Estrogen Prophylaxis of Cholesterol-Induced Coronary Atherogenesis in Chicks Given Adrenal Corticoids or ACTH

By Jeremiah Stamler, M.D., Ruth Pick, M.D., and Louis N. Katz, M.D.

Estrogen prophylaxis of experimental cholesterol-induced coronary atherogenesis in cockerels is unimpaired by the hyperadrenalism and steroid diabetes variously produced by concomitant exhibition of deoxycorticosterone acetate (DCA), hydrocortisone, cortisol, or adrenocorticotropic hormone (ACTH).

Previous work from this department demonstrated that estrogens inhibit coronary atherogenesis in cholesterol-fed cockerels.1-4 The present study shows that estrogen prophylaxis of coronary atherogenesis is unimpaired by concomitant exhibition of adrenal steroids or adrenocorticotropic hormone (ACTH). It thereby serves to clarify certain problems of the mechanism of the estrogen effect.

Methods

The experimental designs and techniques were generally in accord with the standardized procedures established in this department.4, 5 Two series of experiments were completed, utilizing a total of 80 cockerels (table 1). The precise biochemical, nutritional, physiologic and pathologic methods employed were detailed in the previous paper.5

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, III.

This work was supported in part by the Michael Reese Research Foundation and by grants from the National Heart Institute and the Chicago Heart Association.

We are indebted to Dr. John B. Jewell of Ayerst, McKenna and Harrison, Ltd., to Dr. Elmer Alpert of Merek and Co., Inc., to Dr. Abbott Allen of the Schering Corp., and to Dr. C. J. O'Donovan of the Armour Laboratories for generous supplies of estrogens (Premarin), cortisol (Cortone) and hydrocortisone (Hydrocortone), deoxycorticosterone acetate (DCA) (Cortate) and long-acting ACTH (ACTHAR Gel), respectively.

This work was done during Dr. Stamler's tenure of a Fellowship as an Established Investigator of the American Heart Association.

Results

The experimental findings are summarized in tables 2 and 3. None of the hormone regimens effected an elevation of blood pressure. Thus, the estrogens apparently counteracted

<table>
<thead>
<tr>
<th>Table 1.—Experimental Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series</td>
</tr>
<tr>
<td>BC 20</td>
</tr>
<tr>
<td>BC 20</td>
</tr>
<tr>
<td>BC 20</td>
</tr>
<tr>
<td>BC 20</td>
</tr>
<tr>
<td>BC 20</td>
</tr>
<tr>
<td>BC 23</td>
</tr>
<tr>
<td>BC 23</td>
</tr>
<tr>
<td>BC 23</td>
</tr>
</tbody>
</table>

* Hormone dosages were: Estrogens (mixed conjugated equine estrogens), approximately 25-30 mg./chick/day in the drinking water. DCA (deoxycorticosterone acetate), 1-5 mg./chick/day parenterally in oil. Cortisone, 5-20 mg./chick/day parenterally in saline suspension. Hydrocortisone, 1-4 mg./chick/day parenterally in saline suspension. ACTH, 25 mg./chick/day parenterally of a long-acting preparation.

Steroid dosages were increased stepwise at the end of the second, fourth and fifth experimental weeks.† 1 CO is chick starter mash + 1 per cent cholesterol + 5 per cent cottonseed oil.
Table 2.—Blood Pressure, Plasma Preterminal Lipid Levels and Atherogenesis

<table>
<thead>
<tr>
<th>Series and Group</th>
<th>Regimen</th>
<th>Mean Blood Pressure mm. Hg</th>
<th>Total Cholesterol mg%</th>
<th>Lipid P mg%</th>
<th>C/P Ratio*</th>
<th>Gross Thoracic Aorta Atherogenesis</th>
<th>Microscopic Coronary Atherogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Birds with Lesions %</td>
<td>Grade of Lesions</td>
</tr>
<tr>
<td>BC 20 1</td>
<td>1 CO</td>
<td>149 ± 3.2§ 140-162‡</td>
<td>573 ± 66.1 362-791</td>
<td>16.6 ± 1.0 11.5-16.6</td>
<td>37.7 ± 3.1 31.5-47.7</td>
<td>100 1.4 ± 0.2 0.3-2.5</td>
<td>80 15.9 ± 3.6 0.0-33.3</td>
</tr>
<tr>
<td>BC 20 2</td>
<td>1 CO + Estrogens</td>
<td>142 ± 33.3 134-156</td>
<td>692 ± 38.4 530-782</td>
<td>53.7 ± 6.7 33.8-74.6</td>
<td>13.7 ± 1.5 10.5-20.6</td>
<td>100 1.6 ± 0.2 0.8-3.0</td>
<td>13 1.9 ± 1.0 0.0-13.1</td>
</tr>
<tr>
<td>BC 20 3</td>
<td>1 CO + Estrogens + DCA</td>
<td>150 ± 3.4 136-160</td>
<td>1095 ± 100.4 728-1394</td>
<td>111.5 ± 11.3 76.7-147.1</td>
<td>9.9 ± 0.6 8.2-12.1</td>
<td>100 1.4 ± 0.2 0.8-3.0</td>
<td>11 1.5 ± 0.9 0.0-13.3</td>
</tr>
<tr>
<td>BC 20 4</td>
<td>1 CO + Estrogens + Cortisone</td>
<td>132 ± 6.7 116-162</td>
<td>1115 ± 86.5 915-1375</td>
<td>119.6 ± 11.7 89.6-159.6</td>
<td>9.4 ± 0.2 8.5-10.2</td>
<td>100 1.7 ± 0.3 1.0-3.0</td>
<td>0 0</td>
</tr>
<tr>
<td>BC 20 5</td>
<td>1 CO + Estrogens + Hydrocortisone</td>
<td>139 ± 0.8 136-142</td>
<td>1061 ± 98.0 776-1391</td>
<td>83.4 ± 7.6 69.2-117.1</td>
<td>13.0 ± 1.3 8.8-17.3</td>
<td>100 1.9 ± 0.2 0.8-3.0</td>
<td>25 3.0 ± 2.5 0-20.0</td>
</tr>
<tr>
<td>BC 23 1</td>
<td>1 CO</td>
<td>—</td>
<td>1028 ± 102.0 679-1715</td>
<td>19.1 ± 1.4 14.5-27.7</td>
<td>53.4 ± 2.8 42.4-65.0</td>
<td>100 2.1 ± 0.2 1.3-2.5</td>
<td>100 24.8 ± 2.1 15.0-33.3</td>
</tr>
<tr>
<td>BC 23 2</td>
<td>1 CO + Estrogens</td>
<td>—</td>
<td>599 ± 44.3 342-1092</td>
<td>49.6 ± 11.1 19.4-107.0</td>
<td>14.8 ± 1.6 7.8-23.6</td>
<td>100 1.4 ± 0.2 0.3-2.5</td>
<td>30 5.6 ± 3.2 0.0-29.4</td>
</tr>
<tr>
<td>BC 23 6</td>
<td>1 CO + Estrogens + ACTH</td>
<td>—</td>
<td>839 ± 86.4 511-1445</td>
<td>59.4 ± 5.2 35.4-82.8</td>
<td>14.6 ± 1.2 8.2-20.2</td>
<td>100 2.5 ± 0.2 1.5-3.5</td>
<td>30 2.7 ± 1.7 0.0-16.1</td>
</tr>
</tbody>
</table>

* C/P ratio is the plasma total cholesterol to lipid phosphorus ratio.
† Coronary count is the percentage of arteries and arterioles exhibiting microscopic atheromatous or atherosclerotic lesions.
‡ Range.
§ Standard error of the mean.
the hypertensive influence of desoxycorticosterone acetate and cortisone.4–6

All groups receiving estrogens, with or without other hormone, exhibited the typical triad of estrogen effects,1–5 i.e. feminization (low comb indexes), marked enhancement of hyperphospholipemia (with resultant reduction of plasma total cholesterol-lipid phosphorus ratios to normal levels), and prophylactic inhibition of coronary atherogenesis (with no effect on aorta atherogenesis). Thus, none of the estrogen effects were counteracted by concomitant exhibition of steroids or corticotropin in the dosages used.

All steroid-treated groups exhibited retardation of growth and development despite normal feed intake; this phenomenon was most marked in the groups receiving hydrocortisone and corticotropin, respectively. All chicks given hormone developed moderate polydypsia (table 3). Blood sugar determinations on the twentieth experimental day revealed hyperglycemia in the cockerels receiving estrogens plus corticotropin; mean blood glucose value in these chicks was ± 37.6 mg per 100 cc., range 193–425 (control ± 8.4, range 151–178 mg per 100 cc.).

**DISCUSSION AND CONCLUSIONS**

Estrogen prophylaxis of cholesterol-induced coronary atherogenesis in cockerels continues to operate effectively when adrenal corticoids or ACTH is concomitantly administered. Thus, the estrogen effect is not reversed by hyperadrenocorticism or steroid diabetes, or by the multiple influences of the pituitary-adrenal hormones on metabolism, vascular permeability, connective tissue function, and similar effects.5

The findings in this experiment further suggest that estrogen inhibition of cholesterol-induced coronary atherogenesis is not mediated indirectly, via a possible estrogen-induced suppression of the pituitary corticotropin-adrenal corticoid secretion.5 This observation supplements a previous conclusion of ours that the estrogen effect cannot be attributed to estrogen-induced suppression of
pituitary gonadotropic-testicular androgen secretion. The mechanism of the estrogen effect on atherogenesis remains to be elucidated.

SUMMARY

Estrogen prophylaxis of cholesterol-induced coronary atherogenesis in cockerels is unimpaired by concomitant exhibition of adrenal steroids or ACTH.

SUMARIO ESPAÑOL

La profilaxis con estrógeno de la aterogénesis coronaria en gallipollos es inalterada por el hiperadrenalismo y la diabetis esteroidea variablemente producida por el uso concomitante de acetato de desoxicorticosterona (DCA), hidrocortisona, cortisona o la hormona adrenocorticotrófica (ACTH).

ACKNOWLEDGMENTS

The accomplishment of these experiments was possible only by virtue of the excellent services rendered by the technician members of the department's atherosclerosis research team, including Christine Bolene Williams,* Grady Crowley, Marilyn Dudley (deceased), Dolores Friedman, Philip Johnson, Chizuko Kakita, Mildred Michael, John Morris and Ronald Wallace. It is also a pleasure to acknowledge the assistance of Bernice Huddleston of the Department of Metabolism and Endocrinology, who carried out the glucose analyses for this experiment.

REFERENCES


* Deborah V. Dauber Research Assistant.
Estrogen Prophylaxis of Cholesterol-Induced Coronary Atherogenesis in Chicks Given Adrenal Corticoids or ACTH

JEREMIAH STAMLER, RUTH PICK and LOUIS N. KATZ

Circulation. 1954;10:247-250
doi: 10.1161/01.CIR.10.2.247

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1954 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/10/2/247

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org//subscriptions/