Association of Hyperestrogenemia and Coronary Heart Disease in Men in the Framingham Cohort

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The serum levels of estradiol and testosterone as well as established risk factors for coronary heart disease were estimated in 61 men (mean age 70.0 ± 6.4 [SD] years) with coronary heart disease and in 61 matched control subjects enrolled in the Framingham Heart Study. The mean serum estradiol level was significantly higher in the subjects with coronary disease ($p = 0.011$). This difference in estradiol level increased with the exclusion of subjects older than 75 years ($p < 0.001$). The mean serum testosterone level was not significantly different. None of the established risk factors for coronary heart disease was different between subjects with coronary disease and control subjects except blood glucose level, which was higher in the subjects with coronary disease ($p = 0.025$). We conclude that hyperestrogenemia is an important correlate of coronary heart disease in men.

An increase in the mean serum concentrations of estradiol and estrone in a group of men aged 34 to 43 years who had had a myocardial infarction has been previously reported [1]. Evidence that clinical signs of feminization preceded the myocardial infarction [1] suggested that the hyperestrogenemia may also have preceded the myocardial infarction. Further analysis of the data in the patients and control subjects revealed a correlation between the ratio of the serum concentrations of estradiol to testosterone and the areas under the glucose and insulin curves, respectively, in the glucose tolerance test [2]. This correlation along with other evidence suggested that these and perhaps other risk factors for myocardial infarction might be secondary to an increase in the serum estradiol-to-testosterone ratio or some closely related function [3]. It was further hypothesized that hyperestrogenemia may be the major predisposing factor for myocardial infarction and that the glucose-insulin-lipid defect and hypertension may be of secondary importance or even incidental to the development of myocardial infarction [2,3]. In order to evaluate these hypotheses, a matched-pair study was carried out in which the serum estradiol and testosterone levels, as well as established risk factors for coronary heart disease, were measured in a sample of male participants in the Framingham Heart Study. The results of this study, which was carried out in an older, larger, and less selected population than in the previous study [1], and in which the hormones were measured without knowledge of the diagnosis, are consistent with the hypotheses.

SUBJECTS AND METHODS

The Framingham Study has examined 5,209 residents in Framingham, Massachusetts, biennially for the development of cardiovascular disease.

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Subjects enrolled in the study were aged 30 to 62 years at the first examination, occurring between 1948 and 1952. Sampling procedures and analytical techniques have been described previously [4].

The present study was carried out during the 16th biennial examination (1979–1981) of the Framingham Heart Study. The participants considered in this report consisted of 61 males who had a prior diagnosis of coronary heart disease each matched by age (Table I) and seasonal proximity of sampling in Examination 16 with a male control subject who was free of coronary heart disease. The criteria for defining coronary heart disease, which consisted of myocardial infarction (38 patients), coronary insufficiency (8 patients), or angina pectoris (15 patients), have been given elsewhere [5]. All cardiovascular episodes were confirmed by two physicians at the time of examination and verified by a panel of investigators using the established criteria. The mean time between the examination of the subjects (Examination 16) and the first diagnosis of coronary heart disease was 10.8 ± 6.8 years. Two subjects with coronary disease were excluded from the data analysis because of a diagnosis of hypergonadotropic hypogonadism. One had had a myocardial infarction diagnosed nine years before, and the other angina three years before Examination 16. The serum testosterone and estradiol levels in the former were 0.15 ng/ml and 8.9 pg/ml and in the latter 0.71 ng/ml and 5.5 pg/ml, respectively. Had these low values been included, the mean estradiol level of the subjects with coronary disease would still have been significantly higher than that of the control subjects ($p < 0.04$ by paired t test in all subjects, and $p < 0.04$ by analysis of covariance with subjects who had a diagnosis of angina only excluded).

Venous blood samples were drawn from the subjects at random times in the afternoon, and the serum was separated and stored at −20°C. The serum samples, which were drawn and coded in Framingham, were sent frozen (dry ice) in batches to the investigator in New York City (G.B.P.) for hormone analysis. The results of the estradiol and testosterone measurements were received by mail in Framingham before the identity of the subjects with coronary disease was revealed to this investigator. Although unknown to him, about an equal number of samples from subjects with coronary disease and control subjects were analyzed simultaneously in each assay. Measurement of the levels of steroid hormones [6], luteinizing hormone [7], and follicle-stimulating hormone [8] was carried out by radioimmunoassay. The luteinizing hormone and follicle-stimulating hormone assays were standardized using the NIH LER 907 preparation. Estradiol and testosterone were measured in 61 and dehydroepiandrosterone sulfate (DHEAS) in 59 matched pairs. The serum remaining, however, allowed luteinizing hormone and follicle-stimulating hormone to be measured in only 40 and progesterone in 50 matched pairs. The first and second antiserum specimens and the estradiol-17-β-^{125}I and testosterone-^{125}I derivatives used, as well as materials for progesterone and DHEAS assay, were obtained from Radioimmunoassay Systems Laboratories, Carson, California. In the assay for estradiol and testosterone, 0.6 ml of serum was extracted once with 6 ml of ethyl acetate-hexane (3:2), which removed approximately 94 percent of the estradiol and 98 percent of the testosterone; 5 ml of the extract were dried at 40°C with a nitrogen jet and reconstituted in 1.25 ml buffer by incubating at 40°C for 30 minutes and swirling. Duplicate 0.5 ml and 20 μl (50 μl for low samples) aliquots were used for the radioimmunoassay of estradiol and testosterone, respectively. Each serum sample was assayed in this way in at least three separate runs. With each run, two and sometimes three quality-control serum samples were assayed. The interassay means and coefficients of variation for these control samples were 24.1 pg/ml ± 11.1 percent and 56.6 pg/ml ± 6.9 percent for estradiol and 4.19 ng/ml ± 7.73 percent and 0.56 ng/ml ± 6.29 percent for testosterone. Intraassay means and coefficients of variation on other samples were 19.8 pg/ml ± 9.1 percent and 36.6 pg/ml ± 5.2 percent for estradiol and 4.23 ng/ml ± 5.45 percent and 0.37 ng/ml ± 7.39 percent for testosterone.

Also estimated in these subjects were systolic blood pressure, high-density lipoprotein cholesterol and total cholesterol levels, cigarette smoking, exhaled carbon monoxide, blood glucose level, Quetelet's index (weight/height as kg/m^2), and alcohol consumption. Evidence of feminization observed previously [1] was not sought in this study. The techniques have been described for measuring plasma high-density lipoprotein cholesterol and cholesterol levels [9], exhaled carbon monoxide level by Ecolyzer [10], and blood glucose level [4]. Because estimates of plasma high-density lipoprotein cholesterol and total cholesterol levels, the number of cigarettes smoked, and alcohol intake were not made in Examination 16, the values for these risk factors were taken from previous examinations. The data for plasma high-density lipoprotein cholesterol and total cholesterol are from Examination 15 (two years earlier), a time difference which should have little, if any, effect on the results (Castelli, unpublished observations). The data on cigarette smoking are from Examination 12 (eight years earlier); however, the data for carbon monoxide in exhaled breath, a more objective criterion of smoking, are from Examination 16. The correlation coefficients between these two measurements of smoking were 0.57 ($p < 0.001$) for all subjects, 0.39 ($p < 0.01$) for the subjects with coronary disease, and 0.72 ($p < 0.001$) for the control subjects. These data suggest that more subjects with coronary disease than control subjects may have stopped smoking. The data for alcohol intake are also from Examination 12.

Statistical methods used for describing the male sample and for making comparisons between subjects with coronary disease and control subjects included deriving simple and partial correlations, computing paired t tests that controlled for the pair matching, and performing analyses of covariance that controlled for high-density lipoprotein cholesterol, carbon monoxide, and blood glucose levels, Quetelet's index, and the matching variable. The concomitant variables included in the latter analysis were all measured within two years of the estradiol and testosterone measurements.

RESULTS

Measurements of the established risk factors for coronary heart disease in the 61 subjects with coronary disease and 61 control subjects are shown in **Table I.**

TABLE I Risk Factor Data for Subjects with Coronary Disease and Control Subjects*

	Control Subjects	Subjects with Coronary Disease	Control Subjects†	Subjects with Coronary Disease†	Control Subjects‡	Subjects with Coronary Disease‡
Age (years)	70.0 ± 6.6	70.0 ± 6.4	69.6 ± 6.3	69.6 ± 6.3	67.2 ± 4.1	67.3 ± 3.9
Systolic blood pressure (mm Hg)	139.1 ± 20.7	142.9 ± 22.2	138.5 ± 21.1	143.3 ± 22.6	139.2 ± 21.8	142.0 ± 21.2
High-density lipoprotein cholesterol (mg/dl)	44.9 ± 14.9	41.1 ± 10.9[1]	43.5 ± 13.7	42.1 ± 11.5	43.9 ± 14.4	41.5 ± 11.6
Total cholesterol (mg/dl)	219.9 ± 47.6	213.4 ± 32.0	224.0 ± 47.5	213.4 ± 28.0	216.2 ± 45.3	216.3 ± 30.0
Cigarettes (per day)	6.3 ± 13.7	7.2 ± 12.4	6.7 ± 14.9	6.7 ± 11.6	6.2 ± 14.7	7.2 ± 12.8
Exhaled carbon monoxide (ppm)	7.7 ± 7.3	8.2 ± 7.9	7.6 ± 7.9	8.6 ± 8.9	7.4 ± 7.4	8.6 ± 8.6
Blood glucose (mg/dl)	87.7 ± 23.1	109.4 ± 62.5[2]	88.4 ± 21.9	113.4 ± 68.5[2]	86.6 ± 23.6	105.6 ± 59.4[1]
Quetelet's index (kg/m^2)	27.0 ± 4.0	27.2 ± 3.8	27.3 ± 3.1	26.7 ± 3.8	27.5 ± 4.1	27.7 ± 3.8
Alcohol intake (ounces per week)	6.8 ± 6.8	5.2 ± 6.4	5.7 ± 5.9	5.2 ± 6.6	7.4 ± 7.3	5.9 ± 6.8

* Based on 61 subjects with coronary disease and 61 control subjects. Values are means ± standard deviation.
† Excludes subjects with angina only and their matched control subjects, leaving 46 subjects with coronary disease and 46 control subjects.
‡ Excludes subjects with coronary disease older than 75 years and their matched control subjects, leaving 48 subjects with coronary disease and 48 control subjects.
Significantly different from matched controls by paired t test: [1] $p < 0.10$, [2] $p < 0.05$.

Because the diagnosis of angina is subjective and thus less reliable than that of myocardial infarction and coronary insufficiency and may result from coronary spasm, the data are also shown for the subjects with coronary heart disease excluding those who had a diagnosis of angina only and their matched control subjects. In six of the 15 patients with angina only, angina had not been present for two to 10 years at the time of sampling. The data for subjects with coronary disease aged 75 years or younger and their matched control subjects are also listed. The only established risk factor that was significantly different between the subjects with coronary disease and control subjects was the blood glucose level, which was higher in the subjects with coronary disease ($p = 0.025$) and when those with angina only were excluded ($p = 0.043$); when subjects with coronary disease older than 75 years and their matched control subjects were excluded, the p value was <0.07.

The mean serum estradiol and testosterone levels and the mean estradiol-to-testosterone ratios are shown in **Table II.** Of the 15 highest estradiol values, 13 occurred in subjects with coronary disease. With the paired t test, the mean serum estradiol level was significantly higher ($p = 0.011$) in the subjects with coronary disease than in the control subjects. This difference was even greater ($p = 0.006$) when the subjects with a diagnosis of angina only and their matched control subjects were excluded. When subjects with coronary disease older than 75 years and their matched control subjects were excluded, the difference in the mean estradiol levels between the remaining subjects with coronary disease and matched control subjects was even more significant ($p < 0.001$). With the analysis of covariance controlled for carbon monoxide, high-density lipoprotein cholesterol, and glucose levels, Quetelet's index, and the matching variable either individually or together, the mean serum estradiol level was higher in the subjects with coronary disease ($p < 0.05$). The significance of this difference increased when those with angina only were excluded ($p < 0.04$) and was even greater for subjects with coronary disease and control subjects aged 75 years or younger ($p < 0.01$). Differences in the mean levels of testosterone or the estradiol-to-testosterone ratio did not reach significance at the 0.05 level by paired t test or analysis of covariance.

The correlation coefficients between estradiol, testosterone, and the estradiol-to-testosterone ratio, respectively, and the risk factors for coronary heart disease, controlled for age and Quetelet's index, are shown in **Table III.** The estradiol-to-testosterone ratio correlated positively with blood glucose level in all subjects ($p < 0.001$) and in subjects with coronary disease ($p < 0.01$) and control subjects ($p < 0.05$) calculated sep-

TABLE II Mean Hormone Levels for Subjects with Coronary Disease and Control Subjects*

	Control Subjects	Subjects with Coronary Disease	Control Subjects†	Subjects with Coronary Disease†
All Ages				
Estradiol (pg/ml)	32.75 ± 7.44	36.54 ± 9.97[2,4]	32.84 ± 7.49	37.80 ± 10.19[2,4]
Testosterone (ng/ml)	3.90 ± 1.23	4.13 ± 1.45	3.96 ± 1.24	4.28 ± 1.58
Estradiol-to-testosterone ratio	8.95 ± 2.70	9.65 ± 3.74	8.77 ± 2.25	9.80 ± 4.05
Aged 75 Years or Less				
Estradiol (pg/ml)	32.05 ± 7.13	37.81 ± 10.04[3,5]	32.34 ± 7.15	38.95 ± 10.01[3,5]
Testosterone (ng/ml)	3.86 ± 1.17	4.36 ± 1.48[1]	3.94 ± 1.15	4.48 ± 1.62[1]
Estradiol-to-testosterone ratio	8.88 ± 2.85	9.52 ± 3.98	8.64 ± 2.22	9.76 ± 4.31
Aged More Than 75 Years				
Estradiol (pg/ml)	35.09 ± 8.24	31.86 ± 8.49	34.86 ± 8.95	33.06 ± 10.09
Testosterone (ng/ml)	4.04 ± 1.46	3.28 ± 0.99	4.03 ± 1.64	3.46 ± 1.09
Estradiol-to-testosterone ratio	9.20 ± 2.19	10.15 ± 2.75	9.28 ± 2.44	9.97 ± 2.90

* Based on 61 subjects with coronary disease and 61 control subjects. Of these, 48 subjects with coronary disease and their 48 matched control subjects were aged 75 years or less. Analysis of covariance controlled for high-density lipoprotein cholesterol, carbon monoxide, and blood glucose levels, Quetelet's index, and matching information. Values are means ± standard deviation.

† Excludes subjects with angina only and their matched control subjects, leaving 46 subjects with coronary disease and 46 control subjects. Of these, 37 subjects with coronary disease and their 37 matched control subjects were aged 75 years or less.

Significantly different from matched controls: [1] $p < 0.10$, [2] $p \leq 0.01$, [3] $p < 0.001$ (paired t test); [4] $p < 0.05$, [5] $p < 0.01$ (analysis of covariance).

TABLE III Correlation Coefficients between Hormone Levels and Risk Factors for Coronary Heart Disease Controlled for Age and Quetelet's Index

	Control Subjects			Subjects with Coronary Disease			Subjects with Coronary Disease*			All Subjects		
	Est†	Test†	E/T†	Est	Test	E/T	Est	Test	E/T	Est	Test	E/T
Systolic blood pressure (mm Hg)	0.08	−0.03	0.19	0.15	0.09	−0.01	0.18	0.02	0.06	0.13	0.04	0.08
High-density lipoprotein cholesterol (mg/dl)	0.27[2]	0.23[1]	−0.10	−0.04	0.03	−0.12	−0.08	−0.03	−0.11	0.09	0.13	−0.12
Total cholesterol (mg/dl)	0.02	0.08	−0.16	0.03	−0.06	0.05	−0.23	−0.13	−0.12	0.01	0.02	−0.06
Exhaled carbon monoxide (ppm)	0.03	0.11	−0.13	−0.02	−0.21	0.31[2]	−0.06	−0.22	0.29[1]	0.04	−0.01	0.12
Blood glucose (mg/dl)	−0.03	−0.24[1]	0.26[2]	0.15	−0.19	0.36[3]	0.08	−0.22	0.34[2]	0.12	−0.19[2]	0.35[4]

* Excludes subjects with angina only.

† Est = estradiol; Test = testosterone; E/T = estradiol-to-testosterone ratio.

Significantly different from zero: [1] $p < 0.10$, [2] $p < 0.05$, [3] $p < 0.01$, [4] $p < 0.001$.

arately, whereas the testosterone level correlated negatively with the blood glucose level in all subjects ($p < 0.05$). The high-density lipoprotein cholesterol level correlated positively with the estradiol level ($p = 0.039$) in the control subjects only. The values in one subject accounted for the correlation between the carbon monoxide level and the estradiol-to-testosterone ratio in the subjects with coronary disease; when values in this subject are excluded, the corresponding correlation coefficients are not significant and would be −0.06 and −0.13. Significant correlations were also observed in all subjects between estradiol and testosterone levels ($r = 0.54$, $p < 0.001$), the estradiol level and the estradiol-to-testosterone ratio ($r = 0.22$, $p = 0.016$), and the testosterone level and the estradiol-to-testosterone ratio ($r = 0.63$, $p < 0.001$).

The mean (± SD) serum levels of luteinizing hormone, follicle-stimulating hormone, progesterone, and DHEAS in the subjects with coronary disease were 75.4 ± 49.9, 409 ± 362, 0.808 ± 0.351, and 1,151 ± 739 ng/ml; values in the control subjects were 72.5 ± 49.0, 377 ± 324, 0.886 ± 0.384, and 1,235 ± 762, respectively. None of the differences between subjects with coronary disease and control subjects was significant, even with the exclusion of subjects with angina only or subjects older than 75 years. The luteinizing hormone level correlated with the follicle-stimulating hormone level in all subjects ($r = 0.85$, $p < 0.001$) and in subjects with coronary disease ($r = 0.84$, $p < 0.001$) and control subjects ($r = 0.86$, $p < 0.001$) calculated separately.

COMMENTS

In the present study, the subjects with coronary disease were men aged 61 to 88 years, were unselected except for a diagnosis of coronary heart disease in the past, and had samples taken nonfasting at random times in the

afternoon. In the previous study [1], the subjects with coronary disease were men aged 34 to 43 years, were selected not only for a diagnosis of myocardial infarction in the past, but also to exclude other disorders, drug intake, and alcoholism, and had samples taken in the morning while fasting. Despite these differences, the results of the two studies are similar. The mean serum estradiol level was significantly higher in the subjects with coronary disease, whereas neither the testosterone level nor the estradiol-to-testosterone ratio was significantly different in the subjects with coronary disease and control subjects. The elevation in mean serum estradiol level persisted when the analysis controlled for risk factors for coronary heart disease. The similar results in two groups at the different ends of the age spectrum for coronary heart disease and tested under disparate conditions support the validity of the finding of hyperestrogenemia in men with a history of coronary heart disease and suggest its importance.

In the previous study [2], furthermore, the area under the glucose curve in the glucose tolerance test correlated with the serum testosterone level but more strongly with the estradiol-to-testosterone ratio. In the present study, similar relationships were observed between a single random blood glucose determination from a sample obtained in the afternoon and the serum testosterone level and the estradiol-to-testosterone ratio. The relationships persisted after analysis controlled for age and obesity, factors known to affect the blood glucose level [11,12]. Thus, in both studies, the estradiol level but not the estradiol-to-testosterone ratio correlated with coronary heart disease, whereas the estradiol-to-testosterone ratio but not the estradiol level correlated with blood glucose. These similar results in the two studies support the hypothesis that an elevation in the estradiol-to-testosterone ratio leads to the glucose-insulin-lipid defect and an elevation in the estradiol level predisposes to coronary heart disease [2,3]. The correlation between the estradiol level and the estradiol-to-testosterone ratio might then explain the association between risk factors such as a high blood glucose level (diabetes) and coronary heart disease. If this is the case, an elevation in the estradiol level without an accompanying elevation in the estradiol-to-testosterone ratio might predispose to coronary heart disease without risk factors. Conversely, an elevation in the estradiol-to-testosterone ratio without an elevation in the estradiol level might lead to risk factors without coronary heart disease. Thus, the risk factors may not be required for or even contribute to the development of coronary heart disease. It is still possible, nevertheless, that some closely related function of estradiol and testosterone other than the estradiol-to-testosterone ratio, possibly including the levels of free estradiol and testosterone or of another hormone(s) such as progesterone [3], might correlate both with coronary heart disease and risk factors.

In the present study, the only established risk factor for coronary heart disease that was significantly different between subjects with coronary disease and control subjects was the blood glucose level. Except for cholesterol, however, other risk factors, i.e., the levels of systolic blood pressure, high-density lipoprotein cholesterol, and cigarette smoking, were in the expected direction. That cholesterol was not in the expected direction is consistent with the observation that the cholesterol level is no longer a risk factor after age 50 [13,14]. The influence of smoking as a risk factor also diminishes with age [15]. The effect of systolic blood pressure [16] may have been masked in this group by the treatment some were receiving. The difference in the mean high-density lipoprotein cholesterol level between subjects with coronary disease and control subjects was 3.8 mg/dl ($p < 0.1$), a difference similar to that of 4.1 found in larger populations over age 60 [17]. In addition, risk factors may have been affected by a change in patient habits after the diagnosis of coronary heart disease. The correlation between estradiol and high-density lipoprotein cholesterol levels in the control subjects in the present study is unexplained but could reflect a different response to this hormone in the subjects with coronary disease. Administration of estrogens to men does cause an increase in high-density lipoprotein levels [18], but this does not mean that an increase in the natural endogenous estradiol will have a similar effect. A correlation between testosterone and high-density lipoprotein cholesterol levels has been reported in men [19–21]; however, administration of testosterone preparations appears to lower high-density lipoprotein levels (22).

The results of measurements of serum estrogens and other hormones in men with coronary heart disease in other laboratories have been conflicting. Hauss et al [23] reported an increase in estradiol levels in men with myocardial infarction or peripheral vascular disease. However, these investigators [24,25] also measured serum testosterone, growth hormone, luteinizing hormone, follicle-stimulating hormone, cortisol, total corticoid, ACTH, and total thyroxine levels and found all of these hormones significantly elevated except for testosterone and total thyroxine, which they found significantly reduced. Pivovarov et al [26] similarly measured a spectrum of hormones in men with "ischemic heart disease" and reported nine to be abnormal, including an increase in estradiol. Except for estradiol, abnormal levels of the hormones just named have not been found by others [2,27–32]. Entrican et al [28] reported higher estradiol and estrone levels in male survivors of myocardial infarction than in age-matched control subjects; subsequent measurements

of estradiol in these same patients, however, showed no significant difference from levels in control subjects [33]. Heller et al [30] found no difference between the estradiol levels in men who had had a myocardial infarction and those in age-matched control subjects. Luria et al [31] observed an elevation in serum estradiol levels in men studied within two weeks of a myocardial infarction and in men with both angina and coronary artery disease on arteriography. Zumoff et al [32] reported normal estradiol levels in men with a history of myocardial infarction and in men with coronary artery disease on arteriography without a history of infarction; however, they reported that estrone, DHEA, and DHEAS levels were elevated in the former group, whereas these levels were normal in the latter. DHEAS levels of subjects with coronary disease and control subjects were not significantly different in the present study. Klaiber et al [34] found an elevation in estradiol levels in men studied on each of the first three days after a myocardial infarction and again three to nine months later, as well as in men with unstable angina. The reason for the differences in results between laboratories is not clear.

The cause of the hyperestrogenemia is not known. That it was the result of an exogenous factor in this study was considered. It could not be attributed to obesity [35,36] since Quetelet's index was controlled for in the analysis of covariance. One possibility is that the hyperestrogenemia in the subjects with coronary disease resulted from a change in diet intended to lower serum lipid levels. However, a change to this type of diet appears, if anything, to lower serum estrogen levels [37]. Another possibility is that more subjects with coronary disease than control subjects may have been consuming drugs that raise the serum estradiol level. For example, digoxin has been reported to increase serum estrogens and decrease serum testosterone [38]. However, no pattern relating a particular drug to estradiol level could be discerned in this study. For example, of the subjects with the 15 highest estradiol levels, only two were taking a digitalis preparation. Serum testosterone, furthermore, was not decreased in the subjects with coronary disease. In the previous study showing hyperestrogenemia in men who had had a myocardial infarction, none of the patients or control subjects was taking any drugs [1]. In two other studies reporting hyperestrogenemia in men with myocardial infarction, the elevation in serum estradiol levels could not be attributed to drugs [28,31]. No other exogenous factor to account for the hyperestrogenemia could be identified.

The mechanism for the hyperestrogenemia is not known. It could not be explained by an elevation in luteinizing hormone since the serum luteinizing hormone and follicle-stimulating hormone levels in the subjects with coronary disease and control subjects were not significantly different in this and other studies [27,32]. More than half of the serum estradiol produced in men appears to come from the peripheral conversion of serum testosterone [39]. This relationship probably accounts for the high degree of correlation observed between estradiol and testosterone in subjects with coronary disease and control subjects, combined ($r = 0.54$, $p < 0.001$) or separately ($p < 0.001$). Of interest is that in this and the previous study [1], as well as in the reports of others [28,30–32], the testosterone level of the subjects with coronary disease was higher than that of the control subjects, although the difference did not reach statistical significance in any of these studies. Thus it is possible that a significantly increased testosterone level might be found in patients with coronary heart disease if a larger series of subjects were studied and that part of the hyperestrogenemia in patients with coronary heart disease might be secondary to a hypertestosteronemia. No other clues as to the mechanism for the hyperestrogenemia were identified in this study.

Whether the hyperestrogenemia preceded the coronary heart disease is not known. Evidence for clinical signs of feminization preceding myocardial infarction [1] and reports of hyperestrogenemia in men with angina [31,34] and coronary artery disease [31] support this possibility. That administration of estrogens to men leads to myocardial infarction [40] suggests that hyperestrogenemia may also predispose to myocardial infarction. If this is the case, the highly significant association of hyperestrogenemia with coronary heart disease in men in both a younger age group [1] and in this study in an older age group in which established risk factors become weak or nonexistent [13–15] would suggest the importance of hyperestrogenemia as a predisposing factor.

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