

and chlorpromazine in treatment. Chlorpromazine appeared to be the better drug for symptomatic relief, but had no statistically significant effect on the ultimate outcome.

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FURTHER EXPERIENCES WITH HYPOPHYSECTOMY IN ADVANCED BREAST CANCER

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In 1958 a review of the effects of hypophysectomy in disseminated carcinoma of the breast at this hospital from January, 1955, to April, 1957, was published (Baron, Gurling, and Radley Smith, 1958). Since that time many other cases have undergone pituitary ablation, and patients have been observed for periods of up to 47 months after hypophysectomy.

Present Investigation

Clinical Material.—Over the past five and a half years up to July, 1960, 121 patients with disseminated malignant disease have been treated by pituitary ablation. Reports of three patients with malignant melanoma (Radley Smith, Gurling, and Baron, 1958) and 7 with disseminated carcinoma of the prostate (Radley Smith, Baron, and Gurling (1959) have been published. Only those 111 patients who have undergone pituitary ablation for disseminated carcinoma of the breast are considered here; they comprise seven patients who have undergone pituitary ablation by the implantation of either ^{198}Au or ^{90}Y seeds under stereotaxic x-ray control together with 104 who underwent surgical hypophysectomy. The only contraindication to pituitary ablation has been the presence of a tendency to bleed, secondary either to extensive hepatic metastases or to depression of platelet formation. Otherwise the patients are entirely unselected.

Pre-operative Assessment.—Patients are admitted a minimum of 10 days pre-operatively. A careful clinical assessment is made. Accessible lesions are measured and photographed. Pre-operative assessment of pituitary, thyroid, and adrenal function is essential (Baron and Gurling, 1960) in order that the functional

completeness, or otherwise, of hypophysectomy can be established for correlation with the clinical response.

Operative Technique

This has already been described in detail (Baron *et al.*, 1958).

The pituitary gland is approached by the right frontal route. After cutting the pituitary stalk and incising the diaphragma sellae it is sometimes possible to remove the pituitary gland in one piece. More often it is removed piecemeal. The anterior portion is carefully scraped away from under the clinoid processes. We continue to insert ^{198}Au seeds (5 seeds a total of 15 mc) into the pituitary fossa after complete removal of the pituitary. Only very small amounts of pituitary tissue remain in the fossa after surgical hypophysectomy. We believe that in these circumstances radioactive gold seeds, which are technically easier to insert into the fossa during our operative procedure than ^{90}Y , are adequate for the purpose of destroying any residual pituitary tissue.

Under stereotaxic x-ray control pituitary ablation has been attempted by the insertion of either ^{198}Au seeds or ^{90}Y rods into the pituitary fossa. The method has been described in detail elsewhere (Bennett, 1960). It is of particular value in patients with cerebral metastases in whom surgical removal of the pituitary is contraindicated. It has not been found possible to produce functionally complete pituitary ablation by the insertion of ^{198}Au seeds alone. The larger size of the ^{90}Y rods, when used in the stereotaxic procedure, probably produces considerable mechanical destruction of the pituitary, which, together with the β -particle activity emitted, results in pituitary ablation being functionally complete.

We continue to use hypothermia in anaesthesia in patients with extensive pulmonary metastases. In patients not requiring hypothermia, hyperventilation is used to increase the venous return and to reduce cerebral oedema.

Pre- and Post-operative Care

For patients undergoing surgical hypophysectomy, cortisone is administered during the pre-operative and operative period according to the schedule given below. This dosage has been modified in the past year from that previously used, since a marked fall in blood-pressure had occurred 12–24 hours post-operatively in a large number of patients. Although the total dosage over 24 hours is slightly less than that previously used, the cortisone is now given eight-hourly. It appears that eight-hourly administration of cortisone acetate, orally when possible but otherwise given intramuscularly, is essential in order to avoid an acute fall in post-operative blood-pressure. The revised schedule of cortisone administration is as follows:

24 hours pre-operatively:

Cortisone acetate 50 mg. I.M., morning and evening.

Day of operation:

Cortisone acetate 50 mg. I.M., morning.

Hydrocortisone hemisuccinate 50 mg. in 500 ml. 0.18% saline (1/5 isotonic) I.V. over operation.

Cortisone acetate 50 mg. orally (I.M. if not fit), 8-hourly, post-operatively.

Cortisone is reduced by 25 mg. every two days until a maintenance level of 25–50 mg. daily is reached.

For patients undergoing the stereotaxic procedure cortisone has been started and kept at the maintenance dosage of 25 mg. of cortisone acetate b.d. orally from the day of operation.

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Post-operative Assessment

The functional completeness of pituitary ablation is assessed about three weeks post-operatively (Baron and Gurling, 1960). There is no single universally reliable indication of functional completeness of hypophysectomy—probably a combination of plasma-free steroids after cortisone withdrawal (Gore and Baron, 1960) and ^{131}I uptake is the best.

During the cortisone-withdrawal test some patients become anorexic. These anorexic patients, and especially those among them who have hepatic metastases, may become hypoglycaemic. This has been noted in several of our patients, and in one case hypoglycaemic coma developed 36 hours after withdrawal of cortisone.

Mortality and Complications of Surgical Removal

In 21 of the 104 patients on whom surgical hypophysectomy was performed death occurred within a month of operation. Many of these patients were extremely ill at the time of operation, and the cause of death must be attributed to the surgical procedure, together with the continued progression of their metastatic disease. Among the last 15 patients operated upon there has been no mortality directly attributable to operation.

Table I shows the complications noted among our patients. Diabetes insipidus has eventually ceased within five to seven months post-operatively in all

TABLE I.—Complications of Surgical Hypophysectomy

	No. Available for Evaluation	With Complications	
		No.	%
Death 0-4 weeks post-operatively ..	104	21	20
Cerebral haemorrhage ..	104	9	9
" thrombosis ..	104	3	3
Diabetes insipidus ..	86*	53	61
Anosmia ..	86*	15	17
Oculomotor palsy ..	86*	3	3
Visual-field defect ..	86*	2	2
Mental changes ..	86*	5	5

* Those surviving long enough to be evaluated.
Percentages are given to the nearest whole number.

surviving patients. Unilateral anosmia occurs in all cases, since the right olfactory tract is divided during the operative procedure. The 15 patients recorded here are those who complained of total anosmia.

The mental condition of five patients deteriorated post-operatively: two of these, aged 54 and 62 years, had cerebral metastases; one aged 56 had extensive hepatic metastases which did not regress after hypophysectomy; one was somewhat depressed pre-operatively and became worse after operation; and in one the mental changes were secondary to partial removal of the frontal lobes after post-operative haemorrhage into them. The procedure of hypophysectomy itself does not result in significant impairment of intellectual function, a finding in agreement with that of Schon (1958). The mortality and complications of the small number of patients undergoing the stereotaxic procedure included in this series are not discussed here, but the evaluation of a larger series of these patients is shortly to be published.

Clinical Effects

In assessing the effects of hypophysectomy we now use the criteria defined by Luft, Olivecrona, Ikkos, Nilsson and Mossberg (1958). A regression is defined as the decrease or healing of all new detectable lesions

without the appearance of any metastases. Static disease is defined as no detectable progression of any metastases and no new metastases. Quantitative clinical assessment of patients is difficult and most methods introduce their own fallacies. We do not feel that the mean clinical value (Atkins, Falconer, Hayward, and MacLean, 1957) offers as helpful a separation into groups of varying response as do these simpler criteria.

Table II summarizes the response to hypophysectomy. If those patients who showed unchecked progression of

TABLE II.—Response to Hypophysectomy

	Total	Regressions	Static	Remission R+S	Progression
No. evaluated ..	92	30 (33%)	12 (13%)	42 (46%)	50 (54%)
Average survival (months) ..		22.0	7.8	18	4.2
No. still alive ..	17	12	2	14	3

their disease are taken as a control, with an average survival of 4.2 months, then 13% of patients had a temporary arrest of disease with a 3.6 months improvement in expectancy of life to 7.8 months. The 42 patients whose disease showed remission had a 14-months improvement in survival to 18 months; also 14 of 42 patients showing remission are still alive while only 3 out of 50 showing progression survive. In our earlier series with a shorter period of observation, corresponding figures were 3.3-months survival for those patients who showed unchecked progression and 9.8-months survival for those whose disease showed objective improvement; at that time 12 of 22 improved patients were still alive.

Possible Indications for Favourable Response to Hypophysectomy

Previous Endocrine Therapy.—In assessing our results it has been found that previous remission of disease occurring subsequent to any endocrine therapy remains the best indication of a probable favourable response to hypophysectomy (Table III). This finding

TABLE III.—Response to Previous Hormone Therapy

	Response	No Response
No. evaluated ..	26	26
Average survival (months) ..	10.9	7.2
No. regressions ..	11 (42%)	4 (15%)
No. static ..	2 (8%)	4 (15%)
Remission (regression + static) ..	50%	30%
No. still alive ..	4	1

is similar to that shown in several other series of patients evaluated after hypophysectomy (Jessiman, Matson, and Moore, 1959; Pearson and Ray, 1960) but has not been found by all workers (Atkins, Falconer, Hayward, MacLean, Schurr, and Armitage, 1960).

Menstrual Status.—Analysis of the influence of the menstrual status on the response to hypophysectomy has produced varying results in different series. It has been

TABLE IV.—Menstrual Status

	Pre-menopausal	Post-menopausal* (Years)			
		0-2	2-5	5-10	10+
No. ..	22	10	4	7	13
Average survival (months) ..	10.9	18.2	5.7	15.3	4.4
No. regressions ..	6 (27%)	7	0	3	2
No. static ..	3 (14%)	0	0	0	2
Remission (regression + static) ..	41%	70%	0	43%	31%
No. still alive ..	5	3	0	2	1

* Only those patients who underwent a natural menopause have been included.

suggested both that the response to hypophysectomy increases (Pearson and Ray, 1960) and it decreases (Luft *et al.* (1958) with increasing menopausal age. We have considered our patients in four groups (Table IV). With so few patients in each group firm conclusions are impossible, but it is of interest that patients at the menopause and those in the 5–10 year post-menopausal group appear to do best.

Length of Free Interval.—In our series, although the numbers of patients in the later categories are small, it appears that the overall remission rate rises with an increasing free interval between the initial appearance of a carcinoma and the appearance of metastases (Table V). This is in agreement with the findings reported in

TABLE V.—*Years of Free Interval*

Years:	0–1	2–5	6–10+
No. evaluated	43	37	7
Average survival (months)	10.4	10.6	16.0
No. regressions	14 (32%)	12 (32%)	3 (43%)
No. static	4 (9%)	6 (16%)	2 (28%)
Remission (regression + static)	41%	48%	71%
No. still alive	6	8	3

several other series (Luft *et al.*, 1958; Jessiman *et al.*, 1959; Pearson and Ray, 1960).

Completeness of Hypophysectomy.—Table VI shows that in our series the percentage of patients experiencing

TABLE VI

Hypophysectomy:	Complete	Incomplete
No. evaluated	65	23
Average survival (months)	12.2	7.0
No. regressions	27 (42%)	3 (13%)
No. static	6 (9%)	4 (17%)
Remissions (regression + static)	51%	30%
No. still alive	14	2

a regression after hypophysectomy is higher in the group of patients whose hypophysectomy is apparently functionally complete. However, in a few patients in whom the pituitary remains clinically functional, regression of their disease has occurred after pituitary ablation. Regression has occurred in 13% of our patients in whom ablation was incomplete. It has been suggested that all cancers of hormone-dependent organs contain a mixture of cells of varying degrees of hormone sensitivity and resistance (Baron, 1959; Hadfield, 1959; Huggins, Briziarelli, and Sutton, 1959; Franks, 1960). It may be that in those patients in whom a functionally incomplete hypophysectomy produces palliation a higher proportion of the cancer cells are sensitive to hormonal changes and therefore response occurs even to incomplete pituitary ablation.

Gonadotrophin Level Pre-operatively.—Loraine (1958) stated that in patients responding to oestrogen treatment the mean pretreatment gonadotrophin excretion was higher in those who responded badly. Pre-operative levels of urinary gonadotrophin excretion do not appear to give any indication of the probable response to hypophysectomy in our series (Table VII).

TABLE VII.—*Pre-operative Gonadotrophins*

	0–96 M.U.	96+ M.U.
No. evaluated	25	13
Average survival (months)	10.8	10.8
No. regressions	9 (36%)	5 (38%)
No. static	2 (8%)	1 (7.8%)
Remission (regression + static)	44%	46%
No. still alive	2	2

Urinary Mammatrophic Potency.—Mammatrophic activity in the urine of some of our patients has also been estimated, but no consistent correlation has been found between the pre-operative mammatrophic activity and the clinical response (Gurling and Baron, 1960). It has also been suggested that a higher ratio of 17-OH-corticoids to aetiocholanolone is excreted in the urine of patients who fail to respond to hypophysectomy (Bulbrook, Greenwood, and Hayward, 1960). We have no data with reference to this point. However, in nine patients in whom a ratio of 17-OH-corticosteroids to total 17-oxosteroids is available—a value which may be comparable—no similar correlation has been found. The use of this ratio is further complicated by the fact that patients with metastatic carcinoma may have adrenal metastases; these have been detected pre-operatively in 4.5% of our patients, and their presence may alter the steroid ratio. Also, it has been suggested that this ratio may reflect merely the general condition of the patient (Nabarro, 1960).

Effect of Hormones on Cell Metabolism.—It has been shown that hydrogen transfer between pyridine nucleotides can be mediated by certain steroid hormones (Talalay and Williams-Ashman, 1958). It is possible that the presence of such enzyme systems in breast cancer may be related to the response of the tumour to endocrine therapy, and studies on this problem may yield clinically relevant information (Hollander, Jonas, and Smith, 1958; Hershey, 1959; Baron, Gore and Williams, 1960).

Metabolic Effects

After hypophysectomy, patients in this series have not tended to develop clinical oedema although in almost all those who have responded to hypophysectomy a gain in weight has occurred. In patients previously hirsute and in those who have been treated with virilizing androgen therapy prior to hypophysectomy it has been noted that, although pubic, axillary, and limb hair becomes very scant or disappears after hypophysectomy, facial hair persists. This finding has been noted in 5 of the 17 patients surviving at the time of writing. In no case has the growth of facial hair appeared for the first time after hypophysectomy, as has been reported to occur after adrenalectomy (Strong, Bruce, and Falconer, 1959), but it has failed to disappear, in contrast with hair in other sites.

Gastric acidity has been investigated before and after hypophysectomy in three patients. No change in the overnight secretion of acid or in the response to histamine was noted.

In two patients diabetes mellitus was present coincidentally with disseminated carcinoma of the breast. Both of these patients had mild diabetes, and it had been possible to discontinue insulin prior to operation. Insulin therapy was not resumed after hypophysectomy. It is of interest that one of these patients died 12 months after hypophysectomy while her metastatic disease was still in regression. Necropsy findings confirmed that this patient died of hepatic failure secondary to fatty infiltration of the liver associated with her long-standing diabetes.

Thyroid activity may continue independently after hypophysectomy, and we have seen two such cases (Gurling, Baron, Radley Smith, 1959).

The level of serum β -glucuronidase has been estimated before and after hypophysectomy in some

patients. Preliminary results indicate that the initial high levels (Whitaker, 1960) fall coincident with satisfactory clinical response. Serum phosphohexose-isomerase has also been estimated serially (Boesen, unpublished) in many of these patients, and the level, although fluctuant, appears to correlate with the clinical course.

Two patients had dermatomyositis: one had been treated with prednisone with some improvement. The prednisone was discontinued before she underwent hypophysectomy for progression of her disseminated metastatic disease. The dermatomyositis improved after hypophysectomy while the patient was on maintenance cortisone. However, her disseminated metastatic disease continued to progress and she died of bronchopneumonia after hypophysectomy.

Conclusion

This larger series and recent series of surgical hypophysectomy of other workers (Jessiman *et al.*, 1959; Pearson and Ray, 1960; Atkins *et al.*, 1960) have confirmed our previous impressions. Hypophysectomy is no longer an experimental procedure. Its place has been established as a method of palliating advanced carcinoma of the breast. The risks of the operation are reduced with greater experience, although it can never be a routine procedure. The major problem remains the selection of patients for operation, for at present only about half the cases respond.

Summary

Pituitary ablation has been performed on 111 unselected patients with disseminated carcinoma of the breast over the past five years—104 by surgical hypophysectomy and 7 by stereotaxic procedure. The assessment and management of the cases are discussed. Regression or arrest has occurred in 42% of the patients assessed and the average expectation of life was increased by 12 months. A favourable response was more likely in patients who had responded well to previous endocrine therapy, and those in whom there was a long interval between the primary disease and the appearance of metastases. It is also possibly indicated by the menopausal status. Complications and metabolic effects of the operation are reviewed.

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DIETARY AND BIOCHEMICAL CONTROL OF PHENYLKETONURIA

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The screening of young infants for the presence of phenylketonuria, if carried out comprehensively, may be expected to reveal about 40 new cases annually in the United Kingdom alone. Evidence is accumulating that dietary restriction of phenylalanine is effective in preventing subsequent mental deficiency, provided treatment is started in the early weeks of life (Horner and Streamer, 1956; Woolf *et al.*, 1958; Brimblecombe *et al.*, 1959; La Du, 1959; Knox, 1960). It is the purpose of this paper to discuss some practical problems in the management of these patients from the dietary aspect and from that of biochemical control, and also to report the difficulties encountered from excessive restriction of phenylalanine in two children diagnosed in early infancy.

Diagnosis

The introduction of a paper test (Baird, 1958) for the detection of phenylpyruvic acid in the urine has simplified the organization of mass screening of small infants by local health authorities. The test can be made either on a freshly wet napkin from which the urine can be squeezed out or on an ordinary specimen of urine. The paper test has the great advantage of