Increased Sensitivity to Corticosterone as a Possible Factor in the Development of Adrenal Regeneration Hypertension

By Floyd R. Skelton, M.D., Ph.D.

In 1955 it was reported that uninephrectomized, young female rats, given access to 1 per cent sodium chloride solution to drink, developed hypertensive vascular disease during regeneration of the adrenal cortex. Because of the concurrence between blood pressure rise and adrenal regeneration, a working hypothesis was suggested which held that rebound hyperfunction of the regenerated cortex might be the cause of the hypertensive disease. However, it is well known that a period of cortical insufficiency intervenes between enucleation and regeneration of the adrenal cortex, and that increased sensitivity to the hypertensive properties of desoxycorticosterone accompanies Addison’s disease in man. These facts and the lack of evidence for oversecretion of any known steroid by the regenerating gland prompted the suggestion that the period of cortical insufficiency might sensitize to the hypertensive property of steroids secreted by the regenerating gland in normal or even subnormal amounts.

This communication recounts studies testing the validity of the above suggestion in 2 experiments based on the following premises:

1. If sensitization to corticosterone is involved in the pathogenesis of adrenal-regeneration hypertension, then administration of nonhypertensive doses to adrenalectomized rats after an interval of cortical insufficiency similar to that which occurs after adrenal enucleation should result in hypertensive disease. 2. If corticosterone is concerned in the genesis of adrenal-regeneration hypertension, the development of the syndrome should be potentiated by its exogenous administration, especially when started at an interval after adrenal enucleation.

Methods

Experiment 1
Corticosterone was administered to adrenalectomized, immature, female rats in daily subcutaneous doses of 0.5 mg., 1.0 mg., and 2.0 mg., beginning treatment at the time of adrenalectomy and after intervals of 7 to 14 days. Systolic blood pressures and body weights were determined weekly, and saline intake was measured daily and subsequently calculated as the ml. consumed per 100 Gm. body weight per day for each week. At the termination of the experiment, organs were weighed, examined for the presence of gross lesions, and fixed in 10 per cent formalin. Histologic slides of the kidney, heart, brain, adrenal, pancreas and mesentery were prepared by the usual hematoxylin and eosin method and examined microscopically. Both gross and microscopic evaluations were made on a 0 to +++ scale and expressed as a percentage of the possible combined maximum.

Experiment 2
Corticosterone was administered to adrenalec- tomized, immature, female rats in daily subcutaneous doses of 2.0 mg./100 Gm. body weight, beginning such treatment at the time of adrenalectomy and at intervals of 7, 14, and 21 days thereafter. Systolic blood pressures, body weights, and saline intake were measured as in experiment 1; gross and microscopic examination of the tissues also were performed similarly.
ADRENAL REGENERATION HYPERTENSION

SYSTOLIC BLOOD PRESSURE
SODIUM CHLORIDE INTAKE

Figure 1
Systolic blood pressure and sodium chloride intake of control, adrenal-enucleated, and corticosterone-treated adrenalectomized rats. Treatment was begun 2 weeks after adrenalectomy. Upper boundary of shaded areas is one standard error above the mean values (upper solid line) for the normal control group, and the lower boundary is one standard error below the mean values (lower solid line) for the adrenalectomized control group.

Results

Experiment 1

Figure 1 illustrates the effect of these doses of corticosterone on systolic blood pressure and sodium chloride intake when administration of the steroid was begun after a 2 week period of adrenal cortical insufficiency. Perusal of the figure shows that no dose of corticosterone reproduced either the hypertension or the increased saline consumption which had occurred in the rats bearing regenerating adrenals. Similar results were obtained when corticosterone treatment was started at the time of adrenal enucleation and 1 week after adrenalectomy. The data contained in table 1 further illustrate the failure of these doses of corticosterone to produce changes in either body and organ weights or tissue morphology similar to those induced by adrenal regeneration, even when adrenal cortical insufficiency existed for as long as two weeks before steroid treatment was started.

The histologic changes in adrenal-regeneration hypertension and other forms of steroid-salt hypertension in the rat have been previously described. The earliest changes are seen in the glomerulus, while the arterioles and tubules develop lesions later. Most of the changes seen in the kidneys of control rats with intact adrenals (group 1), control rats without adrenals (group 3), and in corticosterone-treated rats (groups 4 to 12) were of the glomerular type. However, 1 rat in each of groups 1 and 6 had more extensive arterial and arteriolar lesions involving the kidney, heart, brain, pancreas, and mesentery. Nevertheless, the difference between the severity and incidence of lesions in animals with regenerating adrenals and in the corticosteronetreated rats convincingly demonstrates that corticosterone did not reproduce the morphologic changes characteristic of rats with adrenal-regeneration hypertension.

Experiment 2

In this experiment, the control (group 1) and adrenal-enucleated (group 2) rats were killed after 5 weeks. Those adrenal-enucleated rats treated with corticosterone (groups 3 to 6) were sacrificed, so that steroid administration was uniformly of 5 weeks duration. When corticosterone injections were begun at the time adrenal enucleation was done (group 3), hypertension was prevented (fig. 2). In contrast to the gradually increasing polydipsia
### Table 1

*Body Weights, Organ Weights and Lesions in Rats with Regenerated Adrenals and in Adrenalectomized Rats Receiving Corticosterone*

<table>
<thead>
<tr>
<th>Group and treatment</th>
<th>No. of rats</th>
<th>Interval post-operative days</th>
<th>Body weight in Gm.</th>
<th>Organ weights in mg./100 Gm. of body weight</th>
<th>Organ lesions—per cent†</th>
<th>Lesion incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Heart</td>
<td>Kidney</td>
</tr>
<tr>
<td>(1) Control</td>
<td>10</td>
<td>—</td>
<td>62±1</td>
<td>205±4</td>
<td>434±19</td>
<td>815±42</td>
</tr>
<tr>
<td>(2) Adr.-enucl.</td>
<td>9</td>
<td>—</td>
<td>65±2</td>
<td>180±13</td>
<td>625±28</td>
<td>1108±26</td>
</tr>
<tr>
<td>(3) Adr.-x</td>
<td>5</td>
<td>—</td>
<td>69±2</td>
<td>191±7</td>
<td>444±18</td>
<td>673±18</td>
</tr>
<tr>
<td>(4) Adr.-x + B</td>
<td>9</td>
<td>0.5</td>
<td>70±2</td>
<td>213±4</td>
<td>418±8</td>
<td>840±50</td>
</tr>
<tr>
<td>(5) Adr.-x + B</td>
<td>9</td>
<td>1.0</td>
<td>72±2</td>
<td>200±4</td>
<td>406±6</td>
<td>762±22</td>
</tr>
<tr>
<td>(6) Adr.-x + B</td>
<td>10</td>
<td>2.0</td>
<td>72±1</td>
<td>201±8</td>
<td>433±30</td>
<td>805±27</td>
</tr>
<tr>
<td>(7) Adr.-x + B</td>
<td>5</td>
<td>0.5</td>
<td>69±3</td>
<td>210±4</td>
<td>431±16</td>
<td>808±25</td>
</tr>
<tr>
<td>(8) Adr.-x + B</td>
<td>9</td>
<td>1.0</td>
<td>67±2</td>
<td>212±4</td>
<td>450±18</td>
<td>952±61</td>
</tr>
<tr>
<td>(9) Adr.-x + B</td>
<td>9</td>
<td>2.0</td>
<td>70±2</td>
<td>204±5</td>
<td>428±9</td>
<td>813±24</td>
</tr>
<tr>
<td>(10) Adr.-x + B</td>
<td>7</td>
<td>0.5</td>
<td>66±1</td>
<td>195±4</td>
<td>444±10</td>
<td>831±22</td>
</tr>
<tr>
<td>(11) Adr.-x + B</td>
<td>7</td>
<td>1.0</td>
<td>67±1</td>
<td>209±2</td>
<td>403±6</td>
<td>904±48</td>
</tr>
<tr>
<td>(12) Adr.-x + B</td>
<td>8</td>
<td>2.0</td>
<td>71±1</td>
<td>200±5</td>
<td>441±9</td>
<td>952±32</td>
</tr>
</tbody>
</table>

*Treatment started at the time of adrenalectomy or at intervals of 1 to 2 weeks after adrenalectomy.
†Represents severity of lesions calculated from combined gross and microscopic evaluation on a 0 to +++ scale.
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SYSTOLIC BLOOD PRESSURE SODIUM CHLORIDE INTAKE

Figure 3
Influence of corticosterone on systolic blood pressure and sodium chloride intake of rats bearing a regenerating adrenal when treatment was begun one week after adrenal enucleation. Boundaries of the shaded areas are one standard error on either side of the mean values for the control group (solid line).

Figure 4
Influence of corticosterone on systolic blood pressure and sodium chloride intake of rats bearing a regenerating adrenal when treatment begun 2 weeks after adrenal enucleation. Boundaries of the shaded areas are one standard error on either side of the mean values for the control group (solid line).

of the rats bearing regenerating adrenals (group 2), those receiving corticosterone showed a marked increase in saline consumption for the first week, followed by a rapid decline almost to control levels thereafter. A slightly higher blood pressure developed in the rats (group 4) whose steroid treatment was initiated 1 week after adrenal enucleation (fig. 3) than in the rats of group 3, but it was still less than in untreated rats bearing regenerating adrenals. Again the consumption of saline was increased for the first week after corticosterone treatment was begun, only to fall to control levels in the latter part of the treatment period. If corticosterone administration was begun 2 weeks after adrenal enucleation (group 5), modest hypertension occurred (fig. 4), but the maximum blood pressure was lower and attained more slowly than that of untreated rats bearing regenerating adrenals. In this group, steroid treatment produced not a transient rise in saline intake but a progressive fall to control levels. When corticosterone treatment was started 3 weeks after adrenal enucleation (group 6), the final blood pressure attained (fig. 5) by these rats was only slightly less than in the untreated animals bearing regenerating glands. Again the transient rise in saline consumption did not occur after initiation of steroid treatment; in this instance the slight drop was followed by a more prolonged increase in intake toward the end of the treatment period.

Table 2 shows that corticosterone treatment started at 0 time inhibited the cardiac, renal and hepatic hypertrophy, as well as the morphologic changes normally occurring in hypertensive rats with regenerating adrenals. When treatment was started 1 week after adrenal enucleation the inhibitory effect of corticosterone was less apparent, and when begun at 2 and 3 weeks it was still less apparent, although some inhibition of the various changes did occur. In all treated groups, corticosterone produced inhibition of adrenal regeneration, although this was most pronounced when treatment was started at 0 time. Except for the thymic involution, corticosterone administration did not potentiate any changes in organ weights induced by adrenal regeneration, nor did it increase the severity or incidence of the lesions in the various organs and tissues. If anything, corticosterone inhibited the development of lesions, even when treatment was begun as late as 3 weeks after adrenal enucleation.
Discussion

When this form of experimental hypertensive disease was first described it seemed that its pathogenesis was relatively simple, probably involving rebound hyperfunction or some derangement in steroidogenesis of the regenerating adrenal cortex. Since that time Masson, Koritz and Peron, Laplante, Chappel, Stachenko and Giroud, Brogi and Pellegino and Weisz, Horváth, Kádas, Köves and Ritter have presented chemical evidence that no oversecretion of either corticosterone or aldosterone occurs during adrenal regeneration. Hence, the suggestion that the period of adrenal cortical insufficiency might sensitize to the hypertensive properties of corticosterone or aldosterone, even though their secretion might be less than normal, seemed especially attractive. The possibility received further credulity when it was shown that both steroids possessed hypertensive properties.15-18

However, studies in other laboratories, as well as our own, have shown that within 7 to 14 days after enucleation the regenerating adrenal cortex regains its capacity to produce sufficient corticosterone to maintain a normal blood level of this hormone. This seems to be a remarkably short time for any sensitization to the hypertension-inducing properties of the steroid to occur. Indeed, the preceding experimental evidence indicates that no sensitization occurred to nonhypertensive doses of corticosterone and seems to rule out the possibility that this mechanism plays a significant role in the pathogenesis of adrenal-regeneration hypertension. A similar conclusion was reached by Chappel et al. who used combined corticosterone and aldosterone treatment under somewhat similar conditions.

Furthermore, the results of the second experiment show that instead of potentiating the hypertensive disease accompanying adrenal regeneration, corticosterone exerted an inhibitory effect. This confirms and extends previously published observations. As the interval between adrenal enucleation and the beginning of corticosterone treatment became longer, the inhibitory effect of the steroid on the hypertensive syndrome became less marked. Nevertheless, it was present even when treatment was started 3 weeks after adrenal enucleation, although by this time the effect was manifest more in the decreased severity of organ lesions and weights of the heart and kidney than in reduced level of blood pressure. Perhaps an effect on blood pressure escaped detection since the method employed for blood pressure determination in this study is sufficiently sensitive to detect only large blood pressure differentials. No evidence of a potentiating effect of corticosterone on adrenal-regeneration hypertensive disease was observed.

It is possible, perhaps, to relate the inhibitory effect of corticosterone to the decreased consumption of sodium chloride by the rats receiving this steroid. The precise relationship between the polydipsia which occurs in rats bearing regenerating adrenals and the development of hypertensive disease has not been clearly established, although they frequently, but not invariably, occur together as the adrenal cortex regenerates. It is currently conceived that the polydipsia, when it occurs, and the hypertension are the result of the functional activity of the regenerating adrenal cortex.
Table 2

Influence of Corticosterone on Body Weights, Organ Weights and Lesions of Rats Bearing Regenerating Adrenals*

<table>
<thead>
<tr>
<th>Group and treatment</th>
<th>No. of rats</th>
<th>Days after operation</th>
<th>Body weight in Gm.</th>
<th>Organ weights in mg./100 Gm. of body weight</th>
<th>Organ lesions — Per cent† incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Heart</td>
<td>Kidney Adrenal Thymus Liver</td>
</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>—</td>
<td>50±1 191±2</td>
<td>386±6 748±22 28.6±0.7 234±7</td>
<td>3607 ±161 5292 159±26 6:10</td>
</tr>
<tr>
<td>(2) Adr.-enuel.</td>
<td>10</td>
<td>—</td>
<td>50±1 155±8</td>
<td>615±45 1201±66 22.9±2.6 159±26</td>
<td>52 47 33 6:10</td>
</tr>
<tr>
<td>(3) Adr.-enuel. + B</td>
<td>10</td>
<td>0</td>
<td>49±1 164±6</td>
<td>425±17 784±31 2.3±0.2 213±9</td>
<td>5292 3741 ±132</td>
</tr>
<tr>
<td>(4) Adr.-enuel. + B</td>
<td>9</td>
<td>7</td>
<td>49±1 170±5</td>
<td>452±14 851±36 4.1±0.4 124±15</td>
<td>4292 ±114 8 5 5 1:9</td>
</tr>
<tr>
<td>(5) Adr.-enuel.</td>
<td>10</td>
<td>14</td>
<td>51±1 176±6</td>
<td>486±21 969±40 8.1±1.4 113±8</td>
<td>4699 ±324 23 15 10 2:10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(6) Adr.-enuel. + B</td>
<td>7</td>
<td>21</td>
<td>54±2 194±6</td>
<td>448±30 957±56 6.2±0.5 87±6</td>
<td>4156 ±287 33 17 19 1:7</td>
</tr>
</tbody>
</table>

*Treatment started at the time of adrenal enucleation or at intervals of 1, 2, and 3 weeks after adrenal enucleation.
† Represents severity of lesions calculated from combined gross and microscopic evaluation on a 0 to +++ scale.
adrenal and that when regeneration of the gland is inhibited both fail to develop, as in the present study.

While these and other studies must be considered strong evidence against the participation of corticosterone in the genesis of adrenal-regeneration hypertension, they are not absolutely conclusive. Final evaluation must await more complete studies of the secretory activity of the adrenal cortex, including blood levels of corticosterone, throughout the course of regeneration, especially encompassing the period when the hypertensive syndrome develops. Particular attention must be paid to the uniformity of experimental conditions existing at the time when such functional studies are done, for Guillemín et al. have shown that the secretory activity of the anterior pituitary-adrenocortical system can be greatly altered in a very short period of time by minimal changes in environmental conditions. This and other studies of the functional characteristics of the regenerating adrenal cortex are presently under investigation in our laboratory.

**Summary**

The suggestion that the pathogenesis of adrenal-regeneration hypertension might involve sensitization to the hypertensive properties of corticosterone by the period of cortical insufficiency which follows adrenal enucleation has been investigated. Nonhypertensive doses of corticosterone were given to uninephrectomized, salt-treated and adrenalectomized rats after periods of insufficiency of variable length and to similar rats bearing regenerating adrenals, beginning such treatment at intervals after enucleation. The following conclusions have been drawn from the data obtained: (1) Adrenal cortical insufficiency for as long as 2 weeks did not sensitize to the hypertension-inducing property of corticosterone; (2) Corticosterone administration to rats bearing regenerating adrenals, beginning treatment up to 3 weeks after operation, did not enhance the development of hypertension or increase the severity of vascular lesions.

**Acknowledgment**

Appreciation is expressed to Mrs. Anne Thornberry, Mrs. Margaret Johnson and Miss Nola Russell for their technical assistance in the performance of these studies.

**Summario in Interlingua**

Esserva investigate le suggestion que le pathogenese del hypertension de regeneration adrenal es possibilemente in connexion causai con un sensibilisation al proprietates hypertensive de corticosterona como consequentia del periodo de insufficientia cortical que seque le enucleation adrenal. Doses non-hypertensive de corticosterona esseva administrate a rattos nephrectomisate unilateralmente, adrenalectomisate, e tractate con sal, post periodos de insufficientia de varie extensiones. Le mesme tractamento esseva applicate a altrus rattos, con le sol exception que istos reteneva adrenales in regeneration. Le sequente conclusiones es supportate per le datos colligate: (1) Insufficientia cortical durante usque a 2 septimanas non sensibilisava le animales al proprietates hypertensive de corticosterona e (2) le administration de corticosterona a rattos con adrenales in regeneration, quando le tractamento esseva communique usque a 3 septimanas post le operation, non promoveva le developpamento de hypertension e non augmentava le severitate del lesiones vascular.

**References**

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