Effects of Cortisone, Hydrocortisone and Corticotropin on Lipemia, Glycemia and Atherogenesis in Cholesterol-Fed Chicks

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

Hydrocortisone markedly affected carbohydrate, protein, lipid and electrolyte metabolism of cholesterol-fed cockerels (intact, alloxanized and depancreatized). Despite steroid-induced diabetes and hyperadrenalinism, associated with enhancement of hypercholesterolemic hyperlipemia, no hypertension or intensification of atherogenesis (aortic or coronary artery) supervened. Corticotropin (ACTH)* produced similar effects. Cortisone was relatively inactive as a glyccorticoid in this avian species. Despite its apparently slight metabolic activity, however, it moderately elevated blood pressure and intensified atherogenesis.

Human beings with hyperadrenocorticism (e.g. Cushing's syndrome) frequently develop premature, severe atherosclerosis.7,8 This fact assumes new importance at the present time, when chronic hyperadrenocortical states are being artificially induced on a large scale for therapeutic purposes. The widespread utilization of corticotropin (ACTH) and adrenal steroids in clinical medicine compels a thorough-going examination of their effects on atherogenesis. Towards this end, we previously studied the influences of desoxycorticosterone acetate (DCA) on avian experimental atherosclerosis.9 The present investigation analyzed the effects of cortisone (compound E), hydrocortisone (compound F), and adrenocorticotropic hormone (ACTH)* on blood pressure, lipemia, glycemia, and aorta and coronary atherogenesis in cholesterol-fed cockerels. Further, these experiments were designed to study the influence of the diabetic state on lipid metabolism and atherogenesis in chicks. Sustained diabetes mellitus was induced for the first time in this avian species by a combination of alloxanization or pancreatectomy plus the glucocorticoid compound F.8,10-15

METHODS

The experimental designs and technics were generally in accord with the standardized procedures of the department's atherosclerosis research group.8 Altogether, five series of chronic experiments were completed, one with cortisone, two with hydrocortisone and two with corticotropin (ACTH), utilizing a total of 178 chicks (table 1). One day old Hyline cockerels were obtained from a commercial hatchery and reared in a battery brooder. They were maintained on a chick starter mash and tap water ad lib. prior to institution of the experimental regimens. In essence, these experimental regimens involved the study of pairs of intact cholesterol-fed cockerels, one group (control) of the pair receiving no hormone, the other (experimental) receiving parenteral hormone (table 1). Further, the experiments with compound F included pairs of alloxanized and depancreatized cockerels, in order to study cholesterol-induced experimental atherogenesis in insulin-deficient steroid-diabetic chicks. Two intravenous injections of alloxan (50 mg.) were given at intervals of one week, one or two weeks before institution of the experimental regimens. Pancreatectomy was similarly accomplished two to three weeks prior to beginning the study. Completeness of pancreatectomy was confirmed at autopsy.

A weekly record was kept of feed intake, weight and comb size of individual birds. Water intake data were also collected over several days during...
the study. Serial blood samples were drawn and heparinized for determination of blood glucose, plasma sodium and potassium,* plasma total cholesterol, and lipid phosphorus. At the preterminal bleeding, sera were also collected for ultracentrifugal analysis of circulating lipoproteins. Blood pressures were obtained just prior to sacrifice by direct puncture of a sciatic artery, utilizing the Lilly electromanometer and the Sanborn polyviso recorder. In a few birds of series BC 13, hematocrits (Wintrobe), insulin tolerance tests and eosinophil counts were done preterminally. The animals were killed by decapitation. Following complete autopsy, including determination of organ weights, thoracic and abdominal aortas were evaluated for gross atherosclerosis; subsequently, Sudan IV-stained frozen sections of the formalin-fixed hearts were studied microscopically for coronary lesions. The standardized methods of the department were utilized for grading gross aorta and microscopic coronary atherogenesis.5, 24

* Sodium and potassium were analyzed with the Beckman flame photometer.
† The ultracentrifuge analyses were accomplished by Drs. Lena Lewis and Irvine H. Page of the Cleveland Clinic Foundation. We gratefully acknowledge their cooperation in this conjoint effort. The ultracentrifuge data will be the subject of a separate communication.

<table>
<thead>
<tr>
<th>Series</th>
<th>Group No.</th>
<th>No. of Chicks</th>
<th>Chick Age During Experiment—weeks</th>
<th>Diet</th>
<th>Type Group</th>
<th>Hormone Dosage—mg/chick/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC9</td>
<td>1</td>
<td>25</td>
<td>1-11*</td>
<td>0.5 C-O†</td>
<td>Intact control</td>
<td>0</td>
</tr>
<tr>
<td>BC9</td>
<td>2</td>
<td>25</td>
<td>1-11*</td>
<td>0.5 C-O</td>
<td>Intact cortisone</td>
<td>1-15‡</td>
</tr>
<tr>
<td>BC11</td>
<td>3</td>
<td>12</td>
<td>9-17</td>
<td>0.5 C-O</td>
<td>Intact control</td>
<td>0</td>
</tr>
<tr>
<td>BC11</td>
<td>4</td>
<td>12</td>
<td>9-17</td>
<td>0.5 C-O</td>
<td>Intact ACTH</td>
<td>6-8‡§</td>
</tr>
<tr>
<td>BC15</td>
<td>3</td>
<td>12</td>
<td>12-19</td>
<td>1.0 C-O†</td>
<td>Intact ACTH</td>
<td>10-25‡¶</td>
</tr>
<tr>
<td>BC15</td>
<td>4</td>
<td>12</td>
<td>12-19</td>
<td>1.0 C-O</td>
<td>Intact control</td>
<td>0</td>
</tr>
<tr>
<td>BC15</td>
<td>5</td>
<td>10</td>
<td>13-21</td>
<td>0.5 C-O</td>
<td>Intact hydrocortisone</td>
<td>1-2‡</td>
</tr>
<tr>
<td>BC15</td>
<td>6</td>
<td>10</td>
<td>13-21</td>
<td>0.5 C-O</td>
<td>Alloxanized control</td>
<td>0</td>
</tr>
<tr>
<td>BC15</td>
<td>7</td>
<td>10</td>
<td>13-21</td>
<td>0.5 C-O</td>
<td>Alloxanized hydrocortisone</td>
<td>1-2†</td>
</tr>
<tr>
<td>BC15</td>
<td>8</td>
<td>10</td>
<td>13-21</td>
<td>0.5 C-O</td>
<td>Pancreatectomized control</td>
<td>0</td>
</tr>
<tr>
<td>BC15</td>
<td>9</td>
<td>10</td>
<td>13-21</td>
<td>0.5 C-O</td>
<td>Pancreatectomized hydrocortisone</td>
<td>1-2‡</td>
</tr>
<tr>
<td>BC13</td>
<td>10</td>
<td>10</td>
<td>14-19</td>
<td>0.5 C-O</td>
<td>Pancreatectomized control</td>
<td>0</td>
</tr>
<tr>
<td>BC13</td>
<td>10</td>
<td>10</td>
<td>14-19</td>
<td>0.5 C-O</td>
<td>Pancreatectomized hydrocortisone</td>
<td>1-3‡</td>
</tr>
</tbody>
</table>

* Six birds in this group were sacrificed at age of 6 weeks, after five weeks on the experimental regimen.
† 0.5 and 1.0 C-O are chick starter mash supplemented with 0.5 and 1.0 per cent cholesterol (C) respectively and 5 per cent cottonseed oil (O).
‡ Dosage increased stepwise during course of experiment.
§ Regular ACTH, given in divided doses, twice daily.
¶ Long-acting ACTH (ACTHAR GEL), one dose per day.
‖ All hormones given parenterally.

Results

1. Plasma glucose and lipid levels (table 2). Hydrocortisone induced a significant sustained hyperglycemia in cholesterol-fed cockerels, which tended to be more marked in the alloxanized, and most marked in the depancreatized birds. Glycosuria was observed in the more hyperglycemic chicks of the three compound F treated groups (groups 6, 8 and 10, series BC 13 and 15, table 2). These steroid-diabetic cockerels responded to insulin injection (0.5 unit per kilogram) with only a slight reduction in blood sugar levels, followed by a marked enhancement ("rebound") of hyperglycemia (table 3). Corticotropin (ACTH) and cortisone in large doses were without effect on glycemia in this study (table 2). *

* In a more recent experiment, chicks treated for 20 days with long-acting corticotropin (ACTH) (ACTHAR GEL—25 mg per bird per day parenterally) plus estrogens (mixed conjugated equine estrogens, Premarin, approximately 25 mg per bird per day orally) developed a definite hyperglycemia. Corticotropin played a key role in
Hydrocortisone and long-acting corticotropin (series BC 19) effected a sustained enhancement of lipemia (lactescence), hypercholesterolemia and hyperphospholipemia in cholesterol-fed cockerels (table 2).* The hormone-induced increases in plasma total cholesterol and lipid phosphorus were proportional, hence the plasma total cholesterol—lipid phosphorus (C/P) ratio was not altered. Cortisone and the lower dosage of regular corticotropin were without influence on plasma lipids.

and hyperphospholipemia in chicks fed a diet of plain mash, devoid of any cholesterol supplement.

* See table 1 for details.
† C/P ratio is, total cholesterol—lipid phosphorus.
‡ Groups 9 and 10 of BC13 and BC15 exhibited essentially identical trends, hence only the latter are recorded here.
§ Range.
‖ Standard error of the mean.

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**Table 2.**—Preterminal Blood Glucose and Lipid Levels‡

<table>
<thead>
<tr>
<th>Series</th>
<th>Group No.</th>
<th>Regimen*</th>
<th>Glucose mg. %</th>
<th>Total Cholesterol mg. %</th>
<th>Lipid Phosphorus mg. %</th>
<th>C/P Ratio†</th>
</tr>
</thead>
<tbody>
<tr>
<td>BC9</td>
<td>1</td>
<td>Intact control</td>
<td>182 ± 2.3 175-187§</td>
<td>260 ± 17 162-410</td>
<td>7.5 ± 0.4 5.6-11.3</td>
<td>36.1 ± 2.2 17.2-50.6</td>
</tr>
<tr>
<td>BC9</td>
<td>2</td>
<td>Intact cortisone</td>
<td>164 ± 2.7 158-173</td>
<td>287 ± 49 140-313</td>
<td>7.9 ± 0.5 5.6-9.3</td>
<td>29.0 ± 3.7 20.8-49.2</td>
</tr>
<tr>
<td>BC11</td>
<td>3</td>
<td>Intact control</td>
<td>161 ± 4.6 153-169</td>
<td>1037 ± 122 589-1492</td>
<td>17.5 ± 1.8 11.2-25.7</td>
<td>58.7 ± 2.9 48.0-71.7</td>
</tr>
<tr>
<td>BC11</td>
<td>4</td>
<td>Intact ACTH (6-8 mg.)</td>
<td>155 ± 7.7 125-192</td>
<td>1011 ± 118 528-1498</td>
<td>18.3 ± 1.2 11.8-22.8</td>
<td>53.9 ± 3.3 38.4-68.5</td>
</tr>
<tr>
<td>BC19</td>
<td>3</td>
<td>Intact control</td>
<td>217 ± 7.1 203-225</td>
<td>577 ± 40 465-705</td>
<td>12.0 ± 1.0 9.8-13.4</td>
<td>48.4 ± 1.4 44.3-52.5</td>
</tr>
<tr>
<td>BC19</td>
<td>4</td>
<td>Intact ACTH (10-25 mg.)</td>
<td>223 ± 2.5 218-234</td>
<td>1102 ± 189 598-1768</td>
<td>20.1 ± 2.0 15.3-26.4</td>
<td>53.3 ± 4.9 39.1-69.0</td>
</tr>
<tr>
<td>BC15</td>
<td>5</td>
<td>Intact control</td>
<td>172 ± 3.7 162-184</td>
<td>421 ± 57 256-598</td>
<td>10.9 ± 1.2 7.5-15.3</td>
<td>38.3 ± 1.9 32.5-44.1</td>
</tr>
<tr>
<td>BC15</td>
<td>6</td>
<td>Intact hydrocortisone</td>
<td>266 ± 29.3 214-395</td>
<td>722 ± 282 189-1397</td>
<td>16.9 ± 2.6 9.8-26.2</td>
<td>39.6 ± 5.9 19.3-61.8</td>
</tr>
<tr>
<td>BC15</td>
<td>7</td>
<td>Alloxanized control</td>
<td>175 ± 4.6 155-186</td>
<td>279 ± 41 182-388</td>
<td>8.9 ± 0.5 7.3-10.4</td>
<td>30.6 ± 3.5 23.6-38.5</td>
</tr>
<tr>
<td>BC15</td>
<td>8</td>
<td>Alloxanized hydrocortisone</td>
<td>308 ± 31.2 230-445</td>
<td>544 ± 76 370-785</td>
<td>17.7 ± 1.8 12.0-25.1</td>
<td>31.4 ± 3.9 17.7-42.0</td>
</tr>
<tr>
<td>BC15</td>
<td>9</td>
<td>Depancreatized control</td>
<td>198 ± 10.8 175-232</td>
<td>420 ± 67 226-634</td>
<td>9.7 ± 1.4 5.9-14.5</td>
<td>42.8 ± 1.9 38.3-48.8</td>
</tr>
<tr>
<td>BC15</td>
<td>10</td>
<td>Depancreatized hydrocortisone</td>
<td>371 ± 86.0 264-715</td>
<td>898 ± 213 220-1424</td>
<td>18.3 ± 3.4 8.5-26.8</td>
<td>46.3 ± 5.2 25.9-54.3</td>
</tr>
</tbody>
</table>
2. Blood pressure* and atherogenesis (table 4). Cortisone apparently induced a moderate increase in the systolic and diastolic blood pressures of cholesterol-fed cockerels. Corticotropin apparently tended to exert a similar hypertensive effect, although to an even smaller degree. Limited data indicate no evidence of a blood pressure rise in depancreatized, steroid-diabetic (hydrocortisone-treated) birds. Cortisone apparently affected a moderate increase in the incidence of cholesterol-induced aorta and coronary atherogenesis in chicks, without intensifying the severity (grade) of aorta lesions (table 4). Neither corticotropin nor hydrocortisone had any demonstrable, definitive effect on atherogenesis in the two vascular beds studied. Data from two series (BC 13 and BC 15) suggest that compound F may partially inhibit coronary atherogenesis in depancreatized cockerels, but the findings are not definitive enough to permit any conclusion. Neither the diabetes nor the hyperadrenocorticism induced by hydrocortisone were associated with any intensification of cholesterol-induced aorta or coronary atherogenesis.

3. Other findings (table 5). Hydrocortisone consistently lowered plasma sodium levels, without affecting hematocrit, water intake, plasma potassium concentration or level of circulating eosinophils. Cortisone had no detectable influence on body fluids; the effects of corticotropin on these functions were not studied.

All experimental (hormone-treated) groups exhibited levels of feed intake equal to or in excess of their paired controls. Nevertheless, hydrocortisone markedly depressed rate of weight gain. Cortisone and corticotropin exerted this effect only minimally.

In conjunction with the moderate hypertension they developed (table 4), the cortisone-treated cockerels had an increase in the ratio, heart weight–body weight. This phenomenon was not present in the corticotropin- or hydrocortisone-treated birds studied.

All three hormones, particularly cortisone, tended to have androgenic and/or gonadotropic effects, as indicated by comb size indexes and testis weights in relation to body weights. Unexpectedly, neither cortisone nor hydrocortisone induced significant adrenal hypoplasia. The smaller dosage of corticotropin (series BC 11) did not effect definitive adrenal hyperplasia; no adrenal weight data were collected in series BC 19. Limited observations indicate no clearcut trend with respect to the influence of these hormones on thyroid weight.

**DISCUSSION AND CONCLUSIONS**

Despite their significant physiological effects, neither compound F nor corticotropin intensified aorta or coronary atherogenesis. Under these experimental conditions in chicks, therefore, neither hyperadrenocorticism nor steroid diabetes nor steroid-pancreatic diabetes was a gross aggravator of experimental cholesterol-induced atherogenesis.† These findings—unanticipated against the background clinical facts of intensified atherogenesis in man with hyperadrenocorticism and/or diabetes—are further noteworthy in view of the fact that these hormones effect a gross intensification of aortic lesions.

* Our observations on the effects of steroids and corticotropin on blood pressure in chicks will be presented and discussed in greater detail in a separate communication.

† In contrast, preliminary findings suggest that chicks fed plain mash, devoid of a cholesterol supplement, may develop gross aorta atherosclerosis consequent upon long term exhibition of hydrocortisone.28 Definitive information on this phenomenon awaits completion of experiments currently in progress.
Table 4.—Blood Pressure and Atherogenesis

<table>
<thead>
<tr>
<th>Series and Group No.</th>
<th>Regimen</th>
<th>Pre-Terminal Blood Pressure mm. Hg</th>
<th>Gross Thoracic Aorta Atherogenesis</th>
<th>Microscopic Coronary Atherogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Birds with Lesions %</td>
<td>Grade of Lesions</td>
</tr>
<tr>
<td>BC9—1</td>
<td>Intact control</td>
<td>§ 116 ± 7.5/102 ± 7.0 100-150/88-135¶</td>
<td>26 0.2 ± 0.07</td>
<td>0.0-1.0¶</td>
</tr>
<tr>
<td>BC9—2</td>
<td>Intact cortisone</td>
<td>§ 138 ± 5.3/125 ± 5.2 115-153/103-140</td>
<td>75 0.6 ± 0.18</td>
<td>0.0-1.5</td>
</tr>
<tr>
<td>BC11—3</td>
<td>Intact control</td>
<td>134 ± 5.0/114 ± 4.9 124-140/105-122</td>
<td>100 2.0 ± 0.30</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>BC11—4</td>
<td>Intact ACTH (6-8 mg.)</td>
<td>146 ± 1.4/128 ± 2.4 141-150/123-140</td>
<td>100 2.1 ± 0.30</td>
<td>1.0-3.5</td>
</tr>
<tr>
<td>BC19—3</td>
<td>Intact control</td>
<td>—</td>
<td>100 1.5 ± 0.15</td>
<td>0.8-2.0</td>
</tr>
<tr>
<td>BC19—4</td>
<td>Intact ACTH (10-25 mg.)</td>
<td>—</td>
<td>100 2.0 ± 0.23</td>
<td>0.8-2.8</td>
</tr>
<tr>
<td>BC15—5</td>
<td>Intact control</td>
<td>—</td>
<td>75 1.1 ± 0.31</td>
<td>0.0-2.5</td>
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<tr>
<td>BC15—6</td>
<td>Intact hydrocortisone</td>
<td>—</td>
<td>88 1.3 ± 0.34</td>
<td>0.0-3.0</td>
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<tr>
<td>BC15—7</td>
<td>Alloxanized control</td>
<td>—</td>
<td>63 1.1 ± 0.41</td>
<td>0.0-2.8</td>
</tr>
<tr>
<td>BC15—8</td>
<td>Alloxanized hydrocortisone</td>
<td>—</td>
<td>86 1.2 ± 0.34</td>
<td>0.0-2.5</td>
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<tr>
<td>BC15—9*</td>
<td>Depancreatized control</td>
<td>146 ± 7.4/118 ± 4.8 122-163/102-130</td>
<td>100 1.7 ± 0.28</td>
<td>0.5-3.0</td>
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<tr>
<td>BC15—10*</td>
<td>Depancreatized hydrocortisone</td>
<td>147 ± 6.3/122 ± 5.0 136-170/112-140</td>
<td>100 2.2 ± 0.18</td>
<td>1.8-2.5</td>
</tr>
</tbody>
</table>

* Groups 9 and 10 of BC13 and BC15 exhibited essentially identical trends, hence only the latter are recorded here.
† Series BC13.
‡ 6 weeks of age, 5 weeks on experimental regimen; at 11 weeks of age (10 weeks on experimental regimen) mean blood pressures of the control and cortisone groups were 142 ± 2.9 (range: 126-159) and 149 ± 5.2 (range: 110-164) respectively.
¶ Range.
‖ Standard error of the mean.

Hypertension and lipemia were not associated with any aggravating influence on atherogenesis. Thus, it may simply be due to the fact that the experimental cholesterol-supplemented diet was, of and by the fact that this enhanced...
Table 5.—Other Findings

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series and Group No.</td>
<td>Regimen</td>
<td>Plasma Na mEq/L</td>
<td>Plasma K mEq/L</td>
<td>H₂O Intake c.c./chick/day</td>
<td>Feed Intake Gm./chick/day</td>
<td>Terminal Body Weight Gm.</td>
<td>Heart Weight Gm.</td>
<td>Heart Weight Gm./Kg.</td>
<td>Pre-terminal Comb Size Index</td>
<td>Testis Weight Gm.</td>
<td>Adrenal Weight mg.</td>
<td>Thyroid Weight mg.</td>
<td></td>
</tr>
<tr>
<td>BC9—1</td>
<td>Intact control</td>
<td>154.0†</td>
<td>6.3†</td>
<td>166</td>
<td>93</td>
<td>1070 ± 38.9§</td>
<td>87</td>
<td>5.16 ± 0.18</td>
<td>4.38-6.24</td>
<td>0.48</td>
<td>17 ± 3</td>
<td>9-27</td>
<td>0.88</td>
</tr>
<tr>
<td>BC9—2</td>
<td>Intact cortisone</td>
<td>153.2†</td>
<td>6.0†</td>
<td>129</td>
<td>131</td>
<td>893 ± 24.4</td>
<td>147</td>
<td>5.33 ± 0.28</td>
<td>3.72-6.84</td>
<td>0.60</td>
<td>28 ± 5</td>
<td>16-43</td>
<td>1.98</td>
</tr>
<tr>
<td>BC11—3</td>
<td>Intact control</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>121</td>
<td>1705 ± 90.5</td>
<td>71</td>
<td>7.64 ± 0.31</td>
<td>7.03-9.11</td>
<td>0.45</td>
<td>32 ± 1.6</td>
<td>18-49</td>
<td>4.25 ± 0.92</td>
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<td>BC11—4</td>
<td>Intact ACTH (6-8 mg)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>125</td>
<td>1460 ± 43.4</td>
<td>86</td>
<td>7.25 ± 0.21</td>
<td>6.46-8.72</td>
<td>0.50</td>
<td>43 ± 6.5</td>
<td>22-94</td>
<td>7.92 ± 1.02</td>
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<td>BC19—3</td>
<td>Intact control</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>111</td>
<td>1950 ± 45</td>
<td>57</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BC19—4</td>
<td>Intact ACTH (10-25 mg)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>110</td>
<td>1967 ± 72</td>
<td>56</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>BC15—5</td>
<td>Intact control</td>
<td>163.5 ± 1.2</td>
<td>160.2-167.0</td>
<td>5.12 ± 0.36</td>
<td>4.40-6.30</td>
<td>242</td>
<td>198</td>
<td>1799 ± 28</td>
<td>1607-1806</td>
<td>113</td>
<td>—</td>
<td>—</td>
<td>48 ± 5.4</td>
</tr>
<tr>
<td>BC15—6</td>
<td>Intact hydrocortisone</td>
<td>150.6 ± 2.8</td>
<td>144.2-158.8</td>
<td>4.54 ± 0.13</td>
<td>3.98-4.84</td>
<td>205</td>
<td>141</td>
<td>1189 ± 22</td>
<td>1132-1274</td>
<td>137</td>
<td>—</td>
<td>—</td>
<td>46 ± 6.1</td>
</tr>
<tr>
<td>BC15—7</td>
<td>Alloxanized control</td>
<td>162.7 ± 1.5</td>
<td>159.0-169.0</td>
<td>4.84 ± 0.07</td>
<td>4.64-5.02</td>
<td>259</td>
<td>176</td>
<td>1790 ± 90</td>
<td>1500-2320</td>
<td>92</td>
<td>—</td>
<td>—</td>
<td>63 ± 6.3</td>
</tr>
<tr>
<td>BC15—8</td>
<td>Alloxanized hydrocortisone</td>
<td>144.9 ± 1.2</td>
<td>140.6-147.0</td>
<td>4.57 ± 0.15</td>
<td>4.12-5.56</td>
<td>181</td>
<td>138</td>
<td>1356 ± 58</td>
<td>1245-1472</td>
<td>101</td>
<td>—</td>
<td>—</td>
<td>46 ± 10.0</td>
</tr>
<tr>
<td>BC13—9* and 15</td>
<td>Depancreatized control</td>
<td>166.6 ± 2.2</td>
<td>159.4-171.2</td>
<td>5.33 ± 0.19</td>
<td>4.92-6.04</td>
<td>307</td>
<td>161</td>
<td>1624 ± 71</td>
<td>1443-1839</td>
<td>86</td>
<td>9.10</td>
<td>0.49</td>
<td>52 ± 76</td>
</tr>
<tr>
<td>BC13—10* and 15</td>
<td>Depancreatized hydrocortisone</td>
<td>144.5 ± 2.1</td>
<td>139.4-151.4</td>
<td>4.26 ± 0.11</td>
<td>3.98-4.68</td>
<td>200</td>
<td>154</td>
<td>1029 ± 90</td>
<td>879-1189</td>
<td>147</td>
<td>5.40</td>
<td>0.51</td>
<td>40 ± 9.3</td>
</tr>
</tbody>
</table>

* Combined data from BC13 and BC15; findings in two series were consistent throughout.
† Pooled sample.
‡ Data obtained on group of 10 chicks as a unit; no data on individual birds.
¶ Range.
§ Standard error of the mean.
itself, maximally atherogenic, thereby masking any hormonal propensity to intensify atherogenesis (with respect to this possibility, see the preceding footnote). Alternatively, the particular pattern of hydrocortisone- and corticotropin-induced enhancement of lipemia may account for absence of aggravated atherogenesis; e.g. the pattern of plasma total cholesterol–lipid phosphorus (C/P) ratios (which did not rise under hormonal influence) or the pattern of plasma lipoprotein classes. A third hypothetic explanation is that local corticoid effects on the arterial wall may have afforded counter-protection to any atherogenesis-intensifying effect possibly resulting from the corticoid influences on lipemia. Finally, it is possible that the specific effects on other endocrine organs, elicited by hydrocortisone or corticotropin exhibition, may act to prevent aggravation of atherogenesis despite increase of lipemia. Obviously, the data of the present experiments do not afford any basis for scientific choice among these and other possibilities.

In contrast to compound F and corticotropin, cortisone apparently intensified both coronary and aorta atherogenesis, without significantly influencing lipemia or other metabolic functions in this avian species. It may be that this intensified atherogenesis induced by compound E was—as would also appear to be the case with desoxytocosterone acetate (DCA)38, 39—a resultant of the moderate steroid-induced increase in blood pressure.

Both experimental and clinical atherogenesis are apparently related intimately to the overall metabolic state of the organism. Hence, it was deemed essential in these experiments to delineate some of the specific metabolic effects of these hormones in this avian species, in the hope that light might thereby be cast upon the mode of their action in atherogenesis. As already indicated, hydrocortisone had marked physiologic activity in chicks, whereas cortisone was relatively inert.* Thus, moderate doses of compound F—in contrast to compound E—elicited multiple evidences of marked hyperadrenocorticism in cockerels. These included alterations in electrolyte, lipid, carbohydrate and protein metabolism, biochemical–physiologic effects which were, for the most part, similar to those elicited in mammals (including man) by the 11,17-oxosteroids.30–41

Corticotropin in large doses also produced moderate hyperadrenocorticism in chicks.42 The metabolic alterations induced by corticotropin, particularly the increase of lipemia, resembled those effected by hydrocortisone, suggesting that compound F was a significant component of the steroid moiety endogenously secreted by the corticotropin-stimulated adrenal cortex of the bird. Similarly, strong evidence is available that hydrocortisone is a major physiologic secretory product of the adrenal cortex of mammals, including man.38–41, 43–48 Thus, it would appear that there are more similarities than differences between avian and mammalian species in the endocrinology of the adrenal cortex.

The finding that corticotropin and compound F increased lipemia, hypercholesterolemia and hyperphospholipemia in cholesterol-fed chicks is in accord with data collected by others in rabbits38–43 and (in some cases) in man.38, 39, 41–46 These recent observations represent significant additions to the meager knowledge of corticoid influences on lipid metabolism, an aspect of adrenal cortical physiology that has received only limited attention.29–36, 57–59 Little is known about the mechanism of the lipemia induced by 11,17-oxosteroids. It has been shown that the pituitary-adrenal system plays an important part in the mobilization of depot fat to the liver.60 Further, it has recently been demonstrated that cortisone increases the rate of incorporation of acetate into cholesterol by its biochemical basis for this difference between mammalian and avian species is not presently apparent. It may be related to differences between avian and mammalian organism in ability to convert exogenous cortisone into hydrocortisone.45–47

† As in mammals, the mineralo-corticoid desoxy-corticosterone grossly influenced only water and electrolyte metabolism in chronic experiments in chicks.7, 8, 9
the perfused rat liver,\textsuperscript{61} whereas hypophysectomy markedly depresses hepatic ability to convert acetate to cholesterol.\textsuperscript{62}

Further work is essential to elucidate the precise sites and modes of influence of these and other hormones on lipid metabolism. Such studies are vital for the final solution of the atherosclerosis problem.

SUMMARY

1. Hydrocortisone (compound F) in moderate doses induced marked sustained hyperadrenocorticism in cholesterol-fed cockerels (intact, alloxanized and depancreatized), including typical 11,17-oxysteroid effects on carbohydrate, protein, lipid and electrolyte metabolism. Despite steroid-induced diabetes and enhancement of hypercholesterolemic hyperlipemia, no intensification of aorta or coronary atherosclerosis supervened.

2. Long-acting corticotropin in large doses induced moderate sustained hyperadrenocorticism in cholesterol-fed cockerels, with a pattern of biochemical-physiologic-pathologic alterations similar to that effected by compound F.

3. Cortisone in large doses was relatively inactive in this avian species, exerting no significant effects on carbohydrate, protein, lipid or electrolyte metabolism. No increase of hypercholesterolemic hyperlipemia was observed. Nevertheless, moderate intensification of aorta and coronary atherosclerosis occurred, in association with moderate hypertensive effects induced by this corticoid in chicks.

SUMARIO ESPAÑOL

1. Hidrocortisona (compuesto F) en dosis moderadas indujo marcado e sostenido hiperadrenocorticismo en gallipollos alimentados con colesterol (intactos, aloxinados y depancreatizados), incluyendo los efectos típicos en el metabolismo electrolítico, de proteínas, carbohidrato y lípidos de 11, 17-oxisteroideos. No obstante la diabetes inducida por los esteroides y el acrecentamiento de la hiperlipemia hipercolesterolemica, no supervino intensificación de la aterogénesis coronaria o de la aorta.

2. Corticotropina de acción prolongada en dosis grandes indujo hiperadrenocorticismo moderado sostenido en gallipollos alimentados con colesterol, con un patrón de alteraciones fisiopatológicas y bioquímicas similares a las producidas por el compuesto F.

3. La cortisona en dosis grandes fue relativamente inactiva en estas especies avíparas, no ejerciendo efectos significativos en el metabolismo de carbohidratos, proteínas, lípidos o electrolitos. No se observó acrecentamiento de la hiperlipemia hipercolesterolemica. No obstante ocurrió intensificación de la aterogénesis coronaria y de la aorta, en asociación a los moderados efectos hipertensivos inducidos por este corticoide en los polluelos.

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REFERENCES


\textsuperscript{*} Deborah V. Dauber Research Assistant.


53 Pierce, F. T., Jr., and Bloom, B.: Relationship of ACTH and cortisone to the serum lipoproteins of the rabbit. Metabolism 1: 163, 1952.


60 Levin, L., and Farber, R. K.: Hormonal factors which regulate the mobilization of depot fat to the liver. Recent Progress Hormone Research 7: 399, 1952.


Effects of Cortisone, Hydrocortisone and Corticotropin on Lipemia, Glycemia and Atherogenesis in Cholesterol-Fed Chicks

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