Effects of Testosterone and Castration on Cholesteremia and Atherogenesis in Chicks on High Fat, High Cholesterol Diets

By R. Pick, M.D., J. Stamler, M.D., S. Rodbard, M.D., Ph.D., and L. N. Katz, M.D.

With the assistance of Dolores Century and Philip Johnson

Testosterone in large doses in intact cholesterol-fed cockerels partially inhibited hypercholesteremia, without affecting aorta or coronary atherosclerosis. Castration, with and without testosterone administration in young male and female chicks, was without influence on hypercholesteremia and atherogenesis.

It is a well documented fact that a significant sex differential exists in severity of coronary atherosclerosis and incidence of coronary heart disease in middle-aged human beings. Considerable evidence is available to indicate that ovarian estrogen secretion is a key factor in protection of premenopausal women from this disease. Little evidence is available concerning the relationship of androgenic secretion to the development of coronary atherosclerosis.

Previous experiments in this laboratory have explored this set of problems, particularly with reference to the role of ovarian estrogen secretion. It was demonstrated that mature hens—in contrast to roosters—are remarkably resistant to cholesterol-induced coronary atherogenesis. Ovariectomy abolished this "immunity." It was also shown that estrogen administration protected male chicks against cholesterol-induced coronary atherosclerosis. This series of studies lent significant experimental support to the hypothesis that estrogenic secretion is a key factor in the immunity of premenopausal women to coronary disease.

The present experiments were undertaken to explore further the over-all problem of the relationships between sex hormones and atherogenesis, particularly the effects of androgens and castration.

Methods

The established procedures of this department for chronic experiments on atherosclerosis in chickens were used throughout. Seven series of experiments were accomplished, involving a total of 18 groups and 180 birds. The experimental designs are presented in table 1. In essence, comparisons were made of intact chicks on a high fat, high cholesterol diet, with and without parental administration of androgen* at various dosages (table 1). Further, castration was carried out in young chicks, both male and female, and the effects of this procedure studied, with and without administration of testosterone. Gonadectomy was accomplished surgically 2 to 3 weeks prior to institution of the experimental feeding regimens.

Results

Testosterone tended to retard hypercholesteremia in cholesterol-oil-fed cockerels (table 1). This effect was marked and significant at the higher dosage levels (10 to 100 mg./bird/day). Despite this influence on cholesteremia, aorta and coronary atherosclerosis were essentially similar in incidence and extent in the control and testosterone-treated groups in all experimental series (table 1).

Gonadectomy was essentially without effect in young male or female chicks. Testosterone

*Testosterone propionate (Oreton). We are grateful to Dr. Edward Henderson of the Schering Corporation, Bloomfield, New Jersey for generous supplies of Oreton.
TABLE 1.—Effects of Testosterone Administration on Plasma Lipids and Atherogenesis in Cholesterol-Oil-Fed Cockerels

<table>
<thead>
<tr>
<th>Series, age, duration</th>
<th>Group dosage of T*</th>
<th>Feed intake (Gm./chick/day)</th>
<th>Terminal weight (Gm.)</th>
<th>Comb index* (em.)</th>
<th>Plasma total cholesterol (mg. %)*</th>
<th>C/P ratio*</th>
<th>Gross thoracic aorta atherogenesis incidence* (%)</th>
<th>Grade*</th>
<th>Microscopic coronary atherogenesis incidence* (%)</th>
<th>Extent*</th>
</tr>
</thead>
<tbody>
<tr>
<td>S 40</td>
<td>2 C-0*</td>
<td>463± 78†</td>
<td>1.37±0.16†</td>
<td>60</td>
<td>0.7±0.3†</td>
<td>60</td>
<td>13%±6†</td>
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<td>1-5 wks. 4 wks.</td>
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<tr>
<td>S 11</td>
<td>0.5-1.0 C-0</td>
<td>303± 50†</td>
<td>1.36±0.05†</td>
<td>67</td>
<td>0.4±0.1†</td>
<td>63</td>
<td>11%±3†</td>
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<td>9-17 wks. 8 wks.</td>
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<tr>
<td>S 24</td>
<td>0.5 C-O</td>
<td>117±21</td>
<td>1410</td>
<td>24±3</td>
<td>457± 91</td>
<td>100</td>
<td>1.8±0.3†</td>
<td>100</td>
<td>19%±4†</td>
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<td>9-16 wks. 7 wks.</td>
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<tr>
<td>S 28</td>
<td>1 C-O</td>
<td>155± 6</td>
<td>1886</td>
<td>48±4</td>
<td>637±146</td>
<td>100</td>
<td>1.5±0.3†</td>
<td>100</td>
<td>13%±2†</td>
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<td>10-15 wks. 5 wks.</td>
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<tr>
<td>S 31</td>
<td>1 C-O + T (10 mg.)</td>
<td>117±16 1675</td>
<td>61±7</td>
<td>292± 47 1.28±0.11 88 1.3±0.3 62 10%±2</td>
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<tr>
<td>10-17 wks. 7 wks.</td>
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*2 C-0, 1 C-0, 0.5 C-O are 2%, 1%, 0.5% cholesterol + 5% cottonseed oil respectively.

T = testosterone propionate in oil (Oreton, Schering)—dosage per bird per day administered by intramuscular injection.

Comb index = the product of the greatest height and greatest length of comb.

Plasma total cholesterol = mean of sacrifice bleeding.

C/P = the ratio total cholesterol/phospholipids.

Incidence = the percentage of birds with lesions.

Grade is the mean grade for birds with lesions, i.e., exclusive of birds graded 0; the grading is on an arbitrary scale 0-4 (2).

Extent is evaluated from a microscopic examination of 2 standard Sudan-IV-stained heart sections on each bird; all arteries and arterioles in each section are counted, and the percentage demonstrating atherosclerotic plaques calculated. The values are the percentage of vessels with lesions in birds with lesions, i.e., exclusive of negative hearts.

†Standard error of the mean.

‡Of experimental period.

in castrated birds (0.05 to 0.10 mg./bird/day in males, 0.10 to 3.00 in females) was also without apparent effect on hypercholesteremia and atherogenesis.

DISCUSSION

The only positive finding in these experiments was a partial inhibition of hypercholesteremia induced by testosterone in large doses. This is in accord with observations in chicks by other workers. The present results were otherwise essentially negative. Neither hyperandrogenism nor hypoandrogenism influenced aorta or coronary atherogenesis. These observations are not in accord with those of the previously cited workers, who reported decreased atherogenesis in testosterone-treated birds.

Based on the present findings, it would seem valid to conclude that androgenicity does not influence susceptibility to diet-induced atherogenesis, aortic or coronary, in chicks. Hypoandrogenic, euandrogenic, and hyperandrogenic birds appear to be equally susceptible.
In a previous experiment, it had been shown that androgens were also without effect on the ability of estrogens to protect against coronary atherogenesis in cholesterol-fed cockerels. This result was obtained even with doses of testosterone (given concomitantly with estrogens) large enough to maintain masculine secondary sex characteristics.

**SUMMARY**

From all these findings with sex hormones in cockerels, it may be concluded that predominant estrogenism is the key factor in protection against coronary atherosclerosis, and that level of androgenism is not of decisive importance.

**ACKNOWLEDGMENTS**

These studies were accomplished by virtue of the fine cooperation of the department’s experimental atherosclerosis research team, Mrs. Christine Bohlen-Williams (Deborah V. Dauber, research assistant), Mrs. Weldon B. Davis, Miss Marilyn Dudley (deceased), Mrs. Eva Levinson, Miss Mildred Michael, Mrs. Eva W. Miller, Mrs. Charlene Thompson, Mrs. Monte Yankinscott and Mr. Grady Crowley.

**SUMMARY IN INTERLINGUA**

Le constatationes del hic reportate studios con hormones sexual in gallettos supporta le conclusion que estrogenismo predominante es le factor cardinal in le protection contra atherosclerosis coronari e que le nivello del androgenismo non es de importantia decisive.

**REFERENCES**

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