In the last few years the operation of hypophysectomy has been used in the treatment of certain types of general disease, particularly malignant disease and diabetes mellitus. This paper is concerned with the use of hypophysectomy and the destruction of the hypophysis by radiation in the treatment of malignant disease, the clinical aspects in outline only, and concentrates on the role of the chemical pathologist and clinical biochemist in the investigation and care of these patients.

Beatson (1896, 1895–96) made the pioneer observations on the control of malignant disease by hormones when he reported the treatment of carcinoma of the breast by removal of the ovaries. It is known that many tumours of the breast and the prostate are hormone-dependent, for their continued growth depends on the presence in the body of actively secreting gonads and adrenal cortex: the rationale of hypophysectomy is primarily the removal of the hypophyseal stimulation of these secretions. It has also been demonstrated that somatotrophin has a direct stimulant action on the growth of a tumour (Pearson, Ray, Harrold, West, Li, and Maclean, 1954). Pearson and his colleagues administered somatotrophin to a patient who had had a hypophysectomy: the secondary deposits in bone extended, and regressed again when somatotrophin administration was stopped. There is also some evidence that luteotrophin has a directly stimulatory action on prostatic growth (Sonenberg, 1952; Scott, 1954; Luft, 1955), and that the beneficial results of hypophysectomy on prostatic carcinoma are due to the removal of luteotrophin as well as of the hormones listed above.

A sidelong on the role of the hypophysis in malignant disease is the work of Archer (1953). He surveyed the world literature on cases of coincident Simmonds's disease and malignant disease, and found eight cases in females and one in a male. None of these women had cancer of the breast (or ovary). This finding is based on a very small number of cases, but is interesting because almost one in three cases of cancer in women is cancer of the breast.

Hypophysectomy could not be performed for the treatment of malignant disease until the knowledge was available of how to prevent the patient dying from post-operative hypopituitarism. The pioneers, since 1951, in the use of hypophysectomy for the treatment of malignant disease are Olivecrona and Luft of the Serafimerlasarett in Stockholm (Luft, Olivecrona, and Sjögren, 1952; Luft and Olivecrona, 1953; Luft, 1954a and b; Luft, Olivecrona, Sjögren, Ikkos, and Ljunggren, 1955; Luft and Olivecrona, 1955; Olivecrona, 1955). Their latest report (Olivecrona, 1955) was of 50 patients with carcinoma of the breast treated by hypophysectomy up to December, 1954. Fourteen of these patients were still alive, with improvement in many cases for over two years. (Favourable results were not expected if the patients were over 60 years old, or if there were brain or extensive liver metastases.) Similar results have been observed in other small published series (Perrault, Le Beau, Klotz, Sicard, and Clavel, 1952; Perrault, 1952; Le Beau and Perrault, 1953; Störtebeker, 1954; Boulard, Descuns, Garre, and Gauray, 1954; Schutte, Picaza, Marinello, and Marquez, 1954; Pearson et al., 1954; Driesen, 1955), and many large series are in progress both in this country and abroad, but no details have yet been published.

Fewer cases of carcinoma of the prostate have been treated by hypophysectomy (Pearson et al., 1954; Scott, 1954). Scott treated five patients, in two of whom a favourable response was obtained. Olivecrona (1955) considers hypophysectomy preferable to adrenalectomy for the treatment of carcinoma of the prostate.

Hypophysectomy had been suggested for the treatment of malignant melanoma on the hypothesis that the tumour may be dependent on
hypophyseal melanocyte-stimulating hormone. However, no improvement was noticed in two patients with melanoma on whom hypophysectomy had been performed (Shimkin, Boldrey, Kelly, Bierman, Ortega and Naffziger, 1952; Olivecrona, 1955).

Hypophysectomy has been performed, without apparent effect, for the treatment of malignant hypertension, hypernephroma, and chorion carcinoma (Luft and Olivecrona, 1953), for adrenocortical carcinoma with Cushing's syndrome (Knowlton, Pool, and Jailer, 1954) and for seminoma (Gilbert-Dreyfus, Pertuiset, Savio, and Sebaoun, 1954). One indication for hypophysectomy which I consider reasonable, but of which we have had no experience, is for the treatment of malignant exophthalmos, in order to remove the hypophyseal exophthalmos-producing substance. Albeaux-Fernet, Guiot, Braun, Cauvin, and Romani (1955) have reported the treatment of one case of malignant exophthalmos by hypophysectomy. There was marked improvement for three months.

In the Royal Free Hospital 13 hypophysectomies have been performed between October, 1954, and July, 1955, all for the treatment of carcinoma of the breast in women. The results, to October 1, 1955, are shown in Table I.

All these patients were under the care of Mr. E. J. Radley-Smith, who performed the hypophysectomies. Further details of these and other patients will be published in due course.

The results can be summarized as follows: Two patients (Nos. 2 and 13) died within 48 hours of the operation. Five patients (Nos. 1, 4, 5, 6, and 8) died within six months of the operation, some of them having had relief of pain for varying lengths of time after the operation. One patient (No. 7) is still alive, having had relief of pain but little objective slowing of the rate of growth of the tumour, and her prognosis is poor. Five patients (Nos. 3, 9, 10, 11, 12) have so far had complete relief of pain and a remarkable increase in their sense of well-being, usually with slowing of the rate of growth of the tumours, and in certain cases disappearance of local or distant metastases.

As it has been said (Luft and Olivecrona, 1955), “The number of patients and the time of observation is too small to give an answer to the question whether hypophysectomy offers patients with metastatic breast cancer anything further than bilateral adrenalectomy in combination with ovariectomy.” Hypophysectomy has theoretical advantages over combined adrenalectomy and oophorectomy. It removes somatotrophin and lutetophrin and hormones from accessory adrenal glands, as well as the adrenal cortical hormones and gonadal hormones which are removed by the combined operation.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Date of birth</th>
<th>Date cancer found</th>
<th>Early treatment: Mastectomy/radiotherapy</th>
<th>Menopause/oophorectomy</th>
<th>Adrenalectomy/hormones</th>
<th>State on admission: Pain, malaise</th>
<th>Local spread</th>
<th>Bony metastases</th>
<th>Visceral metastases</th>
<th>Hypophysectomy</th>
<th>Improvement on discharge 6–10 weeks after operation</th>
<th>Date of death</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1926</td>
<td>1952</td>
<td>M/R</td>
<td>O</td>
<td>H</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>10/54</td>
<td>1.55</td>
<td>1/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
<td>2</td>
<td>1911</td>
<td>1948</td>
<td>R</td>
<td>H</td>
<td>M</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>25/55</td>
<td>2.55</td>
<td>2/55</td>
<td>Operation</td>
</tr>
<tr>
<td>4</td>
<td>1922</td>
<td>1953</td>
<td>R</td>
<td>O</td>
<td>A</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>5/55</td>
<td>5.55</td>
<td>5/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
<td>5</td>
<td>1908</td>
<td>1951</td>
<td>R</td>
<td>O</td>
<td>M</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>6/55</td>
<td>6/55</td>
<td>6/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
<td>6</td>
<td>1913</td>
<td>1951</td>
<td>R</td>
<td>O</td>
<td>A</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>7/55</td>
<td>7.55</td>
<td>7/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
<td>7</td>
<td>1914</td>
<td>1951</td>
<td>R</td>
<td>O</td>
<td>M</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>8/55</td>
<td>8.55</td>
<td>7/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
<td>8</td>
<td>1912</td>
<td>1953</td>
<td>R</td>
<td>O</td>
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<td>XX</td>
<td>XX</td>
<td>X</td>
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<td>7.55</td>
<td>7/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
<td>9</td>
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<td>1953</td>
<td>R</td>
<td>M</td>
<td>R</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>7/55</td>
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<td>7/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
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<td>1954</td>
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<td>R</td>
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<td>XX</td>
<td>XX</td>
<td>X</td>
<td>7/55</td>
<td>7/55</td>
<td>7/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
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<td>R</td>
<td>M</td>
<td>R</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>7/55</td>
<td>7/55</td>
<td>7/55</td>
<td>Spread of cancer</td>
</tr>
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<td>1955</td>
<td>R</td>
<td>M</td>
<td>R</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>7/55</td>
<td>7/55</td>
<td>7/55</td>
<td>Spread of cancer</td>
</tr>
<tr>
<td>13</td>
<td>1902</td>
<td>1954</td>
<td>R</td>
<td>M</td>
<td>R</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
<td>X</td>
<td>7/55</td>
<td>7/55</td>
<td>7/55</td>
<td>Spread of cancer</td>
</tr>
</tbody>
</table>

* By surgery or radiotherapy.
The post-operative care of these patients is easier than after adrenalectomy. The disadvantage is the technical difficulty of the operation.

If it were possible to destroy the whole hypophysis, and only the hypophysis, by radiation, then the relief of malignant disease by hypophysectomy could be more widely practised. Various radioactive isotopes have been used. Bergenstal (1955) has used 5 mc. of $^{90}Y$, and Rothenberg has used 10 mc. of $^{32}P$ (Rothenberg, Jaffe, Putnam, and Simkin, 1955) inserted directly into the pituitary fossa. After surgical hypophysectomy as a precautionary measure 7.5 mc. of $^{198}Au$ is inserted, but the dose is to be increased. There is no definite evidence yet that these measures are successful. Forrest and Brown (1955) and Stanford Cade (personal communication) insert 15 mc. of radon through a nasal cannula: however, the risk with this powerful gamma-ray emitter is of damaging the base of the brain and neighbouring blood vessels, as well as of destroying the hypophysis.

There are four main biochemical problems concerning hypophysectomy performed for the treatment of malignant disease.

If it were known which patients would respond to hypophysectomy, i.e., which tumours were hormone-dependent, a great advance would be made. Histological studies so far give no guidance except that anaplastic growths probably are less responsive. Much work is in progress on the body hormone patterns of patients who suffer from malignant disease, but no abnormalities relative to this problem have yet been found.

The problem that chiefly concerns the chemical pathologist and clinical biochemist is the biochemical assessment of the patients before operation and biochemical control after the operation. Pre-operative assessment must be specially directed towards ascertaining whether adrenal function is normal, for 40% of patients with metastasizing carcinoma of the breast have secondary deposits in the adrenal glands (Stanford Cade, personal communication). The tests employed are (1) a simple water excretion test, when the fasting patient is given 1 litre of water and urinary excretion is measured in four hours (600 ml. is taken as the lower limit of normal, provided that renal function is normal as tested by a specific gravity test); (2) the urine 17-ketosteroid and 17-OH steroid response to A.C.T.H. in which 80 units of A.C.T.H. gel is given on two successive mornings, and a rise of 5 mg. (in 17-ketosteroids) on at least one day is taken as the lower limit of normal; (3) the eosinophil response to A.C.T.H. measured by giving 25 units of A.C.T.H. intramuscularly; a fall of 50% in four hours is taken as the minimal normal response.

The usual tests of liver, thyroid, and kidney function, plasma electrolytes, calcium, phosphorus, phosphatase and urine calcium and phosphorus are performed. In order to investigate changes after the operation the urine gonadotrophins are measured (by the kindness of Dr. Somerville), and it is hoped to examine, in collaboration with the Courtauld Institute, urine 17-ketosteroid excretion patterns and hydrocortisone and aldosterone excretion. Plasma electrophoresis and serum iron estimations are performed, and it has been interesting to see, in certain favourable cases, a reversion of the abnormal electrophoretic pattern (high α2-globulin) seen in advanced malignant disease and a return of the low serum iron to normal.

Table II shows the operative replacement therapy that is adopted when adrenal function is normal and also that which has been found advisable if there is gross adrenal insufficiency, or if the patient has previously had an adrenalectomy. If there is mild adrenal deficiency an intermediate regime is adopted.

During the first 24 hours after the operation 500 ml. of physiological saline and 2,000 ml. of 5% glucose are infused. Noradrenaline and hydrocortisone (free alcohol) are kept available, to be put into the infusion, in case of a catastrophic post-operative fall in blood pressure.

The rate of reduction of cortisone to the maintenance dosage shown on the chart depends principally on the clinical response of the patient, though serial plasma sodium and potassium estimations should be performed. This is usually achieved in one to two weeks. The salt balance of the patients is easy to control because the intact adrenal glands continue to secrete aldosterone, and it is planned to investigate any change in aldosterone secretion with time. The post-adrenalectomy patients are much more difficult to
control, and need more cortisone, presumably because aldosterone is missing. They are given extra salt.

The third problem is to assess whether hypophysectomy has been complete. The Swedish work suggests that if fragments of hypophysis are left they can grow again and maintain relatively normal endocrine status, and optimum results may not be obtained. Re-operation is possible within three weeks of the initial operation. Luft takes his patients off replacement therapy for two or three weeks before re-investigating adrenal function, but this procedure has not yet been used. Indeed, Pearson and his colleagues have reported the development of acute adrenal insufficiency within five days of withdrawing cortisone from a patient after complete hypophysectomy (West, Li, Maclean, Rall, and Pearson, 1954). Amongst the methods that are being used are urine oestrogen and gonadotrophin estimations (but the difficulties here are to measure very small quantities), the eosinophil response to adrenaline (Luft et al., 1955), and studies of thyroid function and of cortisone withdrawal (West et al., 1954).

A method being tried is the differential urinary ketosteroid analysis: dehydroepiandrosterone is not a metabolite of the administered cortisone, and if found must have come from active adrenals. The estimation of plasma dehydroepiandrosterone may also be useful.

The response of water excretion to total hypophysectomy is of great interest, and has been studied in detail by the Stockholm team (Ikkos, Luft, and Olivecrona, 1955), and at the Sloan-Kettering Institute (Lipsett, Maclean, Li, West, Ray, and Pearson, 1955). The excretion of water correlates with changes in the patient's thirst. There is considerable variation in the excretion between different patients, and in the same patient on different days, but the general pattern of response is the same. Fig. 1 shows the water excretion of Case 12, which is a typical response.

In general after operation the daily urine volume rises to 3–7 litres by the third post-operative day (first polyuric phase) because of the removal of the posterior pituitary store of A.D.H. The daily volume then falls to the pre-operative level at about the seventh day (oliguric phase). This is then succeeded by a second polyuric phase by about the 14th day. These phases occur whether or not the patient is receiving cortisone. If cortisone is withheld the urine volume returns to normal as adrenocortical deficiency develops. If cortisone is administered the polyuria persists. One patient whose daily output was about 8 litres asked for and was given pitressin. Ikkos et al. (1955) state that after about six months the thirst and urine output completely return to normal, as the hypothalamus or infundibular stalk takes over the manufacture of A.D.H., but our experience is too short to confirm this. The work at the Sloan-Kettering Institute has shown that the polyuria, which develops in 60% of cases, is independent of whether hypophysectomy has been complete. Our results suggest that it is independent of the presence of intact adrenals. The cause of the oliguric inter-phase is also not known.

Summary

The use of hypophysectomy and of destruction of the hypophysis by radiation in the treatment of malignant disease is described. Of 13 female patients with carcinoma of the breast who had been operated on within a year, five had had a good result so far, with complete relief of pain and variable regression of the metastases.

The tasks of the chemical pathologist in the pre-operative assessment of the patients (with particular regard to their adrenal function), in the biochemical control of the disturbances of metabolism, and in the difficult problem of assessing whether hypophysectomy has been complete, are discussed.

I am grateful to Mr. E. J. Radley-Smith for his advice and for permission to quote the clinical summaries: I would also like to thank Miss Irene Cade, surgical registrar, for allowing me to use her case notes.
REFERENCES


