DESTRUCTION OF THE HYPOPHYSIS WITH RADIO-ACTIVE COLLOIDAL CHROMIC PHOSPHATE IN CANCER OF THE PROSTATE

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(Received for publication August 20, 1957)

TREATMENT of metastatic cancer of the prostate by hypophysectomy has been reported by several investigators.\(^8\),\(^10\),\(^14\) This therapy has been tried in the hope that the tumor cells might be dependent to some degree upon the secretion of adrenal androgens, or upon growth hormone or some other secretion of the hypophysis. The number of cases of cancer of the prostate treated by destruction of the pituitary body is not yet great enough to evaluate adequately the effectiveness of this treatment. Luft and Olivecrona\(^8\) were able to find in the literature 3 cases of cancer of the prostate in which remission occurred after hypophysectomy. They added 5 of their own, making a total of 8 remissions in 16 patients treated by surgical hypophysectomy. Precise interpretation of these data is difficult since orchiectomy had not been performed in all instances. For instance, the patient of Luft and Olivecrona,\(^8\) who had the longest remission (over 24 months), had not had orchiectomy prior to hypophysectomy. It is entirely possible that the prolonged remission in this case may have been caused entirely by the cessation of testicular function. The patient reported by Scott\(^14\) who had a good remission after hypophysectomy also had not had orchiectomy. On the other hand, the reported data are not complete enough to exclude the possibility that at least some of the patients who received no benefit from hypophysectomy might not have been completely hypophysectomized.

The technical difficulties of performing a complete hypophysectomy have limited the use of this operation.\(^1\) In order to avoid surgical hypophysectomy, external irradiation of the pituitary body has been tried. Because of the location of the pituitary body and its resistance to irradiation, it had not been possible to achieve complete permanent interruption of pituitary function with this method.\(^7\) However, the recent use of high-energy proton irradiation of the pituitary body may have solved this difficulty.\(^9\) Internal irradiation of the gland has been tried with several radioisotopic techniques including the implantation of yttrium pellets,\(^16\) radon seeds,\(^5\) and gold.\(^1\),\(^6\)

Recently, Rothenberg et al.\(^11\) attempted the direct injection of radioactive colloidal chromic phosphate containing P-32 into the substance of the gland in 6 patients with neoplasms. Phosphorus-32 would seem to offer some advantages over the other radioisotopes used for this purpose, because of its
relatively long half-life, its energetic beta particle, and because it does not produce gamma radiation. To our knowledge, this preliminary report of Rothenberg et al. and one other preliminary report by the same group12 are the only articles published describing the use of radioactive colloidal chromic phosphorus for destroying the pituitary gland. They performed this procedure in 3 cases of carcinoma of the breast, 2 cases of thyroid carcinoma and 1 case of prostatic carcinoma. For this purpose, they injected 2 ml. of colloidal chromic phosphate containing 10 mc. of P-32 directly into the pituitary substance. We have performed this procedure in 6 patients with far-advanced carcinoma of the prostate in order (1) to evaluate the effect of destruction of the pituitary body on cancer of the prostate, and (2) to investigate the clinical usefulness of this particular method of destroying the pituitary body. The results obtained are presented.

TECHNIC

After a frontotemporal flap is turned, the frontal lobe is retracted gently until the diaphragm sellae is identified. With the exception of the first patient, 0.5 to 1.5 ml. of a solution containing 9-10 mc. of P-32 (Table 2) as colloidal chromic phosphate was injected into the substance of the gland, using a 25-gauge needle. Three ml. of this solution were injected into the pituitary body of the first patient. The subsequent patients received less than 1.5 ml. of the chromic phosphate solution because injections of aqueous methylene blue into the normal pituitary body at autopsy showed that volumes greater than this resulted in marked overflow of the dye. At least four sites of injection were used in an attempt to distribute the radioactivity throughout the gland. Methylene blue was added to the colloidal material so that leakage of the radioactive solution superiorly could be detected and removed by washing with copious amounts of saline. The pituitary stalks in Cases 4, 5 and 6 were clipped and severed prior to the injection of P-32.

Preliminary studies performed on normal pituitary glands at autopsy had shown us that the injected material diffuses fairly evenly throughout the substance of the gland. Usually, any excess of injected material escapes from the sella by migrating laterally and inferiorly under and between layers of the dura mater. Dye can be identified beneath the dura mater behind the posterior clinoids when more than 1 ml. is injected. There is also leakage superiorly out through the top of the sella when large volumes are injected, but when the injected volume is less than 1 ml. this does not usually occur. Since the sella has a capacity of less than 1 ml. it would seem reasonable to limit the volume injected to less than this amount in order to minimize leakage and in this way avoid excessive irradiation of nearby neurologic structures.

CASE MATERIAL

The patients chosen for this procedure had far-advanced metastatic carcinoma of the prostate gland. Each had had symptomatic improvement following orchiectomy except Patient 2 who had not improved after this procedure and Patient 4 who had refused orchiectomy. All patients required narcotics for relief of pain. Each of these patients had become refractory to estrogen therapy before pituitary destruction was attempted. All patients had biopsy proof of prostatic carcinoma. Table 1 summarizes the clinical and
DESTRUCTION OF HYPOPHYSIS WITH RADIOACTIVE P-32

TABLE 1
Clinical summary of 6 patients with prostatic carcinoma treated by radiation of the hypophysis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>62</td>
<td>62</td>
<td>59</td>
<td>59</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Months since transurethral resection</td>
<td>27</td>
<td>1</td>
<td>23</td>
<td>—</td>
<td>—</td>
<td>13</td>
</tr>
<tr>
<td>Months since orchiectomy</td>
<td>26</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>—</td>
<td>12</td>
</tr>
<tr>
<td>Response to orchiectomy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Pain</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bony metastasis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hemoglobin gm.%</td>
<td>9.9</td>
<td>8.8</td>
<td>12.0</td>
<td>8.7</td>
<td>14.0</td>
<td>11.0</td>
</tr>
<tr>
<td>W.B.C. x 10^-3</td>
<td>11.0</td>
<td>7.0</td>
<td>16.0</td>
<td>9.2</td>
<td>9.9</td>
<td>7.8</td>
</tr>
<tr>
<td>Alkaline phosphatase B.U.</td>
<td>4.0</td>
<td>66.0</td>
<td>7.8</td>
<td>17.0</td>
<td>6.6</td>
<td>24.0</td>
</tr>
<tr>
<td>Acid phosphatase B.U.</td>
<td>4.8</td>
<td>0.5</td>
<td>1.0</td>
<td>4.8</td>
<td>2.7</td>
<td>0.7</td>
</tr>
<tr>
<td>N.P.N. mg.%</td>
<td>45.0</td>
<td>18.0</td>
<td>39.0</td>
<td>39.0</td>
<td>36.0</td>
<td>39.0</td>
</tr>
<tr>
<td>24 hr. I-131 uptake %</td>
<td>4.7</td>
<td>27.0</td>
<td>—</td>
<td>3.9</td>
<td>3.9</td>
<td>21.0</td>
</tr>
<tr>
<td>Protein bound iodine iugm.%</td>
<td>4.5</td>
<td>7.1</td>
<td>—</td>
<td>6.2</td>
<td>6.2</td>
<td>5.1</td>
</tr>
<tr>
<td>Cholesterol mg.%</td>
<td>249.0</td>
<td>205.0</td>
<td>175.0</td>
<td>175.0</td>
<td>175.0</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Laboratory findings of the patients before radiation of the hypophysis. The acid or alkaline phosphatase was elevated in all cases. One of the patients had a slight elevation of the nonprotein nitrogen and 3 patients were anemic at the time of surgery. The I-131 uptake was low in 2 of the 4 cases in which it was performed. These patients had no signs suggesting myxedema.

RESULTS

Operative Mortality. Five of the 6 patients regained consciousness after surgery. Four of these 5 had moderately severe to severe headache postoperatively which we believe may have been caused by the effects of the irradiation since it was more severe than the headache that usually occurs after hypophysectomy. Three of the 6 patients died postoperatively. It was in these patients that the pituitary stalk had been severed prior to the injection of P-32. The 3 patients who survived this procedure had not had their pituitary stalks divided. It is possible that division of the stalk in Cases 4, 5 and 6 was a factor in the postoperative mortality. Because the half-life of radioactive phosphorus is about 2 weeks it would be expected that destruction of the pituitary gland by irradiation would occur gradually. For this reason replacement of hydrocortisone was delayed in Cases 4 and 5. Recently Russell13 has called attention to the possibility that division of the
stalk may, in itself, produce infarction of the anterior lobe of the hypophysis. The presence of fever and shock postoperatively in Cases 4 and 5 suggests the possibility that adrenal insufficiency might have resulted from sectioning of the stalk.

Patient 4 was in extremely poor condition before surgery with fever and anemia which had been corrected at another hospital. He had had a pulmonary embolus 1 week before surgery. Even though he was a poor operative risk he was operated upon because of intense generalized pain which was not relieved by large doses of narcotics.

Patient 6 had been treated previously for hypertensive cardiovascular disease. He died 32 hours after surgery. At autopsy the brain was edematous and hemorrhagic, suggesting that his hypertension may have been a factor in his death.

It is possible that more careful selection of our patients and earlier replacement of hydrocortisone would have significantly decreased our mortality with this procedure. The number of cases is too small to determine accurately what the mortality would be under more ideal conditions. In this connection Rothenberg et al.\textsuperscript{11} reported only 1 postoperative death among 6 patients subjected to this procedure.

Effect of Procedure on Pituitary Function. The effect of this procedure on pituitary function is summarized in Table 2. In the 3 patients in whom less than 1.5 ml. of material was injected and in whom pituitary function could be evaluated postoperatively, there was evidence of profound depression of pituitary function. However, in Case 2 pituitary function returned to normal 7 months after surgery.

**TABLE 2**

*Effect of intrapituitary injection of P-32 labeled chromic phosphate on pituitary function*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Stalk Divided</th>
<th>mc. P-32 Injected</th>
<th>ml. Injected</th>
<th>Length of Survival</th>
<th>Effect on Pituitary Function</th>
<th>Pituitary Body at Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>7.2</td>
<td>3.0</td>
<td>3 mos.</td>
<td>No definite laboratory evidence of impairment</td>
<td>Minimal histologic changes</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>11.2</td>
<td>1.5</td>
<td>12 mos.</td>
<td>Severe diabetes insipidus beginning in 6th wk. lasting 5 mos. 4 wks. postop. FSH 6 mouse units/24 hrs., I-131 uptake 4.9%, urinary 17 KS 0.9 mg./24 hrs. Pituitary function returned to normal 7 mos. postop. with FSH &gt;52 MU, I-131 9.9%, 17 KS 9.2 mg.</td>
<td>Minimal histologic changes in anterior lobe with focal areas of fibrosis. Posterior lobe showed glial changes</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>9.7</td>
<td>1.0</td>
<td>10 wks.</td>
<td>3 wks. postop. 24 hr. I-131 uptake 0.0%, FSH &lt;6 MU/24 hrs. No diabetes insipidus</td>
<td>Very few viable cells (about 2%) in anterior lobe. Posterior lobe completely destroyed</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>10.0</td>
<td>1.0</td>
<td>3 days</td>
<td>No autopsy</td>
<td>No autopsy</td>
</tr>
<tr>
<td>5</td>
<td>Yes</td>
<td>10.0</td>
<td>1.0</td>
<td>3 days</td>
<td>Completely necrotic</td>
<td>Completely necrotic</td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>10.0</td>
<td>0.5</td>
<td>24 hrs.</td>
<td>Completely necrotic</td>
<td>Completely necrotic</td>
</tr>
</tbody>
</table>
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Effect of Procedure on the Cancer. Table 3 summarizes the effect of this procedure on growth of the tumor in 3 patients who survived. All of these patients had relief of pain following the injection. The roentgenograms of Case 2 showed a gradual increase in opacification during the first 5 months after the procedure, suggesting increased “blastic” activity, while the roentgenograms did not change in Cases 1 and 3. In Case 2 the serum glycoprotein\textsuperscript{15} levels were elevated before surgery. The glycoprotein values declined to normal during the remission before returning to elevated levels when relapse occurred. The responses of the acid and alkaline phosphatase to this procedure were variable. In Case 2 the postoperative increase in the alkaline phosphatase from 66 Bodansky Units to 88 followed by a gradual fall to 29 units 4 months later together with decrease in the serum glycoprotein values strongly suggest that reduced pituitary function during this time actually caused a decrease in growth of the tumor.

In the 2 patients in whom prolonged suppression of pituitary function was achieved (Cases 2 and 3) there was definite clinical improvement. Only in Case 2 was there objective evidence of inhibition of tumor from this procedure. It is interesting to note that this patient had had only a temporary remission in his symptoms following orchietomy and stilbestrol therapy.

Distribution of Radioactivity. In Cases 5 and 6, the radioactivity was determined in the spinal fluid and blood on the first postoperative day. In each instance approximately 0.01 per cent of the administered dose or 10 microcuries was present in the circulating blood. The radioactivity in the red cells

\textbf{TABLE 3}

\textit{Effect of intrapituitary P-32 on cancer of the prostate}

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Known Duration of Cancer</th>
<th>Effect on Function of Anterior Lobe of Pituitary Body</th>
<th>Length of Survival and Terminal Illness</th>
<th>Relief of Bone Pain</th>
<th>Effect on Serum Glycoprotein (gm. of Bound Hexose per 100 gm. Serum Protein)</th>
<th>Effect on Phosphatase Expressed as Bodansky Units</th>
<th>Effect on Roentgenographic Appearance of Bones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62 yrs.</td>
<td>No definite evidence of impairment</td>
<td>3 mos. Cerebral thrombosis</td>
<td>Complete for 10 wks</td>
<td>None</td>
<td>Acid p. before procedure 4.8; 3 days postop. 0.7. Returned to pre-op. levels 2 wks. later</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>62 yrs.</td>
<td>Marked impairment for 6 mos. after surgery with return to normal</td>
<td>13 mos. Tracheitis pneumonia</td>
<td>Complete for 7 mos</td>
<td>Gradual fall from control of 2.2 to 1.6 six mos. postop. Rise to 9.2 nine mos. postop. at time of exacerbation</td>
<td>Acid p. never elevated. Alk. p. showed initial rise from 60 to 88 with subsequent gradual fall to 29 four mos. postop.</td>
<td>Increased opacification</td>
</tr>
<tr>
<td>3</td>
<td>59 yrs.</td>
<td>Marked impairment within 3 wks. which persisted until death</td>
<td>10 wks. Pyelonephritis</td>
<td>Complete for 10 wks</td>
<td>None</td>
<td>No significant change in initial levels which were 1.0 (acid) and 7.8 (alk.)</td>
<td>None</td>
</tr>
</tbody>
</table>
accounted for almost all of the radioactivity present in the blood. In both patients, the cerebrospinal fluid was bloody and contained approximately three times more radioactivity per ml. than the blood. Almost all of the radioactivity in the spinal fluid was in the red blood cells.

The concentration of radioactivity was determined at autopsy in 2 cases. In Patient 4, who died 5 days after the procedure, the necrotic pituitary tissue contained a greater concentration of radioactivity than any other body tissue. Nevertheless, this represented less than 0.1 mc. of radioactivity or less than 1 per cent of the dose administered. The concentration of radioactivity was less in the liver, but the total amount of radioactivity in this much larger organ was greater (2.5 mc.). The concentration of radioactivity per gram in the liver was approximately 4 times that in the spleen and 400 times that in the thalamus. The concentration of radioactivity in the necrotic pituitary tissue was approximately 34 times that in the hypothalamus.

In Patient 3, studied at autopsy 77 days after intrapituitary injection of P-32, a similar pattern of distribution of radioactivity was found. The greatest concentration was found in the pituitary gland but even after correction for decay the amount of radioactivity in the pituitary gland accounted for only .01 mc. of radioactivity or 0.1 per cent of the dose administered. The liver contained the equivalent of 2.7 mc. after correction for decay, or about one quarter of the administered dose. The concentration of radioactivity in the liver was approximately 3 times that in the spleen and more than 60 times that in cerebral cortex and in bone. The relative distribution of radioactivity was strikingly similar in these 2 patients.

The relative concentration of radioactivity in structures adjacent to the pituitary body was determined at autopsy in Case 3. The hypophysis had a concentration of radioactivity approximately 3 times that of the optic chiasm immediately above it, twice that of the base of the sella, 30 times that of midbrain, and 50 times that of the hypothalamus. The dura mater just behind and below the posterior clinoids contained only slightly less radioactivity than the pituitary body. This confirmed our conclusions based on preliminary studies of normal pituitary glands at autopsy which had shown that leakage of the injected dose is likely to occur posteriorly.

Since almost all of the radioactive material leaves the pituitary body within the first few days and since some of it is deposited in bones, hematologic changes might be expected in these patients. In Cases 1, 2 and 3, there was a drop in hemoglobin postoperatively in spite of transfusions. Whether this was caused by the cancer, or the radiation or other factors cannot be stated. The count of white blood cells in Case 2 dropped to 800, 7 weeks after surgery, returning to normal 9 weeks after surgery.

DISCUSSION

At the present time sufficient data have not been collected to determine the therapeutic value of destruction of the hypophysis on cancer of the prostate in patients who have experienced an exacerbation after orchiec-
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It seems clear, however, that the growth of at least some prostatic carcinomas will be inhibited by destruction of the pituitary body. Whether this is caused entirely by the suppression of adrenal androgens, or whether it is caused by a reduction in growth hormone, or by other factors remains to be determined. Further study of the effects of pituitary destruction on this neoplasm is warranted.

One reason why hypophysectomy is not used more widely in cases of prostatic and breast cancer is the difficulty encountered in performing a complete removal of this gland. Because of the gland’s inaccessibility, it is difficult, if not impossible, to remove the entire gland in every case. If a way could be found to destroy the pituitary body completely in situ, much of the technical difficulty of surgical hypophysectomy would be solved. Radiation, externally and internally applied, has been used for this purpose. More recently sectioning of the stalk with the insertion of a plate between the hypophysis and the hypothalamus has been tried in an attempt to simplify this difficult surgical procedure. The direct injection of radioactive material into the pituitary body should prove advantageous if sufficient radiation is received by the gland to produce complete necrosis and if nearby structures are not damaged by this radiation.

It is well known that the normal hypophysis is quite radioresistant. It has been noted by Kelly et al. that doses of 10,000 r have resulted in no demonstrable histological changes. McCombs found that over 20,000 rad was needed to produce pituitary damage and that a dose as high as 30,000 rad left viable pituitary tissue. The radioactive injection procedure of Yuhl et al. would deliver about $10^6$ rep to the gland using four pellets of $\text{Y}^{90}$, yet at autopsy, he found no case in which a complete destruction of the hypophysis had resulted. It is not possible for us to estimate accurately the radiation dose delivered in the procedure used by us. However, using the incomplete autopsy data from our 2 patients, we could expect a dose of between $9 \times 10^6$ and $9 \times 10^4$ rep to have been delivered to the gland. In at least 1 of our cases, this was insufficient since pituitary function returned 6 months after surgery. The radiation dose that must be delivered to produce complete destruction of the pituitary body has not yet been determined. The above data suggest that in order to produce a complete destruction of the hypophysis by irradiation a dose of $10^6$ rep may be necessary.

In 3 of our patients the pituitary stalk was severed at the time of injection of the radioactive solution. In 2 of these patients no demonstrable pituitary tissue was present at autopsy. This would suggest that division of the stalk combined with irradiation may result in more complete destruction of the pituitary body than does irradiation alone. If dividing the stalk renders the anterior lobe of the pituitary body more sensitive to irradiation it is likely that this effect is ascribable to impairment of blood supply. Further work with direct injections of radioactive materials into the hypophysis might include division of the stalk in an attempt to evaluate the effect of this procedure on the radiosensitivity of the pituitary gland.
The finding of considerable amounts of P-32 in both the spinal fluid and blood as early as the first day after injection shows that this compound is rapidly disseminated throughout the body. This finding is consistent with the results of Bulkley et al. who found that after the injection of this material into the prostate as much as 28 per cent of the injected dose may be found in the blood stream on the first day. They also found changes in bone marrow, possibly caused by irradiation, in their patients treated with chromic phosphate. However, they used a larger dose of P-32 (25–35 mc.) for this purpose than would be theoretically necessary for destruction of the hypophysis. Our finding of a low count of white blood cells in 1 of our patients 7 weeks after the injection is similar to their experience of finding a low count of white cells in 2 patients after the injection.

Because of the 3 postoperative deaths, the rapid disappearance of the radioactivity from the pituitary gland, and the failure to produce permanent interruption of pituitary function in Case 2 we do not plan to continue the use of the procedure described here. However, as pointed out above, it is possible that under more ideal circumstances the mortality rate could be reduced. It might also be possible to find ways to keep the P-32 in the hypophysis for a longer period of time thus increasing the radiation dose to the gland and decreasing the radiation of other areas. In spite of theoretical and technical advantages, the fact remains that destruction of the pituitary body by irradiation is yet to be proven superior to surgical hypophysectomy.

SUMMARY

1. Six patients with far-advanced carcinoma of the prostate gland were treated by direct injection of radioactive P-32 as colloidal chromic phosphate into the hypophysis. Five of these patients had had orchietomy previously.

2. The 3 patients who survived the procedure noted relief of pain in bones. One of these 3 exhibited objective evidence of remission of tumor growth. Panhypopituitarism was present in 2 of these 3 patients. In 1 patient this persisted until his death 10 weeks after surgery. In the other case the hypopituitarism and diabetes insipidus produced by the procedure disappeared 6 months after surgery.

3. Autopsies were done in 5 cases. Of the 3 cases in which the pituitary stalk had not been divided, 2 exhibited only minimal histologic changes in the hypophysis. In the 2 cases in which the stalk was divided, the hypophysis was completely destroyed.

4. Evidence was obtained indicating that the injected material disappeared rapidly from the hypophysis.

REFERENCES

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