Complete Prevention of Cerebral Accidents in Malignant Hypertension

By ANDRÉ ROBERT, M.D.

Ligation of the common carotid arteries was found to prevent the development of cerebral lesions (edema, hemorrhage, softening) in animals rendered hypertensive by daily injections of desoxycorticosterone acetate. The protection was complete when both carotids were ligated, and limited to the homolateral side in the case of unilateral ligation.

IT HAS been shown that arterial necrosis and inflammation seen in malignant hypertension can be prevented in a given territory by partial ligation of the nourishing artery. In the "endocrine kidney" procedure, in which the aorta between the origin of both renal arteries is partially ligated, the vessels situated below the ligature remain normal whereas severe periarteritis develops above it as well as hypertension. Similarly, if during the establishment of experimental hypertension in the rat a partial ligature is applied around a branch of the mesenteric arterial tree, the vessels tributary to the ligated artery will be protected from periarteritis whereas the other mesenteric arterioles show advanced lesions.

More recently it was found that brain edema and cerebral signs of encephalopathy due to malignant renal hypertension are abolished when hypertension is relieved by removal of the renal artery clamp.

In the experiment reported here, we studied the effect of a diminution of blood pressure localized in the head area on the development of hypertensive changes in the brain. The brain was chosen because pathological changes such as cerebral edema, hemorrhage and softening are very common complications of human hypertension and are frequently the immediate cause of death or of very serious functional impairment and because, in the rat, much of the cerebral blood supply can be markedly diminished without any danger of excessive ischemia of the brain taking place.

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MATERIALS AND METHODS

Animals and Hormonal Treatment. Eighty-four young female rats, of an average body weight of 50 Gm., of the Upjohn strain (originally from Sprague-Dawley), were divided into 6 groups as follows: Group I—6 rats, untreated controls; group II—6 rats, left carotid ligated; group III—10 rats, both carotids ligated; group IV—13 rats, DCA; group V—23 rats, DCA and left carotid ligated; group VI—26 rats, DCA and both carotids ligated.

Two mg. of desoxycorticosterone acetate (DCA), in the form of microcrystals (in suspension in 0.2 ml. of a mixture of carboxymethyl cellulose, polysorbate 80, propylparaben and water), were injected subcutaneously daily. All the animals were sensitized for mineralo-corticoid activity by a unilateral (right) nephrectomy and the substitution of 1 per cent NaCl for plain water as drinking fluid. They were fed Purina laboratory chow ad libitum.

Carotid Ligation. The left common carotid artery was sectioned between two ligatures 6 days, and the right carotid, 12 days after the beginning of the experiment. Special care was taken not to injure the sympathetic nerve adjacent to the carotid artery. However, a few of the animals showed a Claude Bernard-Horner syndrome after the operation because of damage to this nerve.

Follow-up. The fluid intake was measured daily and the body weight recorded once a week. The animals were observed daily individually for the detection of any neurological sign associated with hypertension.

Autopsy. After death of each animal, the internal organs were macroscopically examined. The following organs were put into Zenker and weighed after 24 hours of fixation: brain, heart, kidney, adrenals, hypophysis. When an animal was killed or had just died, the same organs and the pancreas and sometimes the mesentery were sectioned for histologic examination. The pancreatic and mesenteric vessels were examined histologically for the presence of periarteritis since they are usually first to show the lesion. After fixation the two cerebral hemispheres and the cerebellum could be easily dissected manually and weighed individually.
During the course of the experiment many animals died; others were killed while moribund. The remaining were killed 45 days following the beginning of hormonal therapy.

RESULTS

Survival Rate and Clinical State. As shown in table 1, DCA-treated animals survived longer when one or both carotids had been ligated. Actually, in each of the last 2 groups 5 animals were still alive at the end of the experiment. Three animals died in group III (both carotids ligated), between the fourth and sixth day after the second operation, hence their death can reasonably be attributed to surgical trauma. The general behavior of the animals of groups II and III (unilateral and bilateral ligation) was indistinguishable from that of group I (controls). Animals of group IV (DCA alone) were obviously sick and excitable after the first 2 weeks, whereas those of group VI (DCA plus bilateral ligation) were alert and in fairly good condition. In group V (DCA plus unilateral ligation) most of the animals were well, although a few appeared prostrated as those of group IV but much less excitable.

Animals treated with DCA alone developed clonic convulsions which were either spontaneous or readily elicited by suspension by the tail. The animal would cross its hind legs together and front legs together (fig. 1A). When one artery (the left) had been ligated, holding by the tail provoked a sudden crossing together of the anterior and the posterior legs on the left side only, while the body was convulsively turned to the left (fig. 1B). On the contrary, no convulsion was observed nor could be elicited in animals with both carotids ligated in spite of the heavy DCA treatment (group VI) (fig. 1C).

Body Weight and Fluid Intake. As expected, the growth of all the DCA-treated animals (IV, V, VI) was greatly retarded (fig. 2). In rats DCA-treated but unilaterally ligated (group V) the values of the body weight reached a plateau on the eighteenth day and this was maintained until the end of the experiment. When both carotids were ligated (VI), the body weight showed a very slow but steady increase throughout the experiment in contrast to the pronounced catabolism exhibited by animals of group IV (DCA without ligation). Similarly, DCA markedly increased the daily fluid consumption especially during the first 2 weeks. Thereafter, it tended to diminish and to reach values about double those of the controls. However, the intake of animals of group IV (DCA alone) fell abruptly after 2 weeks to a level comparable to those of the controls, whereas a steady saline intake was maintained in the DCA-treated animals provided one or both carotid arteries were ligated, probably because of their better clinical condition as compared to those whose artery has not been tied.

Pathological Changes

Brain. Ligation of either one or both carotid arteries (groups II and III) did not produce any visible alteration in the internal organs, even in the brain. On the other hand, the brains of the DCA-treated, unligated animals (group IV) were greatly enlarged. Upon lifting the calvarium, which was distended, the brain was found to be bulging and intense edema could be seen on the cerebral surface where the furrows delimiting the cerebral hemispheres, instead of being deep as in normal animals, were very superficial (fig. 3A). In all the animals of this fourth group (DCA alone) hemor-
Fie. 1. Effect of carotid ligation on the development of neurological signs in DCA-hypertensive rats. The neurological signs shown in this figure have been elicited by suspending the animals by the tail. Duration of treatment 28 days. A. DCA alone. The hind legs are crossed in a contraction, and sometimes the front legs also become contracted. B. DCA plus ligation of left carotid. Only the left side of the animal shows convulsions. The left hind and front legs have the tendency to cross together and the animal turns to the left. This is due to lesions limited to the right side of the brain, that is, the one opposite to the ligation. Note that the palpebral opening is smaller on the left side because of irritation of the sympathetic nerve at the time of operation. This complication, the so-called Claude Bernard-Horner syndrome, occurred in a few animals. C. DCA plus ligation of both carotids. The four legs move freely without any contraction as those of a normal animal. Note that the belly is distended due to the presence of ascites as a consequence of the DCA treatment.

rhages were visible on the surface of the brain. These hemorrhages were either minute, punctate, or, on the other hand, extended to 3 to 4 mm. In some cases, most of one hemisphere was covered by a large clot due to a subdural hemorrhage, which was obviously of recent origin. Sometimes, instead of a red hemorrhagic focus one could see an area of softening of the brain tissue. All of these changes were situated anywhere in the cerebral hemisphere, sometimes deeply in the tissues.

As shown in table 2, the brains of the animals of this fourth group were three times heavier, as expressed per 100 Gm. of body weight, than those of the animals of the first 3 groups, which were not treated with DCA.

In the fifth (DCA plus ligation of the left carotid) and the sixth (DCA plus bilateral ligation) groups (fig. 3B and 3C), there was no

Fig. 2. Growth of DCA-hypertensive rats with and without carotid ligation. The protection afforded by ligation of the carotids is shown here by the fact that the body weight was better maintained in these animals (groups V and VI) than in those receiving DCA with no ligation (group IV).
Fig. 3. Effect of carotid ligation on the development of brain lesions following treatment with DCA. A. DCA alone (group IV). The brain is edematous and both hemispheres show multiple hemorrhages. Duration of treatment 31 days. B. DCA plus unilateral carotid ligation (group V). Note the presence of hemorrhagic foci in the right hemisphere whereas the left one appears normal. The faint furrow dividing both hemispheres denotes the presence of edema. The cleft separating the brain from the cerebellum is clear-cut and straight on the left side, less marked and sinuous on the right side. Duration of treatment: 41 days. C. DCA plus bilateral carotid ligation (group VI). The brain is essentially of normal appearance. Encephalopathy produced by DCA has been entirely prevented by bilateral carotid ligation. Duration of treatment 45 days.

rounding of the skull. In group VI, there was no trace of visible edema nor a single hemorrhagic nor softening focus; both macroscopically and histologically the brains in this group were essentially normal. However, in group V, whereas the left hemisphere was normal, conversely the right one was obviously larger than the left, was edematous and showed several spots of hemorrhages. The weight of the brains in these last two groups was significantly lower than those of group IV (p < 0.01). However, the presence of one or two ligatures did not change appreciably the weight of the brains (compare groups V and VI) (table 2).

Internal Organs. These showed the usual changes of malignant hypertension, namely myocarditis, nephrosclerosis, periarteritis nodosa of the mesenteric, pancreatic, cardiac and renal arteries. All these pathologic changes did not seem to be influenced by the presence of unilateral or bilateral ligation of the carotid. There were also ocular hemorrhages which after histologic examination proved to be in the iris region. At autopsy, the anterior chamber of the eye was found to contain a blood clot in several animals. These ocular hemorrhages never appeared on the same side as the ligation and, in group VI where both carotids were ligated, there were no eye hemorrhages at all.

DISCUSSION

The most interesting finding in this experiment is undoubtedly the marked improvement of some features of the hypertensive disease achieved by ligation of the common carotid artery. The animals survived longer, their body weights and their appetite (at least for fluid which was measured) were much better maintained than without ligation and, finally, at autopsy the brains were found to be protected. It is noteworthy that one can influence at will one or the other hemisphere by ligating one or both arteries. The blood pressure itself in a given area thus appears to play an essential role in the pathogenesis of arteritis and its level in the brain area seems to us to be the deter-
mining factor in hypertensive encephalopathy. In a hypertensive animal, blood hits the arteries harder than in normal conditions. This blood impact may act as a “local stressor” for the tissues against which it is thrown, eliciting an inflammatory reaction of the arterial wall. Thereafter, the vessels become thicker, harder, lose elasticity and as the process goes on, some of the damaged arteries may burst any time in certain “neuralgic” regions, particularly where they are of small caliber and still have to stand a high internal pressure. This is the case particularly for the arterioles of the mesentery, the brain and the eye.

This hypothesis of the pathogenic role of high blood pressure per se is supported by a recent clinical observation. Sealy and Lober and Lillehei reported on patients operated for coarctation of the aorta. In 3 cases, within a few days after removal of the stricture, a very severe periarteritis nodosa developed of which 2 of these patients died. Lober and Lillehei note about their 2 cases that “the most striking event affecting the vascular system was the sudden introduction of elevated systemic blood pressure to the portion of the circulation which had never previously been subjected to that stress. It seems significant that the vascular lesions in the autopsy case and, as far as can be determined, in the second case also, were

### Table 2.—Effect of Carotid Ligation on Brain Weights and on Encephalopathy, with and without DCA Treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>I Unligated</th>
<th>II Left</th>
<th>III Left and Right</th>
<th>IV DCA</th>
<th>V DCA</th>
<th>VI DCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abs. per 100 Gm.</td>
<td>Abs. per 100 Gm.</td>
<td>Abs. per 100 Gm.</td>
<td>Abs. per 100 Gm.</td>
<td>Abs. per 100 Gm.</td>
<td>Abs. per 100 Gm.</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1590±21.6</td>
<td>872±12.9</td>
<td>±18</td>
<td>±159.2</td>
<td>±121.3</td>
<td>±123.7</td>
</tr>
<tr>
<td>Right hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>664±8.1</td>
<td>303±68</td>
<td>±6.7</td>
<td>±66.5</td>
<td>±63.1</td>
<td>±63.5</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diff. right/ left hemispheres</td>
<td>670±9.2</td>
<td>352±7.0</td>
<td>±8.0</td>
<td>±72.4</td>
<td>±51.8</td>
<td>±58.3</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>20†</td>
<td>87</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>17‡</td>
<td>77</td>
</tr>
</tbody>
</table>

The statistical analysis for the organ weights was calculated only for values expressed per 100 Gm. of body weight, since comparison of the absolute weights is not possible in view of the marked variation in the final body weights among the groups.

* Number of animals which showed the organic changes.
† Percentage of the animals which showed the organic changes.
§ In group V, cerebral edema and hemorrhages were present only in the right hemisphere.
$ p > .05 < 0.1."

In a hypertensive animal, blood hits the arteries harder than in normal conditions. This blood impact may act as a "local stressor" for the tissues against which it is thrown, eliciting an inflammatory reaction of the arterial wall. Thereafter, the vessels become thicker, harder, lose elasticity and as the process goes on, some of the damaged arteries may burst any time in certain "neuralgic" regions, particularly where they are of small caliber and still have to stand a high internal pressure. This is the case particularly for the arterioles of the mesentery, the brain and the eye.

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limited to those vessels which originated distal to the coarctation repair." Sealy observed later another similar case (personal communication). One can envisage the possibility that a diminution of blood pressure in the carotid artery, by means of mechanical constriction, would be beneficial in some cases of human hypertensive encephalopathy.

**SUMMARY**

Malignant hypertension has been produced in rats by daily injections of desoxycorticosterone acetate (DCA). All the animals so treated died within a month, showing extensive cerebral edema and hemorrhages. When both carotid arteries were ligated before the second week of treatment, the animals lived longer, showed a better clinical state, and at autopsy their brains were of normal appearance. In another group with only the left carotid tied, the right cerebral hemisphere showed encephalopathy whereas the left was free of lesions.

An influence of high blood pressure per se on the pathogenesis of encephalopathy is suggested.

**Acknowledgment**

The author wishes to express his gratitude to Mrs. M. Louise Brock for her very valuable technical help.

**SUMMARIO IN INTERLINGUA**

Hypertension maligne esseva inducite in rattos per le injection diurne de acetato de desoxycorticosterona. Omne le animalesque esseva assi tractate moriva intra un mense, monstrante extense grados de edema e hemorrhagia cerebral. Quando ambe arterias carotide esseva ligate ante le seconde Septimana del tractamento, le animales habeva un plus longe superviventia, illos monstrava melior statoes clinic, e al autopsia lor cerebros exhibiva aspectos normal. In un altrum gruppo in que solmente le sinistre arteria carotide esseva ligate, le dextere hemisphero cerebral monstrava encephalopathia durante que le hemisphero sinistre esseva libre de lesiones.

Pare justificate supponer un influentia de alte pressiones sanguine per se super le pathogenese de encephalopathia.

**REFERENCES**

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