Abnormal Hormone Levels in Men with Coronary Artery Disease


Plasma concentrations and urinary excretions of various hormones and hormone metabolites were measured in four groups. Group 1 was composed of 13 men with prior myocardial infarction; Group 2 contained 35 clinically normal men; Group 3 consisted of 44 men with normal coronary arteriograms; and Group 4 was composed of 25 men with severe coronary artery disease shown on arteriogram but no infarction. There were four major findings: Group 1 had significantly higher 24-hour mean plasma concentrations of estrone (E1), dehydroisoandrosterone (DHA), and dehydroisoandrosterone sulfate (DHAS) than Group 2, while Group 3 had the same levels as Group 4; Group 4 had significantly lower urinary excretion of androsterone glucuronide (AG) than Group 3, while Group 1 excreted normal amounts. There are three possible explanations for these findings: 1) myocardial infarction occurring in men with coronary artery disease may elevate the plasma levels of E1, DHA, and DHAS and eliminate the preinfarction depression of urinary AG levels; 2) higher than average levels of E1, DHA, DHAS, and AG may favor the development of infarction in men with coronary artery disease; 3) higher than average levels of E1, DHA, DHAS, and AG may favor survival from any infarction that occurs in men with coronary artery disease. Experimental and epidemiological evidence seems to favor the third possibility.


The classical, established risk factors for coronary artery disease are hyperlipidemia, hypertension, and cigarette smoking. In addition, the fact that women show a strikingly lower death rate from coronary disease than men has been recognized for over 40 years.1,2 This observation has focused interest on hormonal factors in the disease. A number of groups3-14 have investigated the hormonal status of men with coronary disease. Earlier studies3-7 measured urinary hormone excretion and described abnormalities of estrogen,4-5 androgen,3-6,7 and corticoid8 metabolite excretion. More recent studies have described plasma hormone levels, using radioimmunoassay methods. Six studies8-13 have reported elevated plasma estrogen levels, one8 has reported elevated plasma cortisol levels, and two8,13 have reported elevations of many different hormones.

All these studies considered only patients who had had one or more myocardial infarctions. Because any abnormalities found in such patients might result from the infarction itself, we felt it essential to study patients with proven coronary artery disease, as defined by the presence or arteriographically demonstrated coronary artery stenosis, who had never had a myocardial infarct and to compare their data with those of arteriogram-negative men and men who had had myocardial infarcts.
Methods

Groups of Men Studied

Group 1: Postinfarction Patients

Group 1 consisted of 13 men aged 35 to 56 years (mean ± so = 48 ± 5.9 years) who had had one or more myocardial infarctions. Infarction was established in 11 cases by a typical history, typical electrocardiographic changes, and typical enzyme changes; in one case, by a typical history, an abnormal electrocardiogram compatible with prior infarction, and the presence of an adynamic segment of ventricular wall on ventriculography; in one case, by the presence of an adynamic segment and nonspecific electrocardiographic abnormalities. In every case, the infarction had taken place a minimum of 6 months before our studies and the patient was clinically well, ambulatory, working or capable of working, and taking no medication, except nitrates in a few cases. No patient had congestive heart failure, hypertension, diabetes, or other major past or current disease; none had had a coronary bypass; none was significantly obese (more than 20% above desirable weight); and all had normal thyroid, kidney, and liver function.

Group 2: Clinically Normal Controls

This group contained 35 men aged 21 to 85 years (mean ± SD = 44 ± 16 years) who were free of any significant past or current disease, on the basis of a complete history, physical examination, and screening laboratory tests (SMA-6, SMA-12, complete blood count, chest x-ray, and electrocardiogram), and who were taking no medication. For plasma hormonal parameters that show secular aging changes (testosterone, dehydroisoandrosterone, dehydroisoandrostenedione sulfate, androsterone, androsterone sulfate and follicle-stimulating hormone), only those values from the 16 age-matched controls (mean ± so = 48 ± 5.5 years) were compared with those of the postinfarction patients; for all other plasma hormonal parameters, values from the total control group were compared with those of the patients.

Group 3: Men with Normal Coronary Arteriograms

In this group there were 44 men, aged 35 to 55 years (mean ± so = 43 ± 5 years) who had been referred to the United States Air Force School of Aerospace Medicine (USAFSAM) for cardiac evaluation because of minor electrocardiographic abnormalities and/or arrhythmias observed in routine electrocardiograms. As part of this evaluation, they had negative coronary arteriograms (defined as no more than minimal roughening in any artery). Men with significant past or current disease or significant abnormalities on screening laboratory tests and men taking medication of any kind were excluded from study.

Group 4: Men with Positive Coronary Arteriograms

This group contained 25 men, aged 35 to 55 years (mean ± SD = 50 ± 5 years) similarly referred to USAFSAM and similarly studied, who were found to have positive arteriograms (defined as more than 50% occlusion of the lumen of one or more arteries). The exclusionary clinical and laboratory criteria were the same as for Group 3. Two of the men originally considered to belong in this group were found to have adynamic ventricular wall segments by ventriculography; in one, an earlier history of typical infarction symptoms was elicited retrospectively, and his electrocardiogram was considered to be compatible with prior infarction. Both men were reclassified into the postinfarction group (Group 1).

Design of the Study

All the men in Groups 1 and 2 had 24-hour plasma hormone studies, as previously described, in the clinical Research Center of Montefiore Hospital and Medical Center. Nine men in Group 1 and four men in Group 2 had 24-hour urine collections for hormone analysis while in the Center. All the men in Groups 3 and 4 had a 24-urine collection early during their evaluation at USAFSAM. The urines were sent to Montefiore Hospital for "blind" analysis; the code was broken after the analysis was complete. Sixteen men from Group 2 (mean age ± so = 43 ± 4 years) and 13 men from Group 4 (mean age ± so = 50 ± 6 years) traveled from their homes to Montefiore Hospital for a 24-hour plasma hormone study; before the study was done, they rested at least 1 day for each time zone traversed.

Parameters Measured

In the plasma studies, the 24-hour mean plasma concentration of 14 hormones or hormone metabolites were measured: cortisol, testosterone, dihydrotestosterone, dehydroisoandrosterone sulfate, androsterone, androsterone sulfate, estrone, estradiol, triiodothyronine, thyroxine, luteinizing hormone, follicle-stimulating hormone, and prolactin. In the urine studies, 15 hormones or hormone metabolites were measured: testosterone glucuronide, dihydrotestosterone glucuronide, androsterone glucu-
Analytical Methods

Plasma cortisol was determined by competitive protein-binding,14 testosterone and dihydrotestosterone were determined as described by Boyar et al.,17 dehydroisoandrosterone was determined as described by Rosenfeld et al.,18 dehydroisoandrosterone sulfate was determined as described by Nieschlag et al.,19 androsterone and androsterone sulfate were determined as described by Kream et al.,20 triiodothyronine and thyroxine were determined as described by O'Connor et al.,21 estrone and estradiol were determined as described by Zumoff et al.,22 luteinizing hormone and follicle-stimulating hormone were determined as described by Midgely,23-24 and prolactin was determined as described by Sinha et al.25 Free cortisol was extracted from urine and quantitated as described previously.28 All other steroids in plasma were determined by radioimmunoassay, by the same methods as previously described.15

The 24-hour mean plasma hormone concentrations were determined by sampling blood from an indwelling venous catheter every 20 minutes, pooling aliquots from each of the 72 samples, and measuring the hormone concentrations of the pool, as previously described.15

Statistical Methods

Most of the plasma hormone and hormone metabolite concentrations showed log-normal rather than normal distribution. Geometric means as well as arithmetic means were calculated for each substance, and two comparisons

Table 1. Plasma Hormone Levels that Were Not Significantly Different In Normal and Postinfarction Men

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Normal (n = 35)</th>
<th>Postinfarction (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (μg/dl)</td>
<td>7.0 ± 1.4</td>
<td>7.3 ± 1.3</td>
</tr>
<tr>
<td>Androsterone sulfate (μg/dl)</td>
<td>47 ± 27</td>
<td>66 ± 48</td>
</tr>
<tr>
<td>Thyroxine (μg/dl)</td>
<td>6.3 ± 2.2</td>
<td>5.0 ± 0.9</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>421 ± 104</td>
<td>463 ± 187</td>
</tr>
<tr>
<td>Dihydrotestosterone (ng/dl)</td>
<td>102 ± 30</td>
<td>121 ± 33</td>
</tr>
<tr>
<td>Androsterone (ng/dl)</td>
<td>57 ± 18</td>
<td>71 ± 36</td>
</tr>
<tr>
<td>Triiodothyronine (ng/dl)</td>
<td>57 ± 16</td>
<td>91 ± 21</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>57 ± 18</td>
<td>91 ± 21</td>
</tr>
<tr>
<td>Luteinizing hormone (mIU/ml)</td>
<td>12 ± 6.1</td>
<td>14 ± 5.3</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (mIU/ml)</td>
<td>9.9 ± 3.1</td>
<td>9.2 ± 6.5</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>12 ± 6.5</td>
<td>12 ± 4.3</td>
</tr>
</tbody>
</table>

All values are arithmetic means ± standard deviation.

*Only the 16 age-matched controls were compared with postinfarction patients for dehydroisoandrosterone sulfate, testosterone, androsterone, androsterone sulfate and follicle-stimulating hormone, because the concentrations of these hormones vary with age.

†The mean value for the postinfarction group excludes the three grossly subnormal values (see fig. 4).

Table 2. Plasma Hormone Levels In Men with Positive or Negative Coronary Arteriograms

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Positive (n = 13)</th>
<th>Negative (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (μg/dl)</td>
<td>6.7 ± 1.4</td>
<td>6.6 ± 1.2</td>
</tr>
<tr>
<td>Dehydroisoandrosterone sulfate (μg/dl)</td>
<td>105 (39-285)</td>
<td>142 (51-396)</td>
</tr>
<tr>
<td>Androsterone sulfate (μg/dl)</td>
<td>61 ± 45</td>
<td>82 ± 34</td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>478 ± 184</td>
<td>533 ± 178</td>
</tr>
<tr>
<td>Dihydroisoandrosterone (ng/dl)</td>
<td>117 ± 44</td>
<td>114 ± 41</td>
</tr>
<tr>
<td>Androsterone (ng/dl)*</td>
<td>361 (168-778)</td>
<td>422 (238-748)</td>
</tr>
<tr>
<td>Triiodothyronine (ng/dl)</td>
<td>80 ± 18</td>
<td>81 ± 28</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>62 (37-103)</td>
<td>57 (32-100)</td>
</tr>
<tr>
<td>Luteinizing hormone (mIU/ml)</td>
<td>26 ± 10</td>
<td>32 ± 14</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (mIU/ml)</td>
<td>11 ± 2.3</td>
<td>13 ± 5.5</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>13 ± 5.8</td>
<td>13 ± 8.8</td>
</tr>
</tbody>
</table>

*Values are geometric mean, with 95% confidence limits in parentheses. All other values are arithmetic mean ± standard deviation.
were made for all of them: Group 1 vs Group 2, and Group 3 vs Group 4. The results for 11 substances that showed no difference between Group 1 and Group 2 (see Results section) are presented in table 1 as arithmetic means with standard deviations, for simplicity. Geometric means and 95% confidence limits are listed in the table for the three substances that did differ (estrone, dehydroisoandrosterone, and dehydroisoandrosterone sulfate); the individual data points were plotted logarithmically, and the significance of the Group 1 vs Group 2 differences were calculated by applying Student's \( t \) test, two-tailed and unpaired, to the logarithms of the plasma concentration.

Comparison of Group 3 vs Group 4 showed no difference for any of the 13 plasma substances measured. Table 2, which presents these data, contains arithmetic means and standard deviations for the 10 substances so presented in table 1, and geometric means and 95% confidence limits for the other three substances, to facilitate comparison with the means shown for them in table 1.

In evaluating the statistical significance of the difference in urinary androsterone glucuronide excretion between Group 3 and Group 4, we used both Student's \( t \) test and the \( \chi^2 \) test with respect to the Group 3 mean level as a discriminant, as further discussed in the Results section.

**Results**

**Plasma Hormone Concentrations**

**Group 1 vs Group 2**

Eleven of the 14 hormones and hormone metabolites measured showed no significant difference between these groups (table 1); in the case of T3 (figure 1), three of the men in Group 1 had subnormal levels (56, 62, and 66 ng/dl) but nine others had values whose range and mean were essentially identical to those of Group 2; (T3 was not determined in the 13th member of this group). The other three hormones, estrone (E1), dehydroisoandrosterone (DHA), and dehydroisoandrosterone sulfate (DHAS), showed significant differences between Groups 1 and 2: the geometric mean E1 in Group 1 (80 pg/ml; 95% confidence limits [CL] 49 to 131) was elevated compared with that of Group 2 (49 pg/ml; 95% CL 24 to 98) \( (p < 0.0001) \) (figure 2); the geometric mean DHA in Group 1 (444 ng/dl; 95% CL 198 to 995) was elevated compared with that of Group 2 (298 ng/dl; 95% CL 143 to 619) \( (p < 0.025) \) (figure 3), and the geometric mean DHAS in Group 1 (112 \( \mu \)g/dl; 95% CL 36 to 347) was elevated compared with that of Group 2 (72...
Figure 3. 24-hour mean plasma dehydroisoandrosterone concentration in normal men and in men who have had a myocardial infarction. $p < 0.025$.

Figure 4. 24-hour mean plasma dehydroisoandrosterone sulfate concentration in normal men and in men who have had a myocardial infarction. $p < 0.025$.

Figure 5. Urinary excretion of androsterone glucuronide in men with positive or negative coronary arteriograms. $\chi^2 = 10.9; p < 0.001; t = 2.16; p < 0.05$. 

It is noteworthy that for each of these three hormones all but one of the postinfarction patients (Group 1) had values that were at or below the upper 95% confidence limit of the control values (Group 2); the significant difference between groups was due in each case to clustering of the patients' values in the upper half of the normal range. This point bears on the interpretation of the results, as will be amplified in the Discussion.

Group 3 vs Group 4

None of the 13 hormones and hormone metabolites measured (thyroxine was omitted in this case) showed a significant difference between these two groups (table 2), including E1, DHA, and DHAS. Interestingly, the combined arteriogram group (i.e., positives plus negatives) had significantly higher mean plasma levels of DHA, DHAS, androsterone, and androsterone sulfate.
Table 3. Plasma Hormone Levels that Were Significantly Higher in the Combined Arteriogram Group than in Normal Men

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Normal men (n = 16)</th>
<th>Arteriogram group (n = 29)</th>
<th>Percentage difference (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydroisoandrosterone (ng/dl)</td>
<td>298 (143–619)</td>
<td>394 (201–771)</td>
<td>32 &lt; 0.025</td>
</tr>
<tr>
<td>Androsterone (ng/dl)</td>
<td>57 ± 18</td>
<td>80 ± 23</td>
<td>40 &lt; 0.001</td>
</tr>
<tr>
<td>Dehydroisoandrosterone sulfate (µg/dl)</td>
<td>83 ± 48</td>
<td>140 ± 65</td>
<td>69 &lt; 0.001</td>
</tr>
<tr>
<td>Androsterone sulfate (µg/dl)</td>
<td>47 ± 27</td>
<td>73 ± 40</td>
<td>55 &lt; 0.025</td>
</tr>
</tbody>
</table>

All values are arithmetic means ± standard deviation except dehydroisoandrosterone, which for comparability with table 4 is given as geometric mean with 95% confidence limits in parentheses.

than the normal controls (table 3). It is not clear why the military group showed higher levels of adrenal androgens and androgen metabolites than did the civilian controls; the mean age of the two groups (47 ± 5 and 44 ± 16 years, respectively) and mean percentage deviation from ideal weight (12 ± 8 and 14 ± 7, respectively) did not differ significantly.

**Urinary Hormone Excretion**

**Group 3 vs Group 4**

Of the 15 hormones and hormone metabolites studied, 14 showed no difference between these groups (table 4). Only androsterone glucuronide showed a difference (3.2 ± 1.1 mg/g creatinine in Group 3 vs 2.6 ± 0.9 mg/g creatinine in Group 4; figure 5). Using Student's t test, two-tailed and unpaired, we found the difference to be significant (p < 0.05). An alternative statistical treatment, using the negative arteriogram group's mean excretion of 3.2 mg/g creatinine as a "discriminant" and comparing the number of persons in each group with excretion above or below this value, yielded a χ² value of 10.9, equivalent to a statistical significance of p < 0.001 for the difference between groups.

**Comparison of Androsterone Glucuronide Excretion In All Groups**

Figure 6 shows that the means and ranges of Groups 1, 2, and 3 were similar. Group 4, the men with positive arteriograms, showed extremes of range that were also similar to those of the other three groups, but 85% of the values were clustered in the lower half of the range, so that the mean of this group was significantly lower than those of Groups 1 (postinfarction) and 3 (negative arteriograms). There were too few subjects in Group 2 (clinically normal) to evaluate the data statistically, but its mean was also higher than that of Group 4.

Table 4. Urinary Hormone Excretion In Men with Positive or Negative Coronary Arteriograms

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Positive (n = 25)</th>
<th>Negative (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androsterone sulfate (mg/g creatinine)</td>
<td>0.5 ± 0.4</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>Etiocholanolone glucuronide (mg/g creatinine)</td>
<td>2.4 ± 1.4</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>Etiocholanolone sulfate (mg/g creatinine)</td>
<td>0.2 ± 0.2</td>
<td>0.3 ± 0.6</td>
</tr>
<tr>
<td>Dehydroisoandrosterone glucuronide (mg/g creatinine)</td>
<td>0.1 ± 0.1</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>Dehydroisoandrosterone sulfate (mg/g creatinine)</td>
<td>0.6 ± 0.6</td>
<td>0.9 ± 0.8</td>
</tr>
<tr>
<td>Tetrahydrocortisol glucuronide (mg/g creatinine)</td>
<td>1.6 ± 0.5</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>Allotetrahydrocortisol glucuronide (mg/g creatinine)</td>
<td>1.2 ± 0.5</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Tetrahydrocortisone glucuronide (mg/g creatinine)</td>
<td>2.0 ± 0.5</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>Testosterone glucuronide (µg/g creatinine)</td>
<td>34 ± 18</td>
<td>29 ± 15</td>
</tr>
<tr>
<td>Dihydrotestosterone glucuronide (µg/g creatinine)</td>
<td>21 ± 13</td>
<td>22 ± 13</td>
</tr>
<tr>
<td>Free cortisol (µg/g creatinine)</td>
<td>38 ± 7.8</td>
<td>27 ± 9</td>
</tr>
<tr>
<td>Estrone glucuronide (µg/g creatinine)</td>
<td>5.6 ± 1.7</td>
<td>5.3 ± 1.2</td>
</tr>
<tr>
<td>Estradiol glucuronide (µg/g creatinine)</td>
<td>2.0 ± 0.8</td>
<td>1.6 ± 0.7</td>
</tr>
<tr>
<td>Estriol glucuronide (µg/g creatinine)</td>
<td>5.4 ± 2.1</td>
<td>5.4 ± 1.9</td>
</tr>
<tr>
<td>Creatinine (g/day)</td>
<td>1.68 ± 0.4</td>
<td>1.70 ± 0.28</td>
</tr>
</tbody>
</table>

All values are arithmetic mean ± standard deviation.
Discussion

Aside from the minor finding that a subset of postinfarction patients (3 out of 12) showed subnormal plasma T3 levels (probably the nonspecific low-T3 syndrome), there were four major observations in this study: 1) postinfarction patients showed significantly elevated plasma concentrations of estrone (E1), dehydroisoandrosterone (DHA), and dehydroisoandrosterone sulfate (DHAS), compared with normal controls; 2) men with positive coronary arteriograms but no history of infarction had values that did not differ from those of men with negative arteriograms; 3) men with positive arteriograms but no history of infarction showed subnormal urinary excretion of androsterone glucuronide; 4) postinfarction patients excreted normal quantities of this steroid.

There have been no previous reports about plasma DHA or DHAS levels in coronary disease. Elevated plasma estrogen levels have been previously reported by six groups, but the details vary. Wagner6 reported that postinfarction patients showed elevations of estradiol, but he did not measure estrone. Phillips10 and Entrican et al.11 reported that postinfarction patients showed elevations of both estrone and estradiol. Levin and Korenman12 reported that patients studied within 2 days of an infarction showed elevated levels of estradiol but not estrone. Pego et al.14 also reported elevated estradiol levels in such patients, but they did not measure estrone. Pivovarov et al.13 reported elevated estradiol levels (estrone levels were not measured) in an incompletely characterized group of men with positive arteriograms, some or possibly most of whom had had previous myocardial infarctions but none of whom were studied in the first few weeks after infarction. We found elevated levels of estrone but not estradiol. Despite these differences, it can be said that all seven groups that have studied postinfarction patients have reported elevated plasma estrogen levels. However, until now no group had reported the plasma estrogen levels of a group of well-characterized men with markedly abnormal coronary arteriograms who had not had a myocardial infarction. Our finding that this group did not have elevated plasma estrogen levels is therefore unique and, we think, of importance in formulating a hypothesis concerning the possible role of hormonal factors in coronary disease.

Two groups of workers have described subnormal urinary excretion of androsterone after myocardial infarction. Rao7 reported subnormal excretion of this steroid in men studied 1 to 2 weeks after infarction, and Marmorston et al.6 reported decreased excretion in patients studied...
HORMONES IN CORONARY DISEASE  Zumoff et al.  65

at least 3 months after infarction. Neither group studied preinfarction patients like ours. Our findings of subnormal urinary excretion of androsterone glucuronide in preinfarction but not in postinfarction patients is again unique.

There are several possible explanations for our finding that postinfarction patients showed three plasma hormonal abnormalities that were not present in “preinfarction” patients (i.e., men with positive coronary arteriograms but no history or evidence of prior infarction), and failed to show one urinary hormonal abnormality that was present in preinfarction patients. One explanation is that infarction itself caused these changes. This is certainly possible, although it seems easier to believe that a physiological catastrophe like infarction can produce new abnormalities than that it can abolish old ones. In any case, if this is the mechanism, it provides justification for the study of preinfarction patients and suggests that the androsterone glucuronide abnormality is the only one of the four that is “basic” in coronary artery disease, since it is present before infarction.

A second possibility is that values for estrone, dehydroandrosterone, dehydroandrosterone sulfate, and androsterone glucuronide that are in the upper half of the preinfarction range predispose to the development of infarction and are therefore over-represented in those who have infarctions, thus raising their mean value compared with preinfarction patients. This is certainly compatible with the distributions of hormonal levels observed in the postinfarction patients.

A third possibility is that upper-half values for these four hormones in preinfarction patients predispose not to the development of infarction but to survival after an infarction occurs, and are therefore higher than normal in postinfarction patients who survive to be studied. This implies that the hormonal levels in the relatively well, highly selected group of postinfarction survivors we studied are not typical of all postinfarction patients.

The best way to distinguish among these three possibilities would be prospective studies. Unfortunately, this is impractical. The relatively low incidence of infarction even in a group of men with positive arteriograms would mandate a very large number of man-years to achieve statistical significance in such a study, and to do the study in a reasonable time interval would therefore require a very large number of men. The logistics and expense of such a study would be prohibitive.

An alternative, though less conclusive, approach would be to draw inferences from the known pharmacological properties and epidemiological correlates of the four hormones concerned. On epidemiological grounds (i.e., the protection that women have from myocardial infarction and the loss of this protection in women castrated young), estrogens could be considered likely to favor a lower incidence of infarction. Indeed, an autopsy study has shown a lower incidence of myocardial infarction in both men and women treated with estrogens. The higher incidence of infarction in women who take oral contraceptives and the higher incidence of reinfarction in postinfarction men who take estrogens do not contradict this finding, since the estrogens used in both cases are all artificial synthetic compounds whose ingestion lowers the endogenous levels of natural estrogens; it has recently been reported that women who take noncontraceptive estrogens do not have an increased incidence of myocardial infarction. Animal experiments show that estrogens inhibit the formation of two types of experimental atherosclerosis.

Additional light can be shed on this problem by considering the influence on myocardial infarction of two disease processes in which affected men have chronically elevated plasma estrogens, namely, obesity and cirrhosis of the liver. In obesity, it has been reported that survival from an infarction is neither lower nor higher than in normal men; the influence of obesity on the incidence of infarction has been controversial, but it now appears that if the confounding effects of associated hypertension, diabetes, and hyperlipidemia are factored out, obesity per se probably does not affect the incidence. Additional light can be shed on the problem by considering the influence on myocardial infarction of two disease processes in which affected men have chronically elevated plasma estrogens, namely, obesity and cirrhosis of the liver. In obesity, it has been reported that survival from an infarction is neither lower nor higher than in normal men; the influence of obesity on the incidence of infarction has been controversial, but it now appears that if the confounding effects of associated hypertension, diabetes, and hyperlipidemia are factored out, obesity per se probably does not affect the incidence. No information is available about the effect of cirrhosis on survival from an infarction, but the weight of evidence is that the incidence of infarction is markedly decreased in cirrhotic patients.

In summary, higher estrogen levels certainly do not increase the incidence of myocardial infarction and may indeed decrease it, and the available evidence does not permit us to evaluate the possibility that higher estrogen levels might increase survival from an infarction.

The production rates of DHA and DHAS have been reported to be increased in obesity, so that all three steroids whose blood levels we find elevated in postinfarction patients (DHA, DHAS, and estrone) are produced in increased amounts in obesity. Both DHA and DHAS have been reported to decrease angina, an effect that has been attributed to the ability of DHA to depress cardiac oxygen consumption, and which would certainly be compatible with improved survival from an infarction when higher DHA and DHAS levels are present.

Androsterone, which is a peripheral metabolite of the testicular and adrenal androgens, was long ago reported to produce a profound lowering of cholesterol in all types of hypercholesterolemia. This property and the present observa-
tion that urinary androsterone glucuronide excretion is subnormal in men with positive coronary arteriograms makes it unlikely that androsterone would increase the incidence of myocardial infarction.

Finally, it would seem desirable to investigate the effects of estrone, dehydroisoandrosterone, dehydroisoandrosterone sulfate, and androstene in one or more animal models of arteriosclerosis.

Acknowledgments

We are grateful for the outstanding assistance of many technicians who helped carry out the arteriographic, blood-sampling, and radioimmunoassay tests, and without whose dedicated efforts these studies could not have been done. We thank Dr. Gerald Phillips for stimulating discussions that helped us in the interpretation of the data, and Lt. Colonel George Kush USAF, MSC (Ret.) whose interorganizational mediation made it possible to get these studies underway.

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Index Terms: coronary artery disease • myocardial infarction • plasma hormone levels urinary hormone excretion • estrogens • estrone • dehydroisoandrosterone • dehydroisoandrosterone sulfate • androsterone
Abnormal hormone levels in men with coronary artery disease.
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