THE EFFECT OF ADRENALINE ON THE WHITE BLOOD PICTURE OF CANCER PATIENTS AFTER HYPOPHYSECTOMY

By

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During the last few years, it has been shown that adrenaline brings about a decrease in the number of the circulating eosinophil cells in the blood if cortisone is present even in the absence of the adrenal cortex (Kark & Muerhcke, 1952). Moreover, adrenaline does not increase the excretion of conjugated hydroxycorticoids in the blood or in the urine (Reddy et al., 1952, Sandberg et al., 1953). Recently, however, experiments by Japanese investigators appear to show that in dogs, adrenaline increases the concentration of glucocorticoids in the adrenal veins even in hypophysectomized animals (Okinaka et al., 1954). The role of the hypophysis as a mediator of the effect of adrenaline has also been much discussed. Long et al. (1954) claimed that adrenaline exerts an eosinopenic effect in rats via the anterior lobe of the hypophysis and the adrenal cortex. In hypophysectomized rats Jakobson & Hortling (1954) too were unable to demonstrate any eosinopenia. In man, after hypophysectomy for malignant disease, eosinopenic effect of adrenaline is abolished (Luft & Olivecrona, 1953), although Luft has recently claimed that during substitution therapy with cortisone, adrenaline again causes eosinopenia (Luft, 1955).

Originally it was thought that cortisone induced lymphocytopenia (White & Dougherty, 1945), though this has received less attention than the effect of eosinopenia. Animal experiments and some observations on man have later shown that these two types of cells behave differently after the administration of adrenaline. Thus in the rat the fall in the number of the lymphocytes is more rapid than the fall in the number of eosinophils (Hungerford, 1949, a. o.). In hypophysectomized rats adrenaline induces no changes in the number of eosinophils but may cause a fall in the number of lymphocytes according to
Jakobson & Hortling, 1954. The neutrophil granulocytes, on the other hand, seem to be independent of the pituitary-adrenal system (White & Dougherty, 1945, Soylemezoglu & Wells, 1951, Jakobson & Hortling, 1945, a. o.).

Even if it seems probable that the effect of adrenaline on the eosinophils prior to and after hypophysectomy is similar to the effect seen in adrenalectomized patients, with and without cortisone administration, the abovementioned observations have made it important to study not only the eosinophils but also the other types of leucocytes before and after hypophysectomy and with and without cortisone administration. Hypophysectomy was performed on patients suffering from advanced mammary cancer.

METHODS AND MATERIAL

0.4 mg. adrenaline (Exadrin Astra) was administered intramuscularly prior to and after hypophysectomy performed on 9 patients with advanced metastasizing mammary cancer. After hypophysectomy adrenaline was also given 4 hours after the oral administration of 50 mg. Cortone Merck (in one patient 25 mg.) at 4 a.m. In 6 cases the effect of cortisone alone given at the same time of the day was observed. The eosinophils were stained according to the method described by Randolph with phloxine-propylene-glycol. The cells in the squares on the two sides were counted in a 0.2 deep Fuchs-Rosenthal counting chamber. Fairly good agreement was found between the values for the two sides of the chamber. The total count for the leucocytes was done in the usual way and differential smears were stained with haematoxylin-v. Gieson. The results have been checked by the t-method.

The hypophysectomies were, as a rule, done some weeks before the adrenaline tests. In 4 of the cases autopsy later revealed, that nothing was left of the hypophysis, in one case cells from the anterior lobe were observed by histological examination but it is difficult to interpret the functional state of these cells. In one case no autopsy was performed and the remaining cases are still alive. In any case one has to assume a very gross lesion of the hypophysis as a result of the surgical intervention in all the patients, although it may perhaps be mentioned that even in the most complete hypophysectomy, rudimentary or aberrant hypophysal tissue may be left unobserved. None of the patients could do without a substitution therapy of from 37.5 to 75 mg. cortisone per day.

RESULTS

The effect of adrenaline on the different types of leucocytes is seen in Table 1. After 4 hours a significant fall in the number of the eosinophils (eo) was seen as well as a fall in the number of the lymphocytes (ly) though a rise in the number of the neutrophil granulocytes (ng) occurred. After the hypophysectomy no significant fall was seen in eo or in ly after adrenaline but the ng rose again. When 50 mg. of Cortone Merck was given to the hypophysectomized patients 4 hours before the adrenaline a clear fall in eo (82 per cent,
Table 1.

The effect of adrenaline on the number of the eosinophil cells, the lymphocytes and the neutrophil granulocytes prior to hypophysectomy. Mean absolute values per cu. mm. and mean values of the percentage changes.

<table>
<thead>
<tr>
<th>Time</th>
<th>Eosinophil cells</th>
<th></th>
<th>Lymphocytes</th>
<th></th>
<th>Neutrophil granulocytes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patient</td>
<td>Absolute count</td>
<td>Percentage change</td>
<td>Number of patient</td>
<td>Absolute count</td>
<td>Percentage change</td>
</tr>
<tr>
<td>Before</td>
<td>9</td>
<td>134</td>
<td></td>
<td>8</td>
<td>1391</td>
<td>+44</td>
</tr>
<tr>
<td>1 hour</td>
<td>114</td>
<td>-16</td>
<td></td>
<td>2147</td>
<td>+44</td>
<td>4892</td>
</tr>
<tr>
<td>2 hours</td>
<td>80</td>
<td>-38</td>
<td></td>
<td>1442</td>
<td>-3</td>
<td>4808</td>
</tr>
<tr>
<td>4 hours later</td>
<td>53</td>
<td>-66</td>
<td></td>
<td>1079</td>
<td>-23</td>
<td>5150</td>
</tr>
</tbody>
</table>

P < 0.0001
P > 0.04
< 0.05
P > 0.02
< 0.03
P < 0.0001) was observed as against −9 per cent without cortisone and −66 per cent before hypophysectomy. The lymphocytes and the neutrophil granulocytes generally presented the same picture as without cortisone. The results are given in Tables 1–3 and in Fig. 1.

The effect of cortisone alone administered at the same time and in the same dosage as when given before the adrenaline injections gave the following mean absolute values of eo: 4 hours after cortisone administration, 75/cu. mm., 2 hours later 124 and 4 hours later 111/cu. mm. (mean percentage change + 4).

See Fig. 1. It seems clear that cortisone alone cannot be responsible for the marked fall in the number of eo found after the injection of adrenaline.

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**Fig. 1.**

The effect of adrenaline on the leucocytes in the peripheral blood of 9 patients with advanced mammary cancer. Mean changes in per cent.
Table 2.
The effect of adrenaline on the number of the eosinophil cells, the lymphocytes and the neutrophil granulocytes after hypophysectomy. Mean absolute values per cu.mm. and mean values of the percentage changes.

<table>
<thead>
<tr>
<th>Time</th>
<th>Eosinophil cells</th>
<th>Lymphocytes</th>
<th>Neutrophil granulocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patient</td>
<td>Absolute count</td>
<td>Percentage change</td>
</tr>
<tr>
<td>Before</td>
<td>9</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>9</td>
<td>254</td>
<td>+44</td>
</tr>
<tr>
<td>2 hours</td>
<td>9</td>
<td>161</td>
<td>-5</td>
</tr>
<tr>
<td>4 hours later</td>
<td>9</td>
<td>130</td>
<td>-9</td>
</tr>
</tbody>
</table>

P = insign.

Table 3.
The effect of adrenaline on the number of the eosinophil cells, the lymphocytes and the neutrophil granulocytes 4 hours after the oral administration of 50 mg. Cortone after hypophysectomy. Mean absolute values per cu.mm. and mean values of the percentage changes.

<table>
<thead>
<tr>
<th>Time</th>
<th>Eosinophil cells</th>
<th>Lymphocytes</th>
<th>Neutrophil granulocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patient</td>
<td>Absolute count</td>
<td>Percentage change</td>
</tr>
<tr>
<td>Before</td>
<td>9</td>
<td>170</td>
<td></td>
</tr>
<tr>
<td>1 hour</td>
<td>9</td>
<td>120</td>
<td>-27</td>
</tr>
<tr>
<td>2 hours</td>
<td>9</td>
<td>97</td>
<td>-46</td>
</tr>
<tr>
<td>4 hours later</td>
<td>9</td>
<td>36</td>
<td>-81</td>
</tr>
</tbody>
</table>

P < 0.0001

P = insign.
DISCUSSION

With regard to the eosinophils in the blood these observations seem to indicate that the hypophysis in man, at any rate, is not essential for the eosinopenia after administration of adrenaline. The presence of cortisone in the tissues seems to be decisive. It is possible that the somewhat smaller fall in the number of the eosinophils before hypophysectomy indicates that in these severely sick patients, the cortisone reserves or the ability to use any available cortisone were insufficient. The lymphocytes, on the other hand, do not seem to behave in the same way as the eosinophils, in that it was not possible to induce a fall in the number of these cells after adrenaline in hypophysectomized patients, when cortisone had been previously administered at least within the time, i.e. 4 hours, used in these experiments. This period is probably sufficiently long to show such a fall since, for instance, in rats the fall in these cells after adrenaline occurs sooner than the fall in the eosinophils, whilst in the human after intravenous adrenaline administration a significant fall was seen 4 hours after the adrenaline injection as well as in those experiments prior to hypophysectomy (Hortling & Pekkarinen, 1949). From the practical point of view these results seem to indicate that the lymphocytes are more useful in the investigation of deficiencies of the function of the hypophysis than are the eosinophil cells. This material does not yet allow of any conclusions about the usefulness of these lymphocytes reactions when assessing the completeness of hypophysectomy. The behaviour of the eosinophils, on the other hand, seems to be mainly dependent on the cortisone available in the tissues. The neutrophil granulocytes in these tests increased in number independently of hypophysectomy after adrenaline administration, whilst previously administered cortisone did not seem to influence these results significantly.

The mechanism of adrenaline eosinopenia is unknown, nor do we know which cells in the bone marrow or in the tissues are influenced by adrenaline in such a way as to cause eosinopenia and lymphocytopenia in the blood, when cortisone is available but this effect may be indirect (Tanos et al., 1953). Recent investigations have further shown that adrenaline does not inhibit the formation of new cells in cultures of eosinophil cells (Krippsche & Osgood, 1955) and previously it was shown that the eosinopenia in the blood is not accompanied by an eosinopenia in the bone marrow (Rosenthal, 1950, Uhrbrand, 1954, a. o.).

SUMMARY

Adrenaline tests made on 9 patients suffering from mammary cancer before and after hypophysectomy with and without previous cortisone administration showed that the eosinopenia and the lymphocytopenia induced before the sur-
gical intervention were not demonstrable subsequently. If cortisone was given 4 hours before adrenaline in the hypophysectomized patients a marked eosinopenia was again induced but no lymphocytopenia. The rise in the number of the neutrophil granulocytes did not seem to be significantly influenced by the measures employed.

ACKNOWLEDGMENT

This investigation has been aided by a grant from the Sigrid Juselius Stiftelse.

REFERENCES

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