Inactivation of Antifibromatogenic Substances
(Progesterone and Desoxycorticosterone Acetate) in the Liver

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INTRODUCTION

It is a well-known fact that estrogens (the fibromatogenic substances) are destroyed in the liver, while it is still debatable whether such hormones as progesterone and desoxycorticosterone (the antifibromatogenic substances) have a similar fate when they reach this organ. Fels and Mónaco (6) found that progesterone, whether injected under the skin, intraperitoneally, or directly into the liver, the spleen, or the uterus, gave the same progestational threshold in the rabbit. These authors concluded that, unlike the estrogens, progesterone is not inactivated by the liver. Eversole and Gaunt (5) found no significant difference in growth and survival between adrenalectomized rats with desoxycorticosterone acetate (DCA) pellets implanted into the spleen, and their various controls with pellets implanted under the skin, in the kidney, or intraperitoneally. Mark (14) obtained the same decrease of sodium chloride intake in adrenalectomized rats with DCA pellets placed under the skin or in the spleen. Accordingly these authors concluded that there is no evidence that DCA is inactivated by the liver or spleen. Burrill and Greene (3), on the other hand, found in adrenalectomized rats with subcutaneously and intramiesenterically implanted pellets that the liver can inactivate DCA but that this ability is quantitatively limited, since with greater quantities of the hormone, absorbed from larger intramiesenterically implanted pellets, survival and growth of adrenalectomized rats was observed.

Progesterone and desoxycorticosterone acetate administered subcutaneously are two of the main antifibromatogenic substances (9, 12, 13). Thus it was thought that placing tablets of these substances in the spleen, that is, draining them directly into the portal circulation, should help to solve the problem under discussion. Bruzzone and Cuevas (2) obtained complete antifibromatogenic action with large tablets of progesterone placed in the liver. However, in view of a possible quantitative limitation in liver inactivation similar to that observed for the fibromatogenic action of estrogens in this laboratory (1, 4), it seemed profitable to perform the following experiments, using various quantities of progesterone and of DCA, administered intrasplenically.

EXPERIMENTS

The method employed for obtaining a fibromatogenic reaction was the same as has been reported before (8). An a-estradiol tablet (the fibromatogenic substance) was placed under the skin of castrated female guinea pigs of approximately 300 gm. body weight (11). In these same animals a tablet of progesterone or of DCA (the antifibromatogenic substances) was inserted well into the spleen (Groups III and IV in Table I). Animals to be used as controls were treated exclusively with the fibromatogenic substance (Group I), while others received both the fibromatogenic and antifibromatogenic substances, both, however, implanted subcutaneously (Groups II and IV).

In an effort to obtain a wide range of absorption all sizes of tablets were used, while some of the tablets were made up of 60 per cent cholesterol and 40 per cent of the desired substance, as it has been proved that the absorption is not selective (7, 9). The experiments lasted 90 to 96 days at the end of which time the animals were autopsied. The amount of hormone absorbed was calculated from the loss of weight of the tablet cleaned of its fibrous capsule, washed, and dried in a vacuum. The results are summarized in Table I.

The fibrous abdominal reaction was classified according to the rules explained in former papers (9, 10): the total, or fibrous tumor, effect (F.T.E.), averaging somewhat more than 5 in the control group (I) and decreasing proportionally with the antifibromatogenic action; the number of animals within each group reaching the control average F.T.E. of 5; finally,
TABLE I: COMPARATIVE ANTIFIBROMATOCGENIC EFFECT OBTAINED WITH SUBCUTANEOUS OR INTRASPLENIC IMPLANTATION OF PROGESTERONE AND DESOXYCORTICOSTERONE ACETATE TABLETS IN 71 CASTRATED FEMALE GUINEA PIGS SIMULTANEOUSLY RECEIVING SUBCUTANEOUS IMPLANTATION OF TABLETS OF a-ESTRADIOL

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Estradiol absorbed daily, µgm.</th>
<th>Progestogen administered</th>
<th>Mode of administration of progestogen</th>
<th>Absorption of progestogen daily, µgm.</th>
<th>Fibrous tumorous effect (F.T.E.), average</th>
<th>Number of animals reaching F.T.E. = 5</th>
<th>Average of tumorous marks, classes 2 and 3, per animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6-21</td>
<td>Progesterone</td>
<td>Subcutaneously</td>
<td>12-30</td>
<td>5.2</td>
<td>10</td>
<td>5.1</td>
</tr>
<tr>
<td>IIa</td>
<td>17-33</td>
<td>Progesterone</td>
<td>Subcutaneously</td>
<td>12-30</td>
<td>1.1</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>IIb</td>
<td>13-31</td>
<td>Progesterone</td>
<td>Intrasplically</td>
<td>33-57</td>
<td>2.8</td>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>IIb</td>
<td>13-31</td>
<td>Progesterone</td>
<td>Intrasplically</td>
<td>33-57</td>
<td>2.8</td>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>IIIa</td>
<td>25-97</td>
<td>Progesterone</td>
<td>Subcutaneously</td>
<td>59-164</td>
<td>1.4</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>IIIb</td>
<td>18-39</td>
<td>Progesterone</td>
<td>Intrasplically</td>
<td>85-148</td>
<td>2.7</td>
<td>9</td>
<td>0.7</td>
</tr>
<tr>
<td>IIIc</td>
<td>24-78</td>
<td>Progesterone</td>
<td>Intrasplically</td>
<td>9-36</td>
<td>5.0</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>IVa</td>
<td>19-134</td>
<td>Desoxycorticosterone</td>
<td>Subcutaneously</td>
<td>9-36</td>
<td>5.0</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>IVb</td>
<td>23-126</td>
<td>Desoxycorticosterone</td>
<td>Subcutaneously</td>
<td>9-36</td>
<td>5.0</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Va</td>
<td>13-92</td>
<td>Desoxycorticosterone</td>
<td>Subcutaneously</td>
<td>9-36</td>
<td>5.0</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>Vb</td>
<td>17-72</td>
<td>Desoxycorticosterone</td>
<td>Subcutaneous</td>
<td>9-36</td>
<td>5.0</td>
<td>4</td>
<td>2.7</td>
</tr>
</tbody>
</table>

It can be seen, as has been repeatedly observed (9), that in the present work the antifibromatogenic threshold, or the amount necessary to prevent abdominal fibroids, was again approximately 12 to 30 µgm. daily for progesterone (Group IIa). The threshold dose was more than 40 µgm. a day for DCA (Group IVa and IVb): there was no antifibromatogenic action with less than 40 µgm. of DCA daily (Group IVa). Progesterone, administered intrasplenically in doses of 16 to 29 µgm. per day, was not able to prevent the appearance of abdominal fibroids (Group IIIa), as the F.T.E. observed was almost as high as in the control group without progesterone. With larger doses some antifibromatogenic action was obtained, as judged by the lower F.T.E. (Groups IIIb and IIIc); but even with these greater quantities of progesterone the antifibromatogenic action was never as distinct as with subcutaneous administration (Group IIb). These differences between the various progesterone groups can be clearly appreciated in Fig. 1, where individual results (F.T.E.) are graphically represented.

![Fig. 1. Fibromatogenic effect with a-estradiol alone (Group I), with a-estradiol and subcutaneously implanted progesterone (Groups IIa and IIb), and with a-estradiol and varying doses of intrasplenically implanted progesterone (Groups IIIa, IIIb and IIIc). Each column corresponds to an individual experiment. The dotted line indicates the average F.T.E. of the control animals (Group I) receiving only a-estradiol.](cancerres.aacrjournals.org)

DCA, administered intrasplenically in small as well as in comparatively large doses, did not prevent the appearance of abdominal fibroids (Group V). It can be seen that animals with intrasplenically implanted tablets of DCA, with an absorption of large doses (Group V), behaved similarly to animals with an absorption of doses not reaching the antifibromatogenic threshold (Groups IVa and IVb). The individual F.T.E. figures are given in Fig. 2.

![Fig. 2. Fibromatogenic effect with a-estradiol alone (Group I), with a-estradiol and varying doses of subcutaneously implanted DCA (Groups IVa and IVb), and with a-estradiol and varying doses of intrasplenically implanted DCA (Groups Va and Vb).](cancerres.aacrjournals.org)
Thus we can deduce from these observations that progesterone as well as desoxycorticosterone acetate passing directly through the liver are inactivated, as judged by the decreased antifibromatogenic effect in those groups in which these substances were absorbed from intrasplenically implanted tablets (Groups IIIa and Vb with a F.T.E. similar to animals with estradiol only). But at the same time our observations show that above a certain dose a portion of the hormone escapes inactivation, as judged by the lowering of the F.T.E. in Groups IIIb and IIIc, compared with Groups I and IIa.

**SUMMARY**

The liver is capable of inactivating antifibromatogenic substances such as progesterone and desoxycorticosterone acetate, but this ability is a quantitatively limited one.

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