterol reagents (Cat No. 148393, Biodynamics/bmc, Indianapolis, Indiana). For plasma cortisol analysis, we used competitive protein binding procedures (Cortipac CPB test, Amersham Corporation, Arlington Heights, Illinois).

Plasma samples for cortisol analyses were obtained by venipuncture during a routine oral glucose tolerance test. The glucose tolerance tests (40g/m²) were all initiated at approximately 0800 hours. Since we had found in an earlier study that cortisol-cholesterol relationships were weaker with the 0800 hour (fasting) samples than with the 0930 hour samples,²⁸ we measured cortisol only in the 0930 specimens in this study.

Behavior Pattern

Assessments of behavior pattern were made from videotapes by Ray Rosenman²⁹ without knowledge of other patient variables. On the basis of the interview, the individuals were classified as Type A-1, A-2, X, or B. Type A behavior is primarily characterized by extremes of aggressiveness, easily aroused hostility, a sense of time urgency, and competitive drive.²⁹ Persons exhibiting the fully developed Type A behavior pattern were classified as Type A-1; those showing most, but not all, of the Type A characteristics were classified as Type A-2. Type X represented a category of persons who had nearly equal amounts of both Type A and Type B characteristics.

An additional calculation of the association between cortisol and cholesterol was made using previously published cholesterol and cortisol values for Type A and Type B individuals.⁴ In that study, nine fully developed Type A and 10 fully developed Type B men who appeared to be in excellent health were studied; their average ages were 43 and 48, respectively.

Statistical Analysis

Association between cortisol and cholesterol within each group of subjects was measured using the Pearson product-moment correlation coefficient. Both cortisol and cholesterol were positively skewed in original units (mg/dl), but calculations of the Shapiro-Wilk statistic W^{30} and the Kolmogorov statistic D^{31} indicated that their log-transformed values had approximately normal distributions. Hence, the correlations were calculated between log cortisol and log cholesterol. Student's t statistic was used to compare correlations against zero, and the approxi-

mate normality of correlations following Fisher's Z transformation was used in comparisons between correlations.

Student's *t* test was used whenever two group means were being compared. The significance levels reported for these were the same whether the tests were performed in original units or on log-transformed values. The test for trend in cortisol levels across quartiles of cholesterol was made using Jonckheere's test for ordered alternatives.³² The effects of age on cortisol and cholesterol means were examined by standard analysis of covariance techniques.

Results

Relationship between Cortisol, Cholesterol, and Coronary Artery Disease

To facilitate study of the association between cortisol, cholesterol, and coronary artery disease (CAD), patients were classified into four separate groups on the basis of the absence, presence, and extent of coronary artery narrowing. The four groups were as follows: 1) a control group of subjects with normal exercise tests, normal noninvasive cardiovascular evaluations, and low cardiovascular risk profiles; 2) a second control group composed of subjects with positive exercise tests, but no angiographic coronary artery disease; 3) a group composed of individuals with abnormal exercise tests and at least one vessel with 20% to 49% disease; and 4) a group with $\geq 50\%$ narrowing of at least one vessel. Patients in the 20% to 49% group were considered to have subcritical or minimal disease, and patients in the 50% group were considered to have significant CAD.

Summary statistics are given in Table 1 for the four groups. Mean cholesterol concentrations were significantly higher ($p < 0.001$) in the two disease groups than in either the negative cath group or the no cath group (Table 1). The mean cortisol concentrations of the 20% to 49% group and the $\geq 50\%$ group, however, were not statistically different from those of the no cath group or the negative cath group.

The correlation between cortisol and cholesterol was statistically larger than zero for the most diseased group ($p = 0.031$) and for the minimally dis-

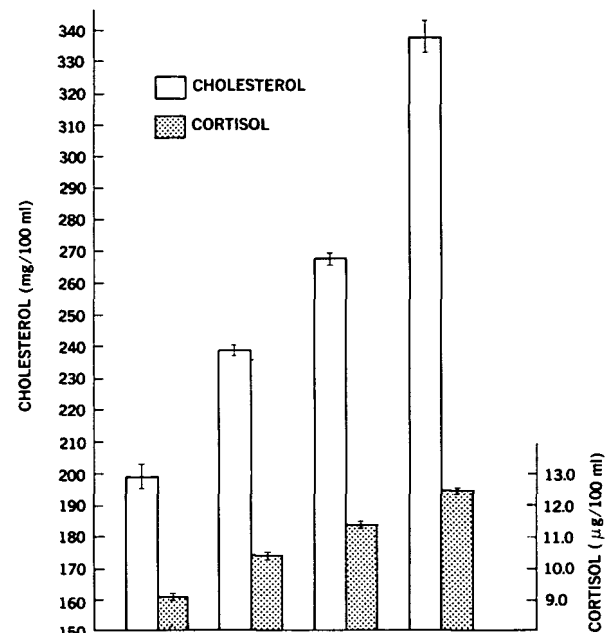


Figure 1. Cortisol means (SE) for each quartile of cholesterol for positive cath patients ($n = 92$).

eased group ($p = 0.012$), but not for the negative cath ($p = 0.24$), and the no cath ($p = 0.46$) groups. The cholesterol-cortisol correlations within the 20% to 49% group and the $\geq 50\%$ group were also statistically larger than those of the no cath group (see column 7, table I). When the correlations were compared to those of the negative cath group, only the minimal disease group was statistically different from the negative cath group (column 8, table I).

We were concerned that the differences between means and correlations reported above might be due simply to age differences between the groups. The mean differences were retested with age as a covariate. Also, partial correlations between cholesterol and cortisol adjusted for age were calculated and tested. The results were nearly identical to those already reported.

To obtain an alternative representation of the association between cholesterol and cortisol, cholesterol values for patients with minimal and significant coronary artery disease were placed into quartiles along with their corresponding cortisol values (Figure 1). The cortisol values of patients with CAD rose

Table 1. Coronary Artery Disease and Cortisol-Cholesterol Correlations

Group	No.	Cholesterol (mg/dl)	Cortisol (mg/dl)	Correlation	1-Tail prob. for corr > 0	1-Tail prob. for corr >		Age (yrs)
						Corr (no cath)	Corr (neg cath)	
No cath	341	207 (39)	10.4 (3.3)	0.006	0.457	—	—	33.9
Neg. cath	185	219 (38)	10.2 (3.9)	0.052	0.240	0.26	—	40.1
20%–49%	22	255 (42)	10.9 (4.5)	0.478	0.012	0.013	0.026	41.8
50%+	70	264 (65)	10.9 (4.0)	0.224	0.031	0.040	0.109	44.7

Values for cholesterol and cortisol are means \pm SD (in parentheses).

progressively as the levels of cholesterol increased from quartile 1 to quartile 4. A similar increase in cortisol, however, did not occur with the negative cath group (Figure 2). The increase in cortisol levels in the group with CAD was tested using Jonckheere's test for ordered alternatives,²⁰ and the resulting probability level was $p < 0.01$. For the negative cath subjects this test was not statistically significant.

Since high density lipoprotein (HDL) cholesterol concentrations were available on some of the more recent patients, we sought to determine if cortisol concentrations were related to HDL cholesterol concentrations. In this study we examined 36 patients with minimal disease and 32 patients with significant disease. Even though HDL cholesterol decreased with the increased severity of disease, the HDL cholesterol-cortisol correlations were not found to be significant for either the minimal disease group ($r = -0.064$, $p = 0.71$, two-tail) or the significant disease group ($r = 0.012$, $p = 0.95$). LDL cholesterol from the very low and low density lipoprotein fractions, however, was found to be correlated with cortisol in the significant disease group ($r = 0.366$, $p < 0.05$, two-tail), but not in the minimal disease group ($r = 0.197$).

Relationship between Cortisol, Cholesterol, and Behavior Pattern

In this part of the study, we sought to determine if an association existed between cortisol and cholesterol in a subset of individuals who had undergone both cardiac catheterization and the structured interview for classification of behavior type. Of the four behavior types studied (A-1, A-2, X, and B) a significantly positive correlation between cortisol and cholesterol was found only for the group with Type A-1 behavior pattern (Table 2). The cortisol-cholesterol correlations of the A-2's, X's and B's were all nonsignificant. As a result, data is only presented for the two extreme groups (A-1 and B). Information on the number and percentage of patients with significant, minimal, or no disease is given for the A-1 and the B groups in the footnote to Table 2.

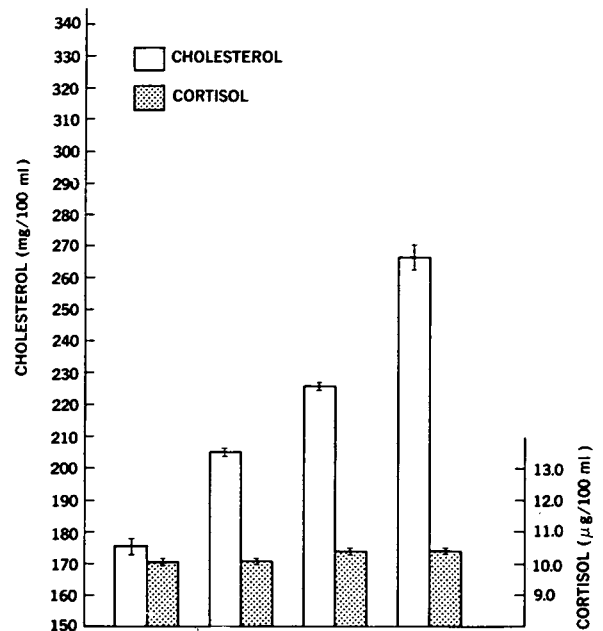


Figure 2. Cortisol means (SE) for each quartile of cholesterol for negative cath patients ($n = 185$).

To gain additional information on the cortisol-cholesterol relationships in type A and B individuals, we calculated cortisol-cholesterol correlations using previously published data for fully developed Type A and B individuals.⁴ As shown in the bottom part of Table 2, cortisol-cholesterol correlations were positively correlated in the Type A individuals and negatively correlated in the Type B individuals.

Discussion

A major feature of this study is the finding of a positive association between cortisol and cholesterol in individuals with CAD but not in individuals without CAD. A similar association between the two steroids was also found in individuals with Type A-1 behavior

Table 2. Behavior Pattern and Cortisol-Cholesterol Correlations

Group	No.	Cholesterol (mg/dl)	Cortisol (mg/dl)	Correlation	1-tail prob for corr > 0
A-1*	21	243 (41)	9.7 (3.3)	0.492	0.015
B*	29	242 (67)	9.9 (4.1)	0.189	0.129
A†	9	301 (31)	20.7 (6.7)	0.624	0.036
B†	10	220 (27)	20.6 (7.6)	-0.543	—‡

Values for cholesterol and cortisol are means \pm SD (in parentheses).

*The number (and percentage) of patients with $\geq 50\%$, 20%–49%, and no disease are as follows: A-1, 11 (52.4), 1 (4.7), 9 (42.9); B, 4 (13.8), 6 (20.7), 19 (65.4).

†Data are compiled from cholesterol and cortisol values previously published by Friedman, Byers, and Rosenman.⁴ Cortisol-cholesterol correlations were based on peak cortisol concentrations.

‡Probabilities are not reported since the sample correlation is negative and the 1-tail alternative was $p > 0$.

but not in individuals with other behavior patterns. Because of the smaller population sizes, the cortisol-cholesterol associations for the groups with different behavior patterns are not as clearly established as for the groups with and without CAD. It should also be pointed out that since a majority (52%) of the individuals with Type A-1 behavior had CAD, the cortisol-cholesterol relationship found for this group could be, in part, due to the presence of CAD.

It is not known why the two steroids are related or if there is a cause-and-effect relationship. In recent studies, cortisol and catecholamine secretions have been shown to be greatly enhanced in Type A individuals in response to mental tasks.²³ This neuroendocrine hyperresponsivity may also be characteristic of individuals with CAD and, even though it is transient in nature, it may be sufficient to result in elevated cholesterol concentrations.

Since cholesterol is a precursor to cortisol, it is equally possible that an elevated cholesterol may cause an elevation in cortisol concentration. There are, however, some arguments against this view. For instance, in patients with abetalipoproteinemia, where low density lipoprotein (LDL) cholesterol is unavailable as a precursor for cortisol synthesis, basal cortisol levels are the same as in normal subjects.³³ Since *de novo* cholesterol synthesis appears to be entirely adequate for normal cortisol adrenal steroid hormone production,³³ we do not think that the essentially normal cortisol levels in CAD patients is the result of the elevated cholesterol concentrations.

There is also the possibility that cholesterol and cortisol may not be linked at all. Instead, both may increase independently in patients with CAD. However, for CAD to occur, both cholesterol and cortisol might have to be slightly elevated.

The association of cortisol with cholesterol is by no means specific for coronary-prone individuals. In ongoing work, we are finding a strong positive association between cortisol and cholesterol in plasma samples taken from eleven women during pregnancy ($r = 0.54$, $n = 51$, $p < 0.001$). Even further increases in cholesterol and cortisol were found during labor and delivery, and after delivery both dropped rapidly within 24 hours. The increase in cortisol was not due to increases in cortisol binding protein since free urinary cortisol concentrations also increased during pregnancy. Even though other hormones such as progesterone and estriol may be involved, the studies do point out another example where endogenous cortisol and cholesterol may be linked.

Elevated cholesterol concentrations are thought to be primarily a reflection of an individual's genetic or nutritional status. However, if cortisol is subsequently found to have a significant effect on cholesterol concentrations, it could represent an alternative explanation for elevated cholesterol levels in individuals who do not have familial hypercholesterolemia and who are on a relatively low cholesterol diet. Such a link between cortisol and cholesterol could also

open new avenues for the control and treatment of hypercholesterolemia resulting from a wide variety of metabolic and environmental conditions that are known to produce elevated cortisol levels in humans.

References

1. Roseman RH, Brand RJ, Sholtz RI, Friedman M. Multivariate prediction of coronary heart disease during 8.5 year follow-up in Western Collaborative Group Study. *Am J Cardiol* 1976;37:903-10
2. Haynes SG, Feinleib M, Kannel WB. The relationship of psychosocial factors to coronary heart disease in the Framingham study. III Eight-year incidence of coronary heart disease. *Am J Epidemiol* 1980;111:37-58
3. Friedman M. Type A behavior pattern: Some of its pathophysiological components. *Bull NY Acad Med* 1977;53:593-604
4. Friedman M, Byers SO, Rosenman RH. Plasma ACTH and cortisol concentration of coronary-prone subjects. *Proc Soc Exp Bio Med* 1972;140:681-4
5. The Review Panel on Coronary-Prone Behavior and Coronary Heart Disease. Coronary-prone behavior and coronary heart disease: A critical review. *Circulation* 1981; 63:1199-1215
6. Dimsdale JE, Herd JA. Variability of plasma lipids in response to emotional arousal. *Psychom Med* 1982;44:413-430
7. Friedman M, Roseman RH, Carroll V. Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress. *Circulation* 1958; 17:852-61
8. Gottschalk LA, Cleghorn JM, Gleser GC, Iacono JM. Studies of relationships of emotions to plasma lipids. *Psychom Med* 1965;27:102-11
9. Wolf S, McCabe WR, Yamamoto J, Adsett CA, Schottstaedt WW. Changes in serum lipids in relation to emotional stress during rigid control of diet and exercise. *Circulation* 1962;26:379-87
10. Thomas CB, Murphy EA. Further studies on cholesterol levels in the Johns Hopkins medical students. The effects of stress at examinations. *J Chronic Dis* 1958;8:661-8
11. French JRP, Caplan RD. Psychosocial factors in coronary heart disease. *Indus Med* 1970;39:31-45
12. Russek HI, Russek LG. Is emotional stress an etiologic factor in coronary heart disease? *Psychosomatics* 1976;17:63-7
13. Patel C. Reduction of serum cholesterol and blood pressure in hypertensive patients by behavioral modification. *J R Coll Gen Pract* 1976;26:211-215
14. Cooper M, Aygen M. A relaxation technique in the management of hypercholesterolemia. *J Human Stress* 1979;5:24-27
15. Roseman RH, Friedman M. Neurogenic factors in pathogenesis of coronary heart disease. *Med Clin North Am* 1974;58:269-79
16. Adlersberg D. Hormonal influences on the serum lipids. *Am J Med* 1957;23:769-89
17. Adlersberg D, Schaefer L, Drachman SR. Development of hypercholesterolemia during cortisone and ACTH therapy. *JAMA* 1950;144:909-14
18. Stern MP, Kolterman OG, Fries JF, McDevitt HO, Reaven GM. Adrenocortical steroid treatment of rheumatic disease. *Arch Intern Med* 1973;132:97-101
19. Skanse B, Von Studnitz W, Skoog N. The effect of corticotrophin and cortisone on serum lipids and lipoproteins. *Acta Endocrinol* 1959;31:442-50
20. Etheridge EM, Hoch-Legeti C. Lipid deposition in aortas in younger age groups following cortisone and adrenocorticotrophic hormone. *Am J Pathol* 1952;28:315-8

21. **Kalbak K.** Incidence of arteriosclerosis in patients with rheumatoid arthritis receiving long-term corticosteroid therapy. *Ann Rheum Dis* 1972;31:196-200
22. **Plotz CM, Knowlton AI, Ragan C.** The natural history of Cushing's syndrome. *Am J Med* 1952;13:597-614
23. **Williams RB Jr, Lane JD, Kuhn CM, Melosh W, White AD, Schanberg M.** Type A behavior and elevated physiological and neuroendocrine responses to cognitive tasks. *Science* 1982;218:483-485
24. **Mason JW.** A historical view of the stress field. *J Human Stress* 1975;1:22-36
25. **Liddle GW.** Physiological review of adrenocortical function. In: Stear EB, Kadish AH, eds. *Hormonal control systems*. New York: American Elsevier, 1969:1-19
26. **Troxler RG, Sprague EA, Albanese RA, Fuchs R, Thompson AJ.** The association of elevated plasma cortisol and early atherosclerosis as demonstrated by coronary angiography. *Atherosclerosis* 1977;26:151-62
27. **Froelicher VF, Thompson AJ, Noguera I, Davis G, Stewart AJ, Triebwasser JH.** Prediction of maximal oxygen consumption. Comparison of the Bruce and Balke treadmill protocols. *Chest* 1975;68:331-6
28. **Clark DA, Rozell PR, Mosser EL.** Evaluation of a kit to measure HDL cholesterol (HDL-C) in serum. *Clin Chem* 1983;29:1311
29. **Roseman RH.** The interview method of assessment of the coronary-prone behavior pattern. In: Dembroski TM, Weiss SM, Sheilds JL, Haynes S, Feinleib M, eds. *Coronary-prone behavior*. New York: Springer-Verlag, 1978:55
30. **Shapiro SS, Wilk MB.** An analysis of variance test for normality (complete samples). *Biometrika* 1965;52:591-611
31. **Stephens MA.** EDF statistics for goodness of fit and some comparisons. *J Am Stat Assoc* 1974;69:730-737
32. **Hollander M, Wolfe DA.** *Nonparametric statistical methods*. New York: John Wiley and Sons, 1973,184-199
33. **Illingworth DR, Orwoll ES, Conner WE.** Impaired cortisol secretion in abeta lipoproteinemia. *J Clin Endocrinol Metab* 1980;50:977-979

Index Terms: coronary artery disease • plasma cortisol • serum cholesterol • Type A behavior • atherosclerosis