do not respond satisfactorily to radiation and these are the cystic ones and those in which a hæmorrhage has occurred. It may be impossible to identify these changes on clinical grounds, but if there is a story of a rapid or sudden loss of vision, with headache, vomiting, and pain behind the eyes, such cases usually demand operation, and promptly. The following is a case in point.

F S, female aged 60 (R.I. 278112/59); admitted 20.8.59. She had had mild symptoms of hypopituitarism for about two years and for six months had thought that her sight was failing. Ten days before admission, on returning from watching a tennis match, she developed a severe headache which she described as being behind the eyes. This persisted and she vomited frequently, and her sight became misty. She was admitted to another hospital where it was found that she had a bitemporal hemianopia and an enlarged sella. The spinal fluid was clear and colourless and the pressure was normal. When she was transferred to the Radcliffe Infirmary, the headache had largely abated, leaving her with a feeling of pressure behind the eyes. The bitemporal defect was confirmed, and V.A. was 6/36, J.16 in each eye. At operation, there was a tense bluish tumour projecting upwards from the sella. Nothing could be obtained on aspiration with a needle, but when the capsule was incised, dark tarry blood escaped and about 8 ml of this was collected. The interior of the tumour was curetted, and the accessible portion of the capsule excised. She improved rapidly and had a course of radiation treatment after operation, and twelve months later she regarded her general health and eyesight as normal. The acuity was 6/9, J.1 in each eye, but although the peripheral fields were full, there was still a bitemporal defect to small objects on the Bjerrum's screen.

The result of treatment, whether surgery or radiotherapy or a combination of both, depends to a large extent on how long the visual pathway has been subjected to pressure. The most dramatic response occurs in those cases of rapid loss of vision in which an operation such as I have described may bring about a full recovery of the fields and acuity, often within a few days. On the other hand, if there is bilateral optic atrophy and a long-standing field defect, operation may do little more than prevent further loss, but even this may be very valuable in preventing complete blindness.

There have been two or three important advances in the management of these tumours. Hormone therapy has undoubtedly given the surgeon a good deal more leeway: in the old days we were always afraid to remove too much of the tumour, because some of these patients made good visual recoveries but were left as pituitary wrecks. There is no doubt that hormones have made the operation and the post-operative period less harrowing, and they are highly effective in the treatment of the general symptoms of hypopituitarism. Of only slightly less value to the surgeon is the introduction of intravenous urea for the reduction of intracranial pressure. This substance shrinks the brain to such an extent that exposure of these tumours is usually quite easy. A third minor technical advance is the small craniotomy: a small bone flap gives all the room that one can use, and there is less risk of complications such as hæmatomata. As I see it now, the surgery of pituitary tumours is safer than it has ever been, and in radiation therapy we have another method, the safety and relative value of which we have yet to establish. And as operation may be called for at any time, I think it important that the neurosurgeon be asked to see these patients as soon as the diagnosis is made.

The Endocrinology of Pituitary Tumours

by E J Ross MD MRCP (*London*)

Tumours in the region of the pituitary are of interest to ophthalmologists because of their local effects to the fibres of the optic chiasma. Their endocrine interest and importance lies in the local damage caused by their presence to the various parts of the pituitary gland and its functionally related areas in the hypothalamus. In its capacity as the master gland, failure of pituitary function secondarily affects the secretion of other endocrine glands of the body, in particular, the gonads, adrenal cortex and thyroid.

The local effect of an expanding tumour within the sella turcica is failure of production of trophic hormones. The clinical effects of failure of these pituitary hormones is typically manifested in a characteristic sequence. It has been shown experimentally (Ganong & Hume 1956) that when varying amounts of pituitary tissue were removed from dogs, gonadal function was the first to be depressed, then thyroid, and finally adrenocortical depression was seen. This sequence of selective failure of end-organs is seen in many cases clinically (Hubble 1952, Nurnberger & Korey 1953); in others signs and symptoms of adrenal insufficiency are noted before those of hypothyroidism (Mogensen 1957). In all cases, however, the cells or perhaps the enzymes which are most sensitive to destruction by pressure are those responsible for the production of gonadotrophins. The result is the cessation of menstruation or impotence, decreased growth of beard and loss of pubic and axillary hair which may precede other symptoms and signs of the presence of a pituitary tumour by many years. The loss of body hair is in part also due to loss of adrenal androgens. Scalp hair retains its previous rate of growth.

Either thyroid or adrenal hypofunction may be the next to appear. Clinically symptoms of

thyroid hypofunction may be present such as cold intolerance, lethargy and mental apathy whilst no symptoms referable to adrenal insufficiency may be apparent. However, if laboratory tests of function of thyroid and adrenals are performed it is usually found that evidence of adrenal hypofunction appears before that of thyroid hypofunction. Signs of adrenal insufficiency may only become clinically apparent if the patient is subjected to some stress, such as a surgical operation, when fatal collapse may suddenly ensue.

The ability of the patient with hypopituitarism to maintain the blood pressure and avoid dehydration and other hazards of salt and water metabolism encountered by the patient with adrenal insufficiency due to Addison's disease is related to the continued secretion of aldosterone in near normal amounts. The secretion of aldosterone is controlled by a trophic hormone ('aldosterone stimulating hormone') which is not liberated by the pituitary and although corticotrophin (ACTH) has a minor role in controlling the amount of aldosterone released, destruction of the pituitary does not result in the loss of this important electrolyte-regulating hormone, so that renal loss of sodium can be minimized. These patients can adapt to reduction of sodium intake adequately. Loss of secretion of hydrocortisone results in an impaired ability to excrete water. Most patients with hypopituitarism adapt to this by drinking very little fluid and have a low urine volume. They may dilute down their plasma sodium concentration to very low levels, e.g. 110 mEq/l., and feel well if somewhat tired. Admission to hospital where the low urine volume may be noted and lead to forcing fluids, may end disastrously by resulting in water intoxication.

It follows from the above that it is of the utmost importance to assess endocrine function before operation on the tumour since this may well precipitate an adrenal crisis. Grant (1948) records 8 deaths in 71 cases due to this cause in the immediate post-operative period.

Clinically, one important pointer to the existence of hypopituitarism is pallor and loss of pigmentation, particularly around the areolæ and in scars. This pallor has two components; one is anæmia, but the pallor is out of proportion to the anæmia and is accounted for by the loss of melanophore-stimulating hormones secreted by the pars intermedia of the pituitary and perhaps to loss of ACTH which has some melanophore-stimulating activity. Loss of body hair is another useful sign. Particular reference should be paid to gonadal function when the history is taken since, as already stated, this may antedate signs of thyroid or adrenal insufficiency by years.

Various tests of endocrine function have been suggested. For practical purposes, failure of the adrenal and thyroid glands is important over the period of operation. Thyroid function is easy to estimate, a twenty-four-hour radioactive iodine uptake being sufficient for the purpose and available in most hospitals. In parenthesis, the plasma cholesterol is normal or low in pituitary hypothyroidism, perhaps due to loss of androgens. Adrenal function is more important and more difficult to assess. One test can be dismissed immediately as too dangerous to perform, namely, insulin sensitivity. Patients with hypopituitarism show hypoglycæmia unresponsiveness and may die in irreversible hypoglycæmia if given insulin. Another, the water load test, can also be dangerous since these patients are unable to excrete more than 10–15% of water load. The administration of a litre or so of water in the performance of this test may lead to water intoxication (Wynn & Garrod 1955). The water load test is non-specific. If abnormal, it must be demonstrated that the administration of 100 mg of cortisone is capable of reverting the test to normal. The most certain way of assessing adrenal function is to measure blood corticoids or urine 17-ketogenic steroids and assess the response to ACTH. In patients with hypopituitarism virtually no response occurs for a couple of days and then slowly climbs to normal.

Patients with primary pituitary tumours very seldom exhibit diabetes insipidus, although the posterior lobe of the pituitary may be destroyed. Recent observations on experimental diabetes insipidus in animals have shown that the classical view, that the posterior lobe of the pituitary was responsible for the elaboration of anti-diuretic hormone (vasopressin), was erroneous. It is now believed that vasopressin is secreted in the cells of the supra-optic and paraventricular nuclei of the hypothalamus and pass down the pituitary stalk to the posterior lobe of the pituitary, which serves as a storage organ (Sharrer & Sharrer 1954). It can be liberated direct from the hypothalamus, so that for permanent diabetes insipidus to ensue there must be destruction of the secretory part of this system, namely the hypothalamic nuclei. Chromophobe adenomata rarely do this. Suprasellar tumours such as craniopharyngiomata can; secondary carcinomatous deposits, or granulomata such as sarcoid, are commoner causes. It should be noted that anterior pituitary failure, leading to loss of glucocorticoids and consequent impairment of water excretion, may mask the manifestations of diabetes insipidus, which will then only become apparent when cortisone replacement therapy is given. The hormonal deficiencies of hypopituitarism can be adequately treated by the administration of cortisone,

25–37·5 mg/day, and l-thyroxine, 0·1–0·3 mg/day. Testosterone œnanthate, 250 mg every three to four weeks intramuscularly will compensate for loss of androgenic secretion. Thyroxine should not be given without cortisone since this may precipitate an adrenal crisis.

Although chromophobe tumours of the pituitary are much more common than are eosinophilic and basophilic, endocrine interest has centred on the latter types, since these tumours were believed to be sources of trophic hormones, whereas chromophobes, were thought to be inactive in this respect.

The eosinophilic cell secretes growth hormone; eosinophilic tumours are associated with acromegaly in adults or gigantism if they develop before the epiphyses have fused. The characteristic skeletal changes of acromegalics are well known, and are often accompanied by arthritic pain. These patients often have psychological difficulties, and suffer from headaches. Acromegaly is a self-limiting disease; the skeletal changes are irreversible so that it is difficult to assess activity of the tumour. Growth hormones decrease the renal excretion of phosphate, so that an elevated plasma phosphorus concentration, in the absence of uræmia, is indicative of activity. Impaired glucose tolerance may also be present. Ballooning of the sella turcica with encroachment on the optic chiasma is common; McCullagh & Brandon (1960) report that 68% of their series showed X-ray evidence of enlargement of the sella whilst 50% had visual field defects, usually upper temporal quadrant defects which may ultimately lead to blindness.

Basophil adenomata of the pituitary are classically associated with Cushing's syndrome. These adenomata are not found in all cases of Cushing's syndrome and when they do occur, their role in its pathogenesis is uncertain. Basophil adenomata are composed of β- and δ-cells; it is thought that β-cells secrete ACTH, but whether excessive amounts of ACTH are secreted in Cushing's syndrome is still a matter which awaits the development of more sensitive methods of detecting this hormone. Basophil adenomata are small and to my knowledge none has been reported which expanded the sella turcica, hence they do not give rise to visual disturbance.

Of great interest is the recent recognition of the development of chromophobe adenomata of sufficient size to enlarge the sella turcica and produce symptoms in patients bilaterally adrenalectomized for Cushing's syndrome (Nelson *et al.* 1958). Such tumours may make their presence known several years after adrenalectomy in cases where before operation there was no detectable tumour present. This is not to say that a small chromophobe adenoma was not initially present; such tumours have been recognized as a cause, or at least to be associated with, Cushing's syndrome (Marks 1959). These tumours, composed of γ-cells or amphophils, secrete ACTH in amounts much greater than those encountered in Cushing's syndrome before operation, suggesting that removal of the end-organ has stimulated their growth and activity. Chromophobe adenomata have also been noted in acromegaly. The classical view that chromophobe adenomata are composed of non-secreting cells is therefore erroneous; some of these tumours, at least, are composed of cells of great metabolic activity.

Finally there are those who believe that all chromophobe adenomata arise as the result of, not the cause of, end-organ failure. This view is based largely on the long latent interval – in some cases decades – which may elapse between the first symptom or sign referable to hypopituitarism and the clinical recognition of the presence of a chromophobe adenoma. It is said that a curious people called the Skopecs, who practise ritual castration, have an unusually high incidence of chromophobe tumours (Tandler & Gross 1910). However, if this theory were true, patients with Addison's disease and myxœdema should develop chromophobe tumours and the incidence of such tumours in these diseases is no higher than normal. The role, if any, which target gland failure plays in the pathogenesis of pituitary tumours in man is thus still far from clear, although animal work has shown that chromophobe adenomata can be produced experimentally, e.g. by thyroidectomy in mice (Furth & Clifton 1958).

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Pathology of Human and Experimental Pituitary Tumours

by C Treip MD (*London*)

A pituitary neoplasm may arise in the anterior or posterior lobes and, if it remains small, keeps an intrasellar position below the diaphragma sellæ (Fig 1). It is more common, however, for the tumour, by expansion, to become extrasellar; and some tumours may be extrasellar from the