CHROMOPHOBE ADENOMA OF THE PITUITARY GLAND CAUSING CUSHING'S SYNDROME

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Interest in adenomas of the pituitary as a cause of Cushing's syndrome has been re-awakened in recent years by the publications of several authors, such as those of Salassa *et al.*[1] and Nelson.[2] Cushing's original article on this disease[3] demonstrated the presence of basophil adenomas in 8 out of 12 cases. However, subsequent workers showed that many people had basophil adenomas without signs of hyperadrenalism, and conversely many patients with hyperadrenalism showed no evidence of pituitary adenomas. However, it is now well recognized that Cushing's syndrome may present initially with a pituitary adenoma, or else that an adenoma of the pituitary may become recognizable following an apparently successful radical adrenalectomy.

It is only since the introduction of cortisone and its derivatives that radical adrenalectomy has been readily undertaken, and it seems likely that this operation is responsible in some cases for the subsequent expansion of the pituitary tumour. Salassa *et al.*[1] showed that this development had occurred in 12 out of 122 patients with Cushing's syndrome subjected to adrenalectomy at the Mayo Clinic. It has been suggested that the dropping of high levels of circulating cortisol removes its inhibitory effect on pituitary cells. There results an unchecked production of ACTH together with the growth of a pituitary adenoma, either by expansion of a pre-existing tumour or possibly by neoplastic change in active cells. Simultaneously with this, in most of the cases described, an extensive pigmentation of the Addisonian type appears. Following removal or destruction of the pituitary tumour this pigmentation regresses. It has been suggested that ACTH itself can cause pigmentation of an Addisonian type.[2] This may be due to the fact that the melanophore-stimulating hormone molecule is in effect a small part of the ACTH molecule, since they share a common sequence of 11 amino acids.[2]

The case reported here was of the type described by Salassa *et al.*, and is of interest because the pigmentation and pituitary tumour were not evident until 5½ years after subtotal adrenalectomy had been performed. These complications commonly occur within 3 - 6 months of adrenalectomy, but have been reported as late as 8 years afterwards.[2]

CASE REPORT

First Admission

C.W., aged 49 years, a Coloured female, presented in January 1955 with 15 months' amenorrhoea followed by the slow development of truncal and facial obesity, malignant hypertension, poor vision and irritability. On examination at that time she had the typical appearance of a patient with Cushing's syndrome, and her blood pressure was 200/120 mm.Hg. X-ray of the skull showed a suspicious enlargement of the pituitary fossa. The 24-hour urinary 17-hydroxycorticosteroids were at the upper limit of normal — 24 mg. — and were raised to 84 mg. following intravenous ACTH stimulation. Left adrenalectomy and right subtotal adrenalectomy were performed in February and March 1955 by Mr. G. Sacks at Groote Schuur Hospital; thereafter there was slow improvement in the patient's vision, facial appearance and striae. The adrenals were enlarged, the weight of the left being 13·6 G., and that of the portion of the right which was removed, 14·6 G. They showed a typical hyperplasia on microscopical examination.

Progress

The patient was maintained on hydrocortisone, 25 - 40 mg. a day, and was seen yearly at the hypertension clinic. The blood pressure remained constant at about 160/110 mm.Hg. Her 'cushingoid' appearance did not entirely regress. However, from January 1961 onwards there was slow development of restricted vision, headaches, weakness, and pigmentation of the face and extremities (Figs. 1 and 3).

Second Admission

She was admitted to Somerset Hospital on 24 July 1961 showing the features described above, and was also found to

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have deeply pigmented moles on the face. There was gross constriction of the fields of vision of both eyes, and X-ray of the skull showed ballooning of the pituitary fossa. Blood-sugar readings during a glucose-tolerance test peaked at 192 mg. per 100 ml. at 1 hour, but were back to normal by 2 hours. Oral cortisone therapy was then discontinued and the patient did not deteriorate over a period of 3 weeks. During this time 24-hour urinary 17-ketosteroid output ranged from 5·2 to 7 mg. and 17-hydroxycorticosteroid output from 12·4 to 15·6 mg. There was no response to intravenous ACTH stimulation.

On 19 August 1961 hypophysectomy was performed by Mr. J. van Niekerk and the patient has since re-

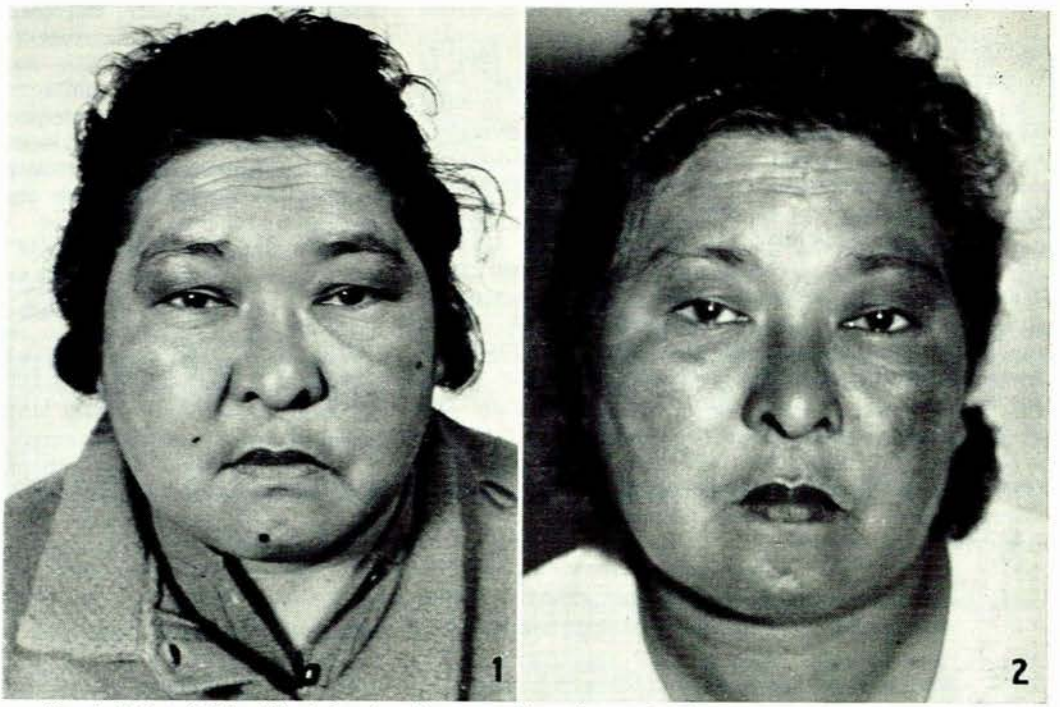

Fig. 1. Patient, 6 July 1961, before hypophysectomy. Note pigmented moles.
Fig. 2. Patient, 14 February 1962, 6 months after hypophysectomy. The pigmented moles have disappeared.

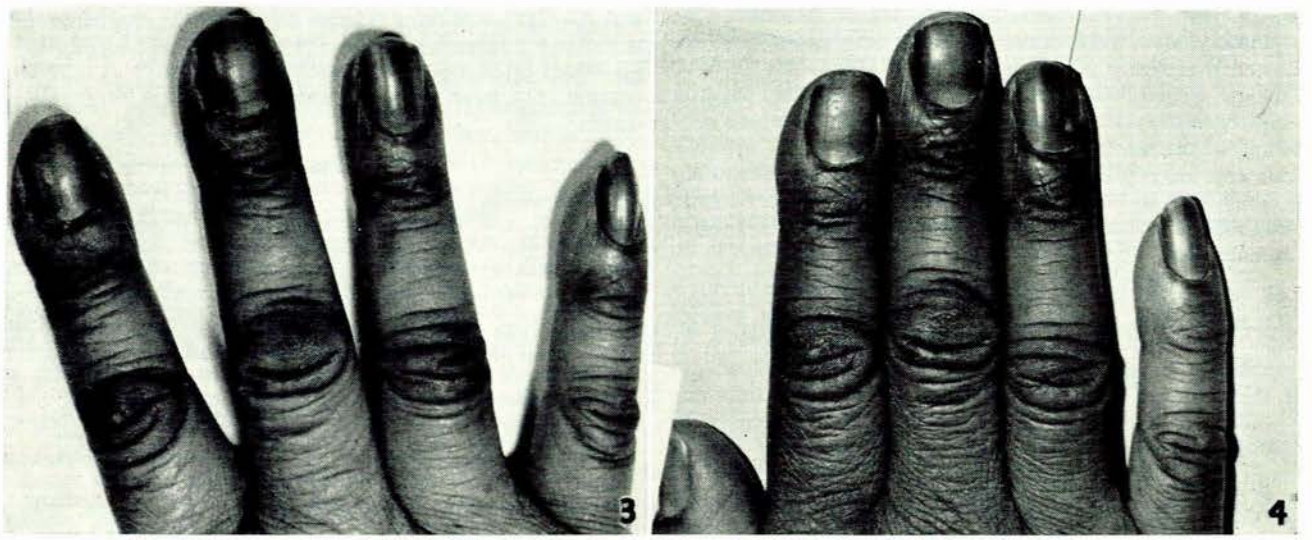

Fig. 3. Patient's right hand, 6 July 1961. Note heavy pigmentation of knuckle creases before hypophysectomy.
Fig. 4. Same hand, 14 February 1962, 6 months after hypophysectomy. Note that the pigment has regressed.

mained well without supplementary steroid therapy, except during one episode of intercurrent infection. Histological examination of the resected tumour showed the presence of a chromophobe adenoma. Her pigmentation has regressed (Figs. 2 and 4) and she feels and looks well. Her pigmented moles are no longer visible, though she still remains rather 'cushingoid' in appearance. Her 17-hydroxycorticosteroid output remains within the normal range, and postoperatively she has a normal level of circulating thyrotrophic hormone (courtesy of Dr. B. Pimstone). Her fields of vision are markedly improved.

An attempt was made postoperatively to suppress adrenal and pituitary function differentially,[6] but there was no difference in 17-hydroxycortico- and 17-ketosteroid output on either the low dose of 2 mg. of dexamethasone a day for 3 days, or the high dose of 8 mg. of dexamethasone a day for 3 days. This cortisone derivative is not estimated by our standard laboratory method of 17-ketosteroid and 17-hydroxycorticosteroid estimations (Table I).

DISCUSSION

Although this condition is uncommon it appears to be a hazard in about 10% of cases following total or subtotal adrenalectomy for Cushing's syndrome. The group of patients in whom the cause of Cushing's syndrome is primary adrenal hyperplasia, excrete more 17-hydroxycorticosteroids then 17-ketosteroids, and show a marked response to intravenous ACTH to a level at least 3 times the basal. If the pituitary tumour is large, visual fields may be constricted, the pituitary fossa may show evidence of enlargement, and the Addisonian type of pigmentation is usually present.

TABLE I. ATTEMPTED DIFFERENTIAL SUPPRESSION OF PITUITARY AND ADRENAL FUNCTION (AFTER THE METHOD OF LIDDLE[6])

	Days					
	1st	*2nd*	*3rd*	*4th*	*5th*	*6th*
Dexamethasone dose (mg. per day)	2	2	2	8	8	8
17-ketosteroids (mg. per 24 hours)	—	5·4	4·8	—	3·2	4·2
17-hydroxycorticosteroids (mg. per 24 hours)	—	18·8	14·4	—	22·3	12·2

Where a pituitary tumour has been present this has usually been chromophobe in type and not basophil. Ezrin[4] and Hubble[5] have described a new classification of cell types in the anterior pituitary:

The progenitor cell is the stem cell (small chromophobe). This can mature into any one of the following 4 types:

(*a*) The gamma cell (large chromophobe).
(*b*) The delta cell } previously combined as the
(*c*) The beta cell } basophil cell.
(*d*) The alpha cell (previously the acidophil cell).

Delta cells produce follicle-stimulating hormone and luteinizing hormone.

Beta cells produce ACTH and thyroid-stimulating hormone.

Alpha cells produce growth hormone and lactogenic hormone.

This classification is based upon new staining methods, and assigns the production of 2 hormones each to 3 cell types, any one of which may revert in type to the large chromophobe cell or gamma cell. This cell is regarded as totipotential and may produce all the 6 main anterior pituitary hormones! It is argued that there may be a small basophil adenoma present which, under the stimulus of hyperplasia after the removal of the 'cortisone-brake' of excess circulating cortisol by adrenalectomy, reverts in type to chromophobe. The very small size of the basophil adenomas frequently found at postmortem examination is no argument against their activity. This is well shown by the fact that hypophysectomy often fails to remove the entire pituitary gland, and that normal pituitary function may be well maintained on no more than 10% of its normal bulk. At present the patient reported in this paper remains well with no added cortisone, and has been shown to have a normal level of thyrotrophic hormone postoperatively.

Treatment of Cushing's Syndrome

The question of the treatment of Cushing's syndrome remains difficult. It seems probable that the best initial approach in the absence of signs of pressure by a pituitary tumour on the optic chiasma or of gross enlargement of the sella turcica, is by unilateral adrenalectomy and pituitary irradiation.[7] It is now fairly generally accepted that adequate subtotal adrenalectomy is a more difficult procedure than, say, subtotal thyroidectomy, and that the amount left may be critically inadequate either immediately or in periods of stress, or that too little is removed and the Cushing's syndrome is not materially affected or recurs later.

This difficulty in assessing the exact amount to remove applies especially to adolescents and people in their 20's. At least in this group, if an attempt at cure is to be made by adrenalectomy, then this should be total and not subtotal, and the patient must be maintained thereafter on oral steroid therapy. If unilateral adrenalectomy and irradiation of the pituitary gland fail, then it will be necessary to proceed to total adrenalectomy, bearing in mind that there may be a 10% chance of the development of a chromophobe adenoma of the pituitary. It is not yet known whether or not previous pituitary irradiation lessens the chance of neoplastic change.

Finally, it is now possible to interfere with the process of biological synthesis of cortisone with the aid of inhibitors at the 11-beta-hydroxylation level using (say) metopirone. Most authorities seem to agree that this is not yet a safe procedure for long-term use.

SUMMARY

A case of proved Cushing's syndrome is described which was treated by subtotal adrenalectomy in 1955. This was followed in 1961 by the development of a chromophobe adenoma of the pituitary (with associated Addisonian type of pigmentation) which was successfully removed.

The therapy of Cushing's syndrome associated with adrenal hyperplasia, and the possible consequences of such therapy, are briefly discussed.

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