Antihypertensive Effect of Hypophysectomy in Dogs with Hypertension Following Bilateral Carotid Sinus Constriction

By Edward W. Hawthorne, M.D., Ph.D., and Mary Gaspar, M.S.

A chronic type of experimental hypertension has been produced in dogs by bilateral sinus area constriction. Hypophysectomy has a prolonged antihypertensive effect in dogs with persistent hypertension resulting from carotid sinus area constriction, while no decrease in mean arterial pressure is seen after hypophysectomy in normotensive control dogs. These findings suggest the possibility that altered hypophysal function participates in the pathogenesis of this type of hypertension.

The experimental production of chronic hypertension in dogs by bilateral carotid sinus constriction has been reported by Wakerlin, Crandall, Frank, Johnson, Pomper, and Schmid. Their studies suggest that the persistent hypertension which follows may be initiated either by altered carotid sinus function or by a change in cerebral hemodynamics. The pathogenesis of this type of chronic hypertension is unknown and the possibility exists that it may be due to some altered humoral mechanism. Studies of others indicate that hypophysectomy in normotensive dogs does not necessarily lead to a fall in mean arterial pressure and in the dog, hypophysectomy does not prevent development of a modest renal hypertension following renal artery constriction. It was our view that in dogs hypertensive after carotid sinus constriction, the finding of a consistent and chronic antihypertensive effect of hypophysectomy would suggest a pathogenic role for altered hypophysal function.

Methods

Mongrel dogs of both sexes, generally weighing less than 12 Kg., were caged and fed the same standard diet. Each dog was allowed a period of one or more months of normotension, followed by bilateral carotid sinus constriction and a postoperative period of 3 or more months to allow for stabilization of the resulting hypertension.

The bilateral carotid sinuses were constricted as described by Wakerlin using the plastic clamps described and generously supplied to us by Dr. Wakerlin.

After these dogs became hypertensive, they were hypophysectomized and observed for periods of varying lengths. Normotensive dogs, without prior carotid sinus constriction, were also hypophysectomized to observe the effect of complete hypophysectomy on their mean arterial pressure.

Preoperatively the dogs were given 25 mg. of cortisone intramuscularly. Brain shrinkage was obtained by administering intravenously 50 ml. of 30 per cent glucose solution approximately 20 to 30 min. prior to surgery. Hypophysectomy was accomplished via a left transtemporal approach, following (in part) the principles of Cushing. The surgical technic was modified in that the entire pituitary was removed under direct vision by suction rather than with Cushing forceps.

Glucose solution (30 per cent) was intravenously injected postoperatively to relieve increased intracranial pressure during the 24 hours immediately following surgery. Small maintenance doses of either prednisolone or cortisone (usually 12 mg. every third day, intramuscularly) were given. Postoperative therapy included antibiotics. Dogs invariably developed hypoglycemic shock—some died—following cessation of maintenance therapy. Occasionally, a dog was not given corticoids but was maintained in good clinical condition by adding a glucose supplement to his diet. Both the normotensive dogs (without bilateral carotid sinus constriction) and the carotid sinus hypertensive dogs were maintained postoperatively in the same manner. In some instances the dogs developed obesity postoperatively, suggesting hypothalamic damage. Such dogs were not included in the results.

Insulin sensitivity studies were also performed on some of the dogs before and after hypophy-
TABLE 1.—Summary of Pressure Changes in Normal Dogs* Three Months After B.C.S.C.†

<table>
<thead>
<tr>
<th>Period of observation</th>
<th>Number of dogs</th>
<th>Mean ± S.D.</th>
<th>Average rise</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>28</td>
<td>119 ± 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>29</td>
<td>155 ± 30</td>
<td>+35</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* Average initial weight, 10 Kg.; range 7 to 14 Kg.
† Bilateral carotid sinus constriction.
‡ Third month post operative.

Effect of Bilateral Carotid Sinus Constriction. Twenty-nine dogs received bilateral carotid sinus constriction. All but 3 developed a chronic and persistent hypertension by the third postoperative month. Sixteen (55 per cent) developed hypertension acutely, that is, within the first month after constriction.

In 10 of the dogs (34 per cent) the mean arterial pressure gradually rose to hypertensive levels over a period of 3 months (fig. 1, table 1).

One of the 3 dogs that did not have a hypertensive response to the carotid sinus area constriction was a "spontaneous hypertensive" (control mean arterial pressure averaged 154 mm. Hg). The other 2 remained normotensive for a period of 4 months after operation. At autopsy, it was found that in these animals the plastic clamps were loose and no constriction had occurred.

Effect of Hypophysectomy on Mean Arterial Pressure in Normotensive Dogs. Five normotensive dogs were hypophysectomized after a control period of one or more months. After hypophysectomy they received maintenance therapy similar to that administered to hypophysectomized dogs with carotid sinus area constriction. None showed a fall in mean arterial pressure below the control level following hypophysectomy (fig. 2).

Hypotensive Effect of Hypophysectomy. Table 2 shows the change in arterial pressure following hypophysectomy.
### TABLE 2.—Antihypertensive Effect of Hypophysectomy in Dogs with Carotid Sinus Hypertension

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>Sex</th>
<th>Initial weight (Kg.)</th>
<th>Average pressure last two months before hypophysectomy</th>
<th>Average pressure first month after hypophysectomy</th>
<th>Change in pressure</th>
<th>Status of hypophysectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>F</td>
<td>8</td>
<td>121</td>
<td>156</td>
<td>+35</td>
<td>—40</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>8</td>
<td>120</td>
<td>150</td>
<td>+30</td>
<td>123</td>
</tr>
<tr>
<td>22</td>
<td>M</td>
<td>9</td>
<td>119</td>
<td>154</td>
<td>+35</td>
<td>119</td>
</tr>
<tr>
<td>24</td>
<td>M</td>
<td>8</td>
<td>109</td>
<td>159</td>
<td>+50</td>
<td>132</td>
</tr>
<tr>
<td>25</td>
<td>F</td>
<td>9</td>
<td>111</td>
<td>151</td>
<td>+40</td>
<td>132</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>7</td>
<td>120</td>
<td>183</td>
<td>+63</td>
<td>119</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>117</td>
<td>159</td>
<td>+42</td>
<td>124</td>
</tr>
<tr>
<td>± 2 S.D.</td>
<td></td>
<td>10.4</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bilateral carotid sinus construction.

that followed hypophysectomy in 6 dogs with hypertension resulting from carotid sinus area constriction. All of these dogs showed a definite fall in pressure, in most instances to normotensive control levels. Figure 3 shows the typical pattern of change in the mean arterial pressure following hypophysectomy in dog number 22. The dog showing the least hypotensive response (no. 25) was found to have an incomplete hypophysectomy at autopsy.

**DISCUSSION**

Our studies show that a chronic experimental hypertension can be produced by bilateral carotid sinus area constriction in dogs using special plastic clamps, confirming previous findings.

The finding that hypophysectomy has an antihypertensive effect on dogs with carotid sinus hypertension appears to be *bona fide*. This seems especially true in view of the lack of a blood pressure lowering effect from hypophysectomy in normal dogs. It might be said that a hypotensive effect from hypophysectomy in the normal dogs was prevented by the small maintenance doses of cortisone administered regularly post-operatively. It is to be stressed, however, that the hypertensive animals on similar post-operative therapy following hypophysectomy showed an average arterial blood pressure fall of 35 mm. Hg. The mean arterial pressure levels in dogs before and after hypophysectomy recorded by Goldblatt and associates showed no clear fall, without postoperative corticoid therapy. These studies suggest that there is an endocrine factor in the pathogenesis of the experimental hypertension which bilateral carotid sinus constriction produces in dogs and that this factor is in some way related to hypophysal function.

In view of our findings it will be interesting to observe the effects of administration of larger doses of corticoids and adrenocorticotrophic hormones as a means of determining whether or not this blood pressure lowering effect of hypophysectomy is mediated solely by way of a decrease in adrenal cortical activity.

**ACKNOWLEDGMENT**

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