factors seems important to me. In the cases described above it appeared that both alopecia areata and chronic urticaria were non-specific responses to non-specific stress in persons of widely differing personality.

It is possible that patients responding with physical symptoms and psychological stress are *potentially* able to respond with the particular symptoms at the particular time. The potential response may depend upon physical disturbance of an organ, abnormal metabolism, or other factors.

In the cases described above there was no relation between intensity of stress and intensity of symptoms. What might be assessed as major stress produced in some cases slight symptoms, and vice versa.

Finally, as regards psychotherapy, it is difficult to assess its effects in the patients suffering from either alopecia areata or chronic urticaria. Both conditions are known to improve spontaneously, with or without treatment of any kind. Many of the patients treated undoubtedly benefited from the psychotherapy in that they were able to accept or alter difficult life situations and in that their anxiety or depression diminished. As mentioned above, those patients who did not improve at all were either profoundly disturbed psychologically or lived in intolerable conditions. Psychotherapy is, as yet, a clumsy and often difficult method of treatment, particularly under out-patient conditions. It is a method of treatment of immense benefit to some and hopelessly inadequate for others. It is surely unwise to come to conclusions on whether symptoms are produced by psychological disturbance or not by judging a patient's response to psychotherapy.

Summary

In an attempt to assess the role of psychological factors in the causation of the two conditions, a study was made, over a period of 19 months, of 52 patients suffering from alopecia areata and 27 patients with chronic urticaria. All patients were treated with psychotherapy for at least three months; most were treated for more than 12 months. Extensive and detailed case histories were made and patients were given long interviews for treatment. In both groups all patients were found to have either very stressful life conditions or moderately severe neurotic symptoms, or both, before the onset of the alopecia and urticaria. Examples of case histories are given. Progress and response to psychotherapy are described. It was concluded that in certain cases stress plays a part in the causation of both alopecia areata and chronic urticaria.

I thank those members of the medical staff of St. John's Hospital for Diseases of the Skin who kindly referred patients to me. I also thank the Medical Committee of St. John's Hospital for permission to use the hospital notes.

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The Minister of Health, Mr. MASON, has called for a report from the Health Department on the current shortage of house-surgeons in New Zealand hospitals. It is possible that the problem will also be examined by the committee investigating the availability and distribution of medical practitioners in New Zealand, which meets again in March. (New Zealand Release A 5/60.)

D

PITUITARY ADENOMA WITH CUSHING'S SYNDROME

BY

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Pluriglandular syndromes were described at the end of the nineteenth century. Certain disorders have since been differentiated, and in each one a single endocrine gland was incriminated as the initiator with secondary changes in the others. In 1912 Harvey Cushing described such a syndrome, which he later attributed to the presence of a basophil adenoma in the pituitary (Cushing, 1932a, 1932b). He did suggest that the adrenal glands might be the main mediators, but he thought that the original stimulus arose from the pituitary neoplasm.

In Cushing's series of cases such an adenoma was found in life only in one case, when a surgical exploration was attempted; most were discovered at necropsy (6 out of 12 cases): in none of his cases had there been any suggestion of either expansion of the pituitary fossa or chiasmatic compression.

A case is presented here in which symptoms and signs of a pituitary neoplasm preceded the development of Cushing's syndrome.

Case History

In October, 1955, a 37-year-old man presented with a four-weeks history of loss of vision. He was of average height, weighed 65 kg., and, apart from prominent eyes, his facial appearance showed no anomaly. His blood-pressure was 130/70. He had a left temporal hemianopsia and a left primary optic atrophy, with a visual acuity of 6/24 in both eyes. Skull x-ray films revealed a greatly expanded pituitary fossa indicative of a long-standing intrasellar tumour. This was confirmed by re-examination of a skull x-ray film taken in 1948 for a minor head injury, which showed a large pituitary fossa; his visual fields were full at that time.

He was admitted to hospital, and investigations showed a haemoglobin of 15 g./100 ml. and E.S.R. of 18 mm./hour (Wintrobe). C.S.F. protein was 90 mg./100 ml., with a slight excess of globulin. An electroencephalogram was normal. Skull x-ray films confirmed the large pituitary fossa, which obliterated the sphenoidal air sinus, the anterior clinoids were deeply undercut and the posterior clinoids eroded, while the superior orbital fissures were enlarged. Carotid arteriograms indicated elevation of both anterior cerebral arteries, left more than right. A lumbar air encephalogram confirmed that the tumour was predominantly intrasellar in site: the ventricular system was normal in size and position. The chest x-ray film showed nothing abnormal.

Surgical treatment was undertaken in order to prevent further loss of vision. At operation, by Mr. Leslie Oliver, a large tumour was seen in the pituitary region, displacing the right optic nerve. When this was aspirated old dark blood was obtained, and further blood and necrotic tumour tissue escaped after the capsule was incised. As much tumour as possible was removed. It was felt that the

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primary aim of the operation—namely, to relieve an optic-nerve compression—had been achieved.

During the next year he became progressively drowsy, falling asleep at any time of the day. He discovered himself to be impotent. He had returned to work as a van driver, but after four accidents it was realized that his sight was too poor, and a transfer to bench work was arranged. In September, 1958, he sustained a spontaneous fracture of his right foot. His weight increased so that in the November he weighed 92 kg. (14st. 7 lb.). It became clear that the changes in his appearance (Fig. 1) were no longer consistent with obesity alone, and a clinical diagnosis of Cushing's syndrome was made.

FIG. 1.—Photographs of patient taken in (left) 1955 and (right) 1958.

He had a red moon-face, a thick neck merging into a buffalo hump, scars of old acne vulgaris on his shoulders, and a grossly distended abdomen with purple striae in the lower half and a girth of 48 in. (122 cm.). There was wasting of the muscles of the thighs and the pectoral and pelvic girdles. He was euphoric though normally orientated in time and space. There was right-sided exophthalmos, and visual testing showed that with the left eye he could only perceive hand movements, while the acuity of the right eye was 6/18 with an upper temporal quadrantic defect. Bilateral primary optic atrophy was now present. His blood-pressure was 190/120; he had ankle oedema and dyspnoea.

Investigation showed a haemoglobin of 13.5 g./100 ml., white-cell count of 14,000/c.mm. (82% polymorphs, 18% lymphocytes, and an absolute eosinophil count of 18/c.mm.), and an E.S.R. of 4 mm./hour (Wintrobe). Urine contained no protein, sugar, or casts. A glucose-tolerance test gave a fasting level of glucose of 120 mg./100 ml., with levels at

half-hourly intervals after 50 g. of glucose of 150, 200, 130, and 100 mg./100 ml. Serum electrolytes on admission were sodium 143, potassium 4.2, chloride 96.5, and alkali reserve 25.3 mEq/l. and a blood urea of 26 mg./100 ml.

The urinary steroid output was measured for two control days and stimulation tests were performed, first with intramuscular corticotrophin gel (100 units daily for three days) and subsequently with intravenous corticotrophin (25 units daily by eight-hourly infusions on two consecutive days). Later a suppression test was carried out with dexamethasone (1.25 mg. six-hourly for three days). The results are shown in Fig. 2, and demonstrate an increased response to corticotrophin, and that the steroid output could be influenced by dexamethasone. Plasma corticotrophin concentration was measured by Dr. Barbara Clayton and found to be 80 international milliunits (i.m.u.) per 100 ml. (normal level is less than 1 i.m.u./100 ml.). During the stimulation test with corticotrophin the plasma potassium level fell to 2.9 mEq/l. and the alkali reserve rose to 34 mEq/l. The patient complained of muscle weakness in his thighs and buttocks. After the above tests these values returned to their normal ranges with disappearance of the symptoms. Radioisotope studies one week later showed that the total exchangeable potassium was 1,850 mEq (normal is 45 mEq/kg. of body weight). The radiographic appearance of the skull did not show any change, but there was a true increase in the size of the heart, with widening of the aortic arch. The dorsal spine showed the changes of osteoporosis, and in the right foot there was evidence of previous fractures in the second and third metatarsals. A ventriculogram showed that the floor of both anterior horns, right more than left, and also of the third ventricle, was displaced upward.

It was concluded that a recurrence of the pituitary adenoma was responsible for the clinical picture, and a further attempt at direct removal was made. Pre-operative therapy consisted of 100 mg. of cortisone acetate daily by intramuscular injection for four days. At operation on January 1, 1959, by Mr. Valentine Logue, an approach was made under general anaesthesia through the old right frontal bone flap. The tip of the right frontal lobe was amputated to give adequate exposure. A cystic tumour was found and incised; there was a gush of 3-4 ml. of a yellowish fluid. When the capsule was dissected away the tumour was seen to fill an enormous pituitary fossa, infiltrating and blocking both cavernous sinuses. All accessible tumour, apart from that around the ocular nerves and chiasm, was removed. Packs and gutta-percha were used to control excessive bleeding, and the wound was closed but not sutured. Two days later the operation site was re-exposed and a dry field obtained; suture was then performed.

Post-operative therapy comprised cortisone acetate in the first three days by intramuscular injection in daily doses of 100 mg. and then by mouth in a dose of 75 mg. daily, with a gradual withdrawal over the next six weeks.

Post-operative studies showed a haemoglobin of 12.2 g./100 ml., a glucose-tolerance test with a fasting blood sugar of 75 mg./100 ml. and levels at half-hourly intervals after 50 g. of glucose of 125, 175, 160, and 120 mg./100 ml. Fig. 2 shows that the augmented response to corticotrophin was still present. Plasma corticotrophin concentration was 80 i.m.u./100 ml.

¹³¹I studies before and after operation showed:

Date	24-Hour Uptake of ¹³¹ I
30/12/58	19%
22/1/59	Less than 6.5%
10/3/59	17%

Because it was thought that active tumour remained in his right orbit, a course of radiotherapy was given. The patient was transferred for this to Mount Vernon Hospital under the care of Dr. A. M. Jelliffe, and was treated with the linear accelerator. He received 3,528 r to the right lateral temporal region and 2,128 r to the left anterior oblique facial region. He remained well for three weeks and then developed marked ankle oedema, for which he

FIG. 2.—Urinary steroid output.

was treated with mersalyl and a low-salt diet. The course of radiotherapy failed to produce any improvement in his "Cushingoid" state, and after a further two weeks he became incontinent of urine and complained of further visual deterioration in his left eye. He was transferred back to the Middlesex Hospital, where he was found to be confused, dyspnoeic, and cyanosed, with a temperature of 104.6° F. (40.3° C.). There was a coarse tremor of his left hand and profound weakness in all limbs but no other neurological signs. His blood-pressure was 115/85.

Investigations showed the plasma potassium to be 2.4, sodium 156, chloride 94, and the alkali reserve over 40 mEq/l. Blood urea was 49 mg./100 ml. Urinary electrolyte levels were potassium 58, sodium 2, and chloride 7.9 mEq/l.

He was treated with ammonium chloride, oxygen, and hydrocortisone, but he collapsed, dying 12 hours later.

Post-mortem Report (Dr. R. E. Cotton)

A large irregular and partially necrotic tumour mass was centred around the expanded and distorted pituitary fossa. The tumour was 1½ in. (3.8 cm.) in diameter with little upwards projection but gross invasion of surrounding structures in the base of the skull. Serial slices through this region demonstrated extension of the tumour into the sphenoidal air sinus, both cavernous sinuses, the retro-orbital tissues through the fissures, and downwards to erode and ulcerate the roof of the nasopharynx. Much of the tumour was infected, and infection had tracked forward below the right frontal lobe, giving rise to an abscess 1 in. (2.5 cm.) in diameter in the region of the amputated tip of the frontal lobe. There was oedema and softening of the surrounding brain but no evidence of rupture into the ventricular system. The hypothalamic region of the brain showed some distortion and there was slight hydrocephalus, most pronounced in the third and right lateral ventricles.

Sections of the tumour showed infection and necrosis in an invasive adenocarcinoma of the pituitary. Much of the tumour was well differentiated and recognizable chromophobe and chromophil cells were present, though in more anaplastic areas distinguishing features were lost.

The heart weighed 17 oz. (482 g.) and showed hypertensive left ventricular hypertrophy. There was bilateral adrenal cortical hyperplasia, most pronounced in the zona fasciculata; the right adrenal gland weighed 18.8 g. and the left 20.3 g. The thyroid gland weighed 18 g. and was of normal naked-eye and microscopical appearance. The testes were normal in size, though showing slight atrophic changes in the seminiferous tubules.

Discussion

Harvey Cushing, when he first described his syndrome, suggested that it might be due to a basophil adenoma of the pituitary. Allbright (1943) emphasized the importance of disturbance of adrenal cortical function in this condition, and there now seems to be little doubt that the essential abnormality is an increased level of circulating hydrocortisone. This may come from a functioning tumour of the adrenal cortex or from hyperplasia or hyperfunction of the glands. Knowlton (1953), from a review of the literature, found that an adrenal cortical adenoma or carcinoma was present in 30% of published cases; more recent figures suggest that the proportion of cases due to neoplasm is between 10% and 15% (Nabarro, personal communication).

Overproduction of hydrocortisone by a hyperplastic adrenal cortex could result from an excess of circulating corticotrophin or from abnormal responsiveness of the adrenal cortex to normal amounts of corticotrophin. Attempts to demonstrate an excess of corticotrophin in the plasma of patients with untreated Cushing's

syndrome have seldom been successful (Taylor *et al.*, 1949; Paris *et al.*, 1954). The methods available are relatively insensitive and the presence of a slight excess cannot be excluded. It has, however, been possible to show increased levels of melanophore-expanding substance (Sulman, 1952), and an adrenal growth-promoting factor (Jailer *et al.*, 1957). There is some evidence to suggest that while the adrenal glands are producing an excess of hydrocortisone they exert an inhibitory effect on the pituitary even in a patient with Cushing's syndrome.

If the condition is treated by total adrenalectomy the level of circulating hydrocortisone is reduced and increased production of corticotrophin follows. This may be detected clinically by the occurrence of pigmentation, which is known to be associated with increased secretion of corticotrophin, as, for example, in Addison's disease (Sulman, 1952; Nelson *et al.*, 1958; Rees, 1959). Total adrenalectomy for Cushing's syndrome has been followed in a number of cases by the appearance of symptoms and signs indicating the presence of a pituitary tumour. It has been suggested that while the adrenal glands are present they secrete an excess of hydrocortisone and that this inhibits the activity of the pituitary adenoma, but after total adrenalectomy and a drop in the level of circulating hydrocortisone not only does the pituitary adenoma produce more corticotrophin but also it actually grows more rapidly and so becomes clinically apparent (Salassa *et al.*, 1959).

It has therefore become necessary to re-examine the relationship of pituitary adenomata to Cushing's syndrome. Cushing found a basophil adenoma in 6 of his 12 original cases. Susman (1935) pointed out that basophil adenomata were often found in the pituitary gland at necropsy without any evidence of Cushing's syndrome. Knowlton (1953) collected 58 reports of necropsies in patients with Cushing's syndrome due to adrenal hyperplasia. She noted that 24 were found to have basophil adenomata of the pituitary, and 10 had chromophobe or mixed adenomata or carcinomata.

One point to be considered is the speed with which the two conditions—pituitary tumour and Cushing's syndrome—develop symptoms and signs. Since steroid therapy has been used for the treatment of collagen diseases it has become apparent that gross changes appear within a few months of administration of large doses; the speed of recurrence after operation in patients with secondary deposits of functioning adrenal cortical carcinoma also leaves little doubt that Cushing's syndrome is a condition that develops rapidly and is obvious clinically in many cases in a matter of months. Pituitary tumours, however, are much slower to produce clinical or radiological manifestations. Richmond (1958), in a series of 220 cases of pituitary tumour, found an average delay of seven and a half years between the onset of symptoms and the presentation to the doctor. Hence, if the syndrome were produced initially by an overfunctioning adenoma of the pituitary, symptoms and signs referable to it might not be evident at the time of presentation of the endocrine disorder.

Cases of concomitant Cushing's syndrome and chiasmatic compression are recorded by Cohen and Dible (1936), Petit-Dutaillis *et al.* (1938), Lissner (1944), Forbes (1947), McCormick *et al.* (1951), Sheldon *et al.* (1954), Bayliss (1957), and Mogensen (1957) in which chromophobe adenomata were found in five cases, basophil

carcinomata in those of Cohen and Sheldon, and an eosinophil adenoma with acromegaly in McCormick's case. All showed bilateral adrenal cortical hyperplasia.

Cases in which the symptoms and signs of pituitary tumour developed after the onset of Cushing's syndrome are reported by Glenn *et al.* (1958), Nelson *et al.* (1958), Rees (1959), and Salassa *et al.* (1959). In all these cases subtotal or total adrenalectomy had been performed prior to the appearance of chiasmatic compression. Skull x-ray films before adrenal surgery were thought to be normal. The pituitary tumours found were mostly chromophobe adenomata, but Salassa did find basophil adenomata as well.

The course of the present case is unusual. The presence of a pituitary abnormality was found accidentally seven years before it produced evidence of chiasmatic compression. A local invasive pituitary lesion was demonstrated surgically three years before Cushing's syndrome was diagnosed. A high level of circulating corticotrophin was found, but pigmentation was not a striking feature. Despite the high level of corticotrophin, exogenous corticotrophin produced an abnormal response by the adrenal glands. The output of corticotrophin was apparently suppressed by dexamethasone, indicating that the pituitary carcinoma was not autonomous in its activity.

Only two other cases have been found in the literature, in which it is clear that a pituitary tumour was present before Cushing's syndrome manifested itself. Messimy *et al.* (1950) describe the case of a woman of 57; when 28 she had had a year's amenorrhoea, obesity, and poor sight, which responded to radiotherapy to her skull; this treatment was repeated, but in her early fifties Cushing's syndrome appeared. On presentation she had, as well as her endocrine disorder, a bitemporal hemianopsia and an eroded pituitary fossa shown by radiography. Feiring *et al.* (1953) record the case of a woman of 32 who had amenorrhoea and poor vision, and had gained 30 lb. (13.6 kg.); her pituitary fossa was irradiated without relief. At craniotomy a chromophobe adenoma was removed with remission of her symptoms; she subsequently had two pregnancies, one resulting in the birth of a healthy infant. Four years later she developed Cushing's syndrome and died. Necropsy revealed an invasive pituitary carcinoma with metastasis to the anterior cranial fossa, and there was bilateral adrenal cortical hyperplasia, each gland weighing 12 g.

It seems clear that a proportion of cases of Cushing's syndrome may be started by a pituitary adenoma, which is often chromophobe and sometimes basophil in cell-type. This tumour may be clinically detectable before the syndrome develops, coincidentally with it, or after it has been successfully treated.

A careful study of the sella turcica by skull x-ray films and the charting of visual fields are essential in any case of Cushing's syndrome, especially in those believed to be associated with bilateral adrenal cortical hyperplasia. It is important to look for subsequent changes in these findings after adrenalectomy.

In the presence of a pituitary tumour that threatens the visual pathways a direct surgical approach to the tumour is necessary. It is problematical whether in the absence of chiasmatic compression it is still advisable to perform a hypophysectomy if the pituitary is shown to be the instigator of bilateral adrenal cortical hyperplasia. In the present case surgery was not helpful in alleviating the endocrine disorder; post-mortem study

confirmed both the failure and the impossibility of complete surgical removal, and, furthermore, showed that radiotherapy had neither halted the tumour's growth nor arrested its function.

Summary

A case is described in which the presence of a pituitary tumour was demonstrated at least seven years before the detection of Cushing's syndrome.

Investigations showed that there was a high plasma corticotrophin level, associated with a raised urinary 17-hydroxycorticosteroid output, which was further increased by parenteral corticotrophin. It was concluded that the adrenal glands were not responding maximally to the endogenous stimulus, and that in this case of bilateral adrenal hyperplasia there was still an adrenal reserve. The response to dexamethasone suggested that the pituitary tumour was not autonomous.

Surgery and radiotherapy failed to correct the course of the disease, and necropsy confirmed the presence of an invasive carcinoma of the pituitary gland.

The possible time-relations between the presentation of a pituitary tumour and of Cushing's syndrome are discussed, emphasizing that it is rare for the clinical signs of a pituitary tumour to precede those of Cushing's syndrome.

It is suggested that an active Cushing's syndrome may retard the growth of a pituitary tumour and so prevent its early detection; but it may manifest itself after adrenalectomy.

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