Endogenous Sex Hormones and Cardiovascular Disease in Men
A Prospective Population-Based Study

Elizabeth Barrett-Connor, MD, and Kay-Tee Khaw, MRCP, MSc

Plasma obtained and frozen in 1972–1974 from 1,009 white men (40–79 years old) who have been followed for 12 years was examined for endogenous sex hormone levels according to prevalent or subsequent cardiovascular disease. In these older men, no sex hormone measured (testosterone, androstenedione, estrone, or estradiol) was significantly associated with known cardiovascular disease at baseline or with subsequent cardiovascular mortality or ischemic heart disease morbidity or mortality. Sex hormone–binding globulin levels were also similar by disease status. Analyses of hormone: sex hormone–binding globulin ratios or of estrogen: androgen ratios showed a similar lack of association with cardiovascular disease. Testosterone levels were significantly inversely associated with levels of blood pressure, fasting plasma glucose, and triglyceride and body mass index. In contrast, the only significant estrogen risk factor associations were positive correlations of estrone with total plasma cholesterol, triglyceride, and glucose. These data do not support a causal role for elevated endogenous estrogen levels and heart disease. (Circulation 1988;78:539–545)

Among the many risk factors for cardiovascular disease, few are more important than male sex.1,2 Several case-control studies have tested the hypothesis that one or more endogenous sex hormones are related to cardiovascular disease risk in men. Most investigators found significantly elevated endogenous estrone and/or estradiol levels,3–10 but some reported significantly lower testosterone levels3,11–13 or no significant difference in estrogens or testosterone14,15 in men who had survived a myocardial infarction compared with men who had not had an infarction. Based on results of coronary angiography, some case-control studies reported higher levels of estradiol in men who had coronary artery stenosis compared with men without coronary artery stenosis,16,17 but a majority did not.6,10,18–20 One prospective study of endogenous sex hormones and cardiovascular risk has been published, the 6–8-year follow-up of disease-free but high-risk men recruited to the Multiple Risk Factor Intervention Trial.21 This study, based on stored sera from 163 men who had a definite myocardial infarction or coronary heart disease death and 163 controls matched for age, clinic, randomization group, and baseline cholesterol, found no significant differences between cases and controls in baseline total or free estradiol, total or free testosterone, or androstenedione or estrone. Taken as a whole, the case-control studies suggest that endogenous estrogen either is causally related to infarction or prevents death after infarction. In contrast, results of the prospective study do not support a causal association unless one postulates that an estrogen–heart disease association is obscured in men who have high cardiovascular disease risk for other reasons.

We report here a prospective population-based study of 1,009 men who were followed for 12 years after baseline evaluation for heart disease risk factors was completed and blood was obtained for sex hormone assays.

Subjects and Methods
Between 1972 and 1974, 2,023 white men (40–79 years old) who were residents of Rancho Bernardo, a geographically defined community in southern California, were studied as part of a Lipid Research Clinic prevalence study. The participation rate was 82%, and participants did not differ significantly

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from the target population. All participants were ambulatory and without acute illness at the time of the visit. Height, weight, and blood pressure were measured by a standard protocol; a personal history of heart disease, hypertension, stroke, and diabetes, as well as a personal history of cigarette smoking and exogenous gonadal hormone use, was obtained by a trained interviewer using a standardized questionnaire. Blood pressure in seated subjects was measured with a standard mercury sphygmomanometer. Height and weight were measured with the participants wearing light clothing and no shoes. Plasma was obtained by venipuncture between 7:30 and 11:00 AM from fasting subjects. Total plasma cholesterol and triglyceride were measured in a standardized Lipid Research Clinic laboratory; lipoprotein levels were not determined at this visit. Fasting plasma glucose was measured in a hospital diagnostic laboratory with a hexokinase method for true glucose.

Specimens for the sex hormone assays were kept frozen at −70°C and first thawed in 1984–1986 for hormone assays. Analyses showed no trend for decreased hormone levels in specimens frozen for longer periods; previous work in this laboratory had demonstrated no hormone deterioration over 15 years when sera were frozen and stored in tightly sealed containers. The selection of samples was based only on the availability of frozen plasma in the men aged 40–79 years at the baseline evaluation who were not taking exogenous hormones. Hormone assays were performed blind to current or subsequent disease or death in a research laboratory with a radioimmunoassay method for endogenous sex hormones. The sensitivity and the intra-assay and interassay coefficients of variation, respectively, were androstenedione 30 pg/ml, 4.0% and 8.0%; testosterone 25 pg/ml, 4.1% and 10.0%; estrone 7 pg/ml, 15.0% and 16.0%; and estradiol 5 pg/ml, 8.0% and 12.0%. Sex hormone–binding globulin, which binds testosterone and estradiol, was determined by the method of Rosner.

This cohort was followed yearly for vital status for an average of 12 years, with 99.8% ascertainment. Death certificates were obtained for all decedents. Underlying cause of death was coded by a certified nosologist according to the Eighth Revision of the ICDA; cardiovascular disease encompassed codes 400–438 and ischemic heart disease encompassed codes 410–414. In one third of the cohort, all death certificates with any mention of cardiovascular disease, hypertension, or diabetes were validated by interviews with next of kin, physicians, and hospital records. A mortality classification panel determined that these data supported the nosologist diagnosis in 86%. Ischemic heart disease morbidity was determined in 1983 by the use of a postal questionnaire and in 1984–1986 by interviews. In 1983, validation of self-reported heart attack (by chest pain, enzyme elevation, and electrocardiogram) was achieved for 72% of the 173 cases in which hospital records could be obtained.

The hormone distributions, particularly sex hormone–binding globulin, were slightly skewed. Analyses were undertaken with both real and log-transformed hormone values; because results were similar, the logarithmic analyses are not shown. Both the age-adjusted partial correlation coefficients of cardiovascular risk factors with hormone levels and the mean crude and age-adjusted hormone levels by cardiovascular risk factor category, dichotomized by clinical criteria, were calculated.

Mean hormone levels (age specific and age adjusted with analysis of variance) were determined for all men aged 40–79 years according to the presence or absence of known cardiovascular disease (a personal history of heart attack, heart failure, or stroke) at baseline and according to subsequent cardiovascular mortality; in the latter analysis, subjects with cardiovascular disease at baseline were excluded to remove men whose hormone levels might vary as a consequence of disease or its treatment. Crude and age-adjusted (by the Mantel-Haenzel procedure) cardiovascular mortality rates by tertile of each hormone were also examined. The Cox proportional hazards model was used to determine the independent contribution of each hormone to cardiovascular death, after age adjustment alone and after adjusting for age and other classic cardiovascular risk factors (cigarette smoking, systolic blood pressure, fasting plasma glucose, cholesterol, and body mass index). To examine any possible effect of season or year of venipuncture on measurable hormone levels, we also undertook a nested case-control analysis for all ischemic heart disease deaths, selecting as controls men who had no subsequent cardiovascular disease at follow-up; each case had a control matched for age and date of visit.

Results

Table 1 shows the age, baseline, and subsequent cardiovascular disease distribution in the 1,009 men aged 40–79 for whom hormone assays were performed.

Age-adjusted partial correlation coefficients of sex hormones with other cardiovascular risk factors for all men and for those without cardiovascular disease at baseline were similar and changed little by further adjustment for obesity. In men without cardiovascular disease at baseline, androstenedione was positively and significantly (p<0.01) associated with total cholesterol and negatively associated with obesity (Table 2). Testosterone was negatively and significantly (p<0.01) associated with blood pressure, triglyceride, fasting plasma glucose, and obesity but was not associated with total cholesterol. Estrone, but not estradiol, was positively and significantly (p<0.01) associated with total cholesterol, triglyceride, and fasting plasma glucose. At similar levels of statistical significance, sex hormone–binding globulin was negatively associated with
obesity, diastolic blood pressure, total cholesterol, triglyceride, and fasting plasma glucose.

Table 3 shows the mean age-adjusted hormone levels by categorically defined risk factors in men without cardiovascular disease at baseline. Again, higher androgen levels tended to be associated with more favorable risk factor status, the exception being cigarette smoking. In contrast, hypercholesterolemia, hyperglycemia, and cigarette smoking were associated with significantly higher levels of estrone. Estradiol was unrelated to categorical risk factors in these men. Sex hormone–binding globulin was most strongly and inversely associated with obesity.

No sex hormone measured was significantly associated with cardiovascular or ischemic heart disease either cross-sectionally (Table 4) or prospectively (Table 5) after excluding those with baseline cardiovascular disease from the analysis. As shown in Table 4, the 132 men with a history of cardiovascular disease at baseline (1972–1974) had lower age-adjusted levels of androgens and higher estradiol and sex hormone–binding globulin levels than men without such a history, but none of these differences approached statistical significance (at $p<0.10$).

Mean estrone levels were identical in men with and without a history of cardiovascular disease. Similarly, only slightly and not significantly lower androgens and higher estrogens were seen in men free of known heart disease at baseline who later died with fatal cardiovascular or ischemic heart disease (Table 5). Mean baseline hormone levels were similar in the 35 men with nonfatal myocardial infarction compared with those with fatal ischemic heart disease cases and with men with no ischemic heart disease (data not shown).

We also examined mean hormone levels by 12-year ischemic heart disease status separately in men less than 60 years old at baseline. Larger but not statistically significant hormone differences between men with and without fatal heart disease were seen in these younger men. In the 266 men less than 60 years old who were free of known cardiovascular disease at baseline, the eight men who subsequently had a fatal heart attack had higher baseline estrone levels and lower baseline testosterone and estradiol levels than the men who did not (estrone levels, $56 \pm 18$ vs. $47 \pm 17$ pg/ml, respectively, $p=0.22$; estradiol levels, $33 \pm 9$ vs. $36 \pm 9$ pg/ml, respec-
tively, \( p = 0.41 \); and testosterone levels, \( 4.761 \pm 1.270 \) vs. \( 5.370 \pm 1.657 \) pg/ml, respectively, \( p = 0.23 \)).

In men free of known heart disease at baseline, the age-adjusted 12-year cardiovascular and ischemic death rates were also examined by tertile of each hormone. Rates did not vary significantly or consistently by tertile, either in the whole cohort (Table 6) or in men less than 60 years old (not shown). There was also no effect of season or year of venipuncture on hormone levels, based on a nested case-control comparison of men who died with ischemic heart disease and their controls matched for age, sex, and date of visit.

A Cox proportional hazards analysis adjusting for the classic heart disease risk factors (including blood pressure, plasma lipids and glucose, cigarette smoking, and obesity) did not materially alter the absent association of endogenous hormone levels with outcome. For example, the age- and risk factor–adjusted relative risks of testosterone for cardiovascular death were 0.94 (confidence limits, 0.08–1.4) and for ischemic heart disease death were 1.05 (confidence limits, 0.84–1.31). Multivariate analyses were also performed after adjusting for sex hormone–binding globulin (with the testosterone: sex hormone–binding globulin or estradiol: sex hormone–binding globulin ratio as a surrogate for free testosterone or estradiol) with similar results. In contrast, both age and systolic blood pressure independently predicted fatal cardiovascular and fatal ischemic heart disease in this cohort (\( p<0.001 \) for age and blood pressure; data not shown).

### Discussion

In this prospective population-based study of older men, none of the androgens or estrogens measured in frozen plasma were significantly associated with the risk of subsequent death from cardiovascular disease or myocardial infarction. Why are these results at variance with a majority of case-control studies of survivors of myocardial infarction but similar to the absent association reported in most angiographic studies of men with coronary artery disease and in the prospective study of high-risk men studied in the Multiple Risk Factor Intervention Trial? The limitations of a single measurement of any biological variable for epidemiological studies are well known. This limitation should apply equally to the published cross-sectional and to prospective studies such as this one, however. Though only a single hormone estimation was used, several studies have suggested that the error in a single estimation is no worse than that of other biological variables, including cholesterol; the interindividual variation is greater than intraindividual variation.
and a single morning specimen is reportedly adequate to characterize the testosterone of individuals. In the present study, all blood was obtained from fasting subjects in the morning to control for circadian variation in hormone levels. In addition, matching on season of sampling and on date of visit did not alter the results, so the lack of associations are unlikely to be attributable to seasonal variation in endogenous hormone levels.

Most of the case-control studies with positive findings reported higher endogenous estrogen (estrone or estradiol) levels in survivors of myocardial infarction but similar androgens. Case-control studies are not obliged to use frozen serum or plasma, and it is possible that endogenous estrogens are less stable in frozen plasma than androgens, although there is no evidence for this. A low level of hormone, approaching the sensitivity of the assay method, could make any loss in storage more misleading; the average estrogen levels reported here are consistent with expected estrone and estradiol levels in middle-aged men and well above the assay sensitivity. The average levels of estrogen measured in blood frozen in 1972 were no lower than levels in blood obtained and frozen in 1974. Therefore, loss of estrogen in frozen plasma seems an unlikely explanation for the absence of an estrogen heart disease association in our cohort.

Published studies of higher endogenous estrogen levels in male survivors of myocardial infarction compared with male controls3-10 and the much less consistent association of endogenous estrogen levels with atherosclerosis in angiographically studied men10,16-20 are compatible with the hypothesis that higher estrogen levels improve survival after a heart attack rather than cause atherosclerosis. In our cohort, however, hormone levels were similar in the men with or without known heart disease at baseline and in the men with or without incident nonfatal myocardial infarction. Similarly, in the Multiple Risk Factor Intervention Trial, the sex hormone levels did not differ in men with both fatal and nonfatal heart disease compared with men without. Thus, a survivorship benefit seems an unlikely explanation for the differences between case-control and prospective studies.

Though most case-control studies measured only total hormone levels without accounting for protein binding, it has been suggested that only the free (i.e., unbound) hormones might be biologically significant. However, the Multiple Risk Factor Intervention Trial measured both free and bound hormones and found no association with coronary artery disease. Similarly, in this cohort, hormone:sex hormone–binding globulin ratios, used as surrogate estimates for free hormones, were also not related to cardiovascular disease.

Hospitalization and stress after a heart attack could mediate changes in endogenous hormones, but all of the published case-control studies of myocardial infarction cited here were conducted at least 2 months after the acute event. It is possible that some lifestyle change or medication commonly used after myocardial infarction caused higher estrogen levels in cases compared with controls. For example, digitalis has been reported to raise estrogen levels. Another possible confounder not excluded in most case-control studies is cigarette smoking, which is associated with both higher estrogen levels and an increased risk for cardiovascular disease. In the present study, the proportion of current cigarette smokers was low (19%), and analysis controlling for smoking did not significantly change the results. Alternatively, some postinfarction behavior change in exercise or diet could lead to altered hormone levels.

The average age of men in this cohort was 63 years. It is possible that the estrogen heart disease association is seen only in younger men. In this cohort, estradiol levels were lower and estrone levels were higher, although not significantly so, in men less than 60 years old whose death was attributed to ischemic heart disease. Although the early case-control studies studied younger men, significantly higher estradiol levels were reported by Phillips et al in postinfarction men whose average age was 70 years. Therefore, age of the population studied seems unlikely to explain the lack of a hormone–heart disease association.

Misclassification as to cause of death based on death certificates, as used in the present study, could be more likely than misdiagnosis based on hospital records, as used in case-control studies. As noted, we confirmed the death certificate diagnosis in 86% of cardiovascular deaths for whom valida-

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**Table 4. Mean Crude and Age-Adjusted* Hormone Levels by Personal History of Cardiovascular Disease in Rancho Bernardo Men 40–79 Years Old in 1972–1974**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>No history of cardiovascular disease (n = 872)</th>
<th>History of cardiovascular disease (n = 137)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>836 (345)</td>
<td>761 (241)</td>
<td>0.24</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>831</td>
<td>796</td>
<td></td>
</tr>
<tr>
<td>Testosterone (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>5,361 (1,824)</td>
<td>5,350 (1,833)</td>
<td>0.95</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>5,355</td>
<td>5,345</td>
<td></td>
</tr>
<tr>
<td>Estrone (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>49 (18)</td>
<td>50 (21)</td>
<td>0.83</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>49</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>37 (11)</td>
<td>38 (13)</td>
<td>0.31</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>37</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Sex hormone–binding globulin (×10^-6 M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>321 (184)</td>
<td>344 (242)</td>
<td>0.91</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>324</td>
<td>326</td>
<td></td>
</tr>
</tbody>
</table>

*Age adjusted by analysis of variance.
tion was sought. The Multiple Risk Factor Intervention Trial, which also found no association of sex hormones to subsequent cardiovascular disease, validated all cases and used very strict definitions of cardiovascular disease and coronary heart disease death. Therefore, endpoint misclassification seems unlikely to explain the lack of hormone heart disease association in these two prospective studies.

A negative study, of course, raises the question of statistical power, but it is unlikely that a larger study would demonstrate a statistically and clinically significant hormone–heart disease association. There were 82 ischemic heart disease deaths in this cohort, more cases than were reported in any cross-sectional study except that of Goldberg et al., who found no association of endogenous estrogen with coronary artery stenosis. Based on the events rate for ischemic heart disease in this cohort, at a power of 0.90 and α = 0.05, the potentially detectable differences are comparable with those reported in other studies where significant differences have been found.

If a prospective study were to reveal any significant hormone–heart disease association, our data suggest that an androgen deficit, not an estrogen excess, would be found in men with heart disease. The most consistent finding in the present study was the lower level of testosterone associated with cardiovascular risk factors and disease. Further, the inverse association of plasma testosterone with several major heart disease risk factors noted in the present and other studies makes it a protective effect of testosterone biologically plausible, whereas there is no similar mechanism (through more favorable risk factor status) attributable to high endogenous estrogen levels in men. Men with lower levels of plasma testosterone also tend to have lower levels of high-density lipoprotein cholesterol and lipoprotein lipase. In nearly all case-control studies that measured testosterone, and in the prospective Multiple Risk Factor Intervention Trial, testosterone levels were lower in men with ischemic heart disease, although, as in the present study, differences were not always statistically significant.

Although the present study, like its predecessors, does not completely resolve the question of whether endogenous gonadal hormones are related to cardiovascular disease risk in men, these data make it increasingly unlikely that higher plasma estrogens are causally related to cardiovascular disease in older men. In any case, if higher estrogen levels or lower testosterone levels were associated with increased cardiovascular risk, the male preponderance in ischemic heart disease would be even less explicable in terms of endogenous sex hormones per se. Investigation of the sex-, age-, and possible dose-related differences in the relation of similar hormones to cardiovascular risk factors may be more fruitful in terms of elucidating mechanisms for cardiovascular disease.

### References

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### Table 5. Mean Crude and Age-Adjusted* Hormone Levels by 12-Year Mortality in Rancho Bernardo Men 40–79 Years Old in 1972–1974 With No Personal History of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Mean (SD)</th>
<th>p value</th>
<th>Ischemic heart disease death</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 758)</td>
<td>Yes (n = 114)</td>
<td></td>
<td>No (n = 790)</td>
</tr>
<tr>
<td>Androstenedione (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>848</td>
<td>752</td>
<td>&lt;0.01</td>
<td>842</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>837 (351)</td>
<td>815 (278)</td>
<td>0.52</td>
<td>835 (349)</td>
</tr>
<tr>
<td>Testosterone (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>5,382</td>
<td>5,206</td>
<td>0.32</td>
<td>5,380</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>5,412 (1,839)</td>
<td>5,210 (1,727)</td>
<td>0.29</td>
<td>5,385 (1,840)</td>
</tr>
<tr>
<td>Estrone (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>49 (18)</td>
<td>49 (17)</td>
<td>0.86</td>
<td>49 (18)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>48</td>
<td>48</td>
<td>0.81</td>
<td>49</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>37 (11)</td>
<td>37 (10)</td>
<td>0.98</td>
<td>37 (11)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>37</td>
<td>36</td>
<td>0.62</td>
<td>37</td>
</tr>
<tr>
<td>Sex hormone–binding globulin (× 10⁻⁶ M)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>315 (178)</td>
<td>353 (216)</td>
<td>0.08</td>
<td>317 (177)</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>321</td>
<td>320</td>
<td>0.97</td>
<td>320</td>
</tr>
</tbody>
</table>

*Age-adjusted by analysis of variance.

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### Table 6. Age-Adjusted 12-Year Ischemic Heart Disease Mortality Rates in Rancho Bernardo Men 40–79 Years Old With No History of Cardiovascular Disease by Tertile of Hormone Distribution

<table>
<thead>
<tr>
<th>Tertile (%)</th>
<th>Lowest</th>
<th>Middle</th>
<th>Highest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androstenedione</td>
<td>10.5</td>
<td>9.2</td>
<td>8.9</td>
</tr>
<tr>
<td>Testosterone</td>
<td>8.8</td>
<td>11.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Estrone</td>
<td>9.9</td>
<td>8.6</td>
<td>9.6</td>
</tr>
<tr>
<td>Estradiol</td>
<td>10.3</td>
<td>8.3</td>
<td>9.1</td>
</tr>
<tr>
<td>Sex hormone–binding globulin</td>
<td>9.0</td>
<td>10.0</td>
<td>10.1</td>
</tr>
</tbody>
</table>

**KEY WORDS** • estrogen • prospective studies • testosterone • ischemic heart disease
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