by improving tissue perfusion and causing activated platelets to return to their normal morphology (Gilroy *et al.*, 1969). Haemoconcentration, which may be accompanied by cerebral oedema, is a feature of severe decompression sickness, and plasma expansion alone has been used successfully in two cases (Brunner *et al.*, 1964). In the present case the initial packed cell volume was 48%, suggesting haemoconcentration and cerebral oedema, and thus mannitol was given.

The use of heparin in fat embolism has been described (Cobb *et al.*, 1968), its actions on lipoprotein lipase and platelets probably being the most important. Heparin has also been used successfully as adjuvant therapy to recompression in five cases (Barthelemy, 1963). Also rapidly decompressed dogs when treated with heparin (2 mg/kg) have shown 100% survival, while the controls died (Pauley and Cockett, 1970). In the present case 100% oxygen was given to counteract the patient's arterial hypoxaemia, which may have been caused by microemboli in the pulmonary circulation, and to increase

the capillary-alveolar diffusion gradient for nitrogen elimination. At present, recompression is the only generally accepted treatment for type II decompression sickness. The rationale for medical treatment of such cases, however, is supported by the successful management of this patient.

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Hypopituitarism after Extracranial Irradiation: Evidence for Hypothalamic Origin

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In contrast with the known radioresistance of the normal pituitary gland (Kelly *et al.*, 1951) the hypothalamus appears to be radiosensitive (Arnold *et al.*, 1954). To our knowledge, however, there has been only one report of hypopituitarism occurring after irradiation for extracranial neoplasia (Tan and Kunaratnam, 1966). We report two such cases after external irradiation of carcinomas of the nasopharynx and maxillary antrum. Case 1 was previously mentioned in discussion by Bradley (1965).

Case 1

A man aged 45 presented in 1954 with multiple cranial nerve lesions. After extensive investigation, including exploration of the posterior fossa with negative results, the diagnosis of a small anaplastic carcinoma of the nasopharynx, confirmed by biopsy, was made. Deep x-ray therapy was administered, a 250-kV machine being used and a 3,000-r tissue dose given over 25 days. Four oblique fields, which included the base of the skull in the region of the sella turcica, were used to deliver the radiation from both sides of the skull. An identical course was repeated five months later because of residual facial nerve weakness.

In 1962, although there was no evidence of recurrence, typical clinical features of hypopituitarism were present, including tiredness, intolerance of cold, impotence, loss of body hair, pallor, and testicular atrophy. Radiographs of the skull were normal. The clinical diagnosis was confirmed by the following investigations: serum protein-bound iodine 1.6 µg/100 ml, urinary gonadotrophins

<5.0 mouse units/24 hr, urinary 17-hydroxysteroids 2.0 mg/24 hr before and 3.2 mg/24 hr after metyrapone, and acute water load excretion increased from 17% to 81% after prednisolone 10 mg. Clinical improvement followed treatment with cortisone, testosterone, and thyroxine, but he subsequently developed right-sided conductive deafness and epilepsy, which were attributed to radiation damage. In 1968, after a haemoptysis, a chest radiograph showed a carcinoma of the lung, and evidence of metastases in bone and liver rapidly appeared. Death occurred in February 1970.

Necropsy showed no evidence of recurrence of the nasopharyngeal tumour, but the presence of a bronchial carcinoma was confirmed, with metastases in the liver, lung, and spine. Macroscopically, the brain and the pituitary were normal. Unfortunately, a more detailed examination was not performed.

Case 2

A man aged 39 presented in 1964 with a carcinoma of the left maxillary sinus involving the floor of the orbit. This was treated by irradiation; a megavoltage machine was used to deliver 6,500 r in 20 increments over 32 days. Subsequently the left eye was enucleated and he developed bilateral conductive deafness attributable to radiation damage.

In 1971, when admitted for exploration of suspected tumour recurrence or osteomyelitis of the frontal bone, he gave a history suggestive of hypopituitarism and examination showed pale skin, absent body hair, and testicular atrophy. Urinary gonadotrophins were < 5.0 mouse units/24 hrs, and serum protein-bound iodine 2.9 µg/100ml. An x-ray film of the pituitary fossa was normal.

Investigation of Hypothalamic Pituitary Function

Stimulus	Plasma Concentration	Time in Minutes							
		0	5	10	20	30	60	90	120
Insulin (0.1 IU/kg intra-venously)	Sugar (mg/100ml)	56				17	42	45	—
	Cortisol (µg/100 ml)	2.4				2.8	3.6	3.2	—
	Growth hormone (ng/ml)	3.6				1.9	4.0	2.6	—
Vasopressin (5 IU intramuscularly)	Cortisol (µg/100 ml)	5.9					20.6		—
	Growth hormone (ng/ml)	1.5					1.5		—
Thyrotrophin-releasing hormone (200 µg intra-venously)	Thyroid-stimulating hormone (µU/ml)	2.8	3.5	4.6	7.4	9.5	14.4		14.8

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Plasma cortisol and growth hormone levels did not rise when hypoglycaemia was induced, but plasma cortisol rose after an intramuscular injection of 5U of vasopressin. Further, the plasma thyroid-stimulating hormone level measured by radioimmunoassay, responded to thyrotrophin-releasing hormone 200 µg given intravenously (see table). No evidence of tumour recurrence was found at operation, and replacement therapy with cortisone, testosterone, and thyroxine produced increased energy, hair growth, and decreased cold sensitivity.

Comment

Chronologically, the development of unequivocal pituitary failure was consistent with the usual latent period of several years preceding chronic radiation damage. The macroscopic appearances at necropsy in Case 1 and the radiological and operative findings in Case 2 made the involvement of the pituitary by tumour unlikely.

In case 2 evidence for a hypothalamic site of the lesion was provided by a thyroid-stimulating hormone response to thyrotrophin-releasing hormone which was normal but delayed, typical of the pattern seen in hypothalamic disease and in contrast to the lack of response in patients with local pituitary destruction (Hall *et al.*, 1972). Further, in contrast to hypoglycaemia, which elicits corticotrophin release via a hypothalamic effect mediated by corticotrophin-releasing hormone, vasopressin appears to act in part directly upon the pituitary (Gonzalez-Luque *et al.*, 1970). The plasma cortisol response to vasopressin but not to hypoglycaemia suggested that the pituitary was intact but that the hypothalamus was not. In the case of Tan and Kunaratnam (1966) pituitary dwarfism resulted from irradiation of a naso-

pharyngeal carcinoma in a 12-year-old girl who received a total dose of 9,000 r; panhypopituitarism was unequivocal, but the data did not discriminate between a hypothalamic and a pituitary origin. Arnold (1954) and Lawrence *et al.* (1971) have suggested that the therapeutic effect of irradiation for pituitary dysfunction may result from hypothalamic damage rather than an action on the pituitary itself.

Both the patients reported here received large but conventional doses of irradiation with apparent complete regression of their tumours, and the pituitary and ventral hypothalamus received most of the total tumour dose. The development of hypopituitarism after radiotherapy of the head and neck may be more common than has been suspected in the past, and with the greater sophistication of current tests of pituitary function evidence of this complication should be sought more diligently.

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Primary Hypothyroidism Presenting as Pituitary Failure

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An 18-year-old male presented with dwarfism and failure to undergo puberty. Routine investigations showed evidence of pituitary failure but serum thyrotrophin levels were raised, indicating primary hypothyroidism. After treatment with thyroxine thyrotrophin was suppressed and other aspects of pituitary function were recovered.

Case History

An 18-year-old Indian male presented with shortness of stature and failure to undergo puberty. Development had been normal until the age of 10 when he was overtaken in height by his younger sister. His height had remained unchanged for the past two years.

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His parents and four siblings were all of normal build. His diet was the same as the rest of the family and he had not received any drugs. There was no past history of head injury or other illness.

At examination his height was 134 cm (<3rd percentile), weight 36 kg. He was mentally and physically slow, with dry thick skin and delayed relaxation of tendon reflexes. He was prepubertal and there was no gynaecomastia or galactorrhoea. There were no visual field or cranial nerve defects. Results of investigations are shown in the Table.

Results of Investigations in Case of Primary Hypothyroidism

	Before Treatment	3 Months After Treatment
Growth:		
Peak human growth hormone (µIU/ml) (W.H.O. 1st I.R.P.) after hypoglycaemia*	<1	32
Bone age (years) (Greulich and Pyle)	8	9
Alkaline phosphatase (K.A. units)	16	48
Gonads:		
Basal luteinizing hormone mU/ml (M.R.C. research standard A) (normal adult range 1.8-4.1)	1.0	1.1
Luteinizing hormone response to clomiphene	absent	absent
Luteinizing hormone peak after LH/FSH-RH (mU/ml)†	—	2.6
17 β-hydroxyandrogens (ng/ml)‡ (normal adult range 4.9-21.5)	1.0	0.6
Adrenal:		
Basal 9 a.m. cortisol (µg/100 ml)	9.0	8.0
Peak after hypoglycaemia	9.0	33.0
Thyroid		
Protein bound iodine (µg/100 ml)	0.8	—
Cholesterol (mg/100 ml)	450	179
Electrocardiogram	Flat T-waves	normal
Antibodies§	negative	—
Thyroid stimulating hormone (µU/ml) (M.R.C. research standard A) (normal range < 1.4-5)	620	2.0

Pituitary fossa tomography and air encephalogram: no enlargement of the fossa and no suprasellar extension.

* Insulin tolerance test: glucose fell to <25 mg/100 ml.

† Measured 20 and 60 minutes after 100 µg intravenous gonadotrophin releasing hormone (LH/FSH-RH).

‡ Measured by Dr. D. C. Anderson.

§ Measured by Dr. W. J. Irvine.