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Volume 8

Edited by
A.R.Horler and J.B.Foster

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PROGRESS IN CLINICAL MEDICINE

Volume Eight

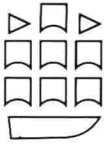
EDITED BY

A. R. HORLER MD FRCP

Consultant Physician, Royal Victoria Infirmary,
Newcastle upon Tyne

J. B. FOSTER MD FRCP

Consultant Neurologist, Newcastle University Hospitals;
Honorary Reader in Neurology, University of
Newcastle upon Tyne



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PREFACE

Our previous volume in this series appeared in 1978 after an interval of 6 years, the first under our joint editorship. Our intention was to continue the style and composition that had been followed so successfully by our predecessors, and we included contributions from most of the medical specialities as well as from other disciplines which regularly impinge upon the sphere of the general physician.

In this present volume we have confined our contributions entirely to the field of clinical medicine, comprising a shorter list of chapters, and we have endeavoured to include advances in subjects of direct relevance to those for whom the book is primarily intended. It is necessary, therefore, to consider this volume as a continuation of the last, rather than as a completely new venture. Medical progress is a continuing phenomenon and a book such as this can be only selective. We hope our present selection will continue to attract the interest of practising physicians and postgraduate students.

We are grateful to Mrs Heather Russell for her invaluable assistance with script reading and to those authors and publishers whose material we have been permitted to reproduce. We also appreciate the continuing interest and encouragement of Dr Raymond Daley who for so long shared the responsibility of editorship.

Newcastle upon Tyne, 1983

A.R.H.
J.B.F.

CONTRIBUTORS

P. L. Amlot MB BS MRCP
Senior Lecturer, Department of Medicine, Guy's Hospital Medical School, London

John Anderson MB BS FRCP
Academic Sub-Dean and Senior Lecturer in Medicine, The Medical School, University of Newcastle upon Tyne; Honorary Consultant Physician, Royal Victoria Infirmary, Newcastle upon Tyne

J. B. Foster MD FRCP
Consultant Neurologist, Newcastle University Hospitals; Honorary Reader in Neurology, University of Newcastle upon Tyne

Reginald Hall BSc MD FRCP
Professor of Medicine, Welsh National School of Medicine, Cardiff

Alan R. Horler MD FRCP
Consultant Physician, Royal Victoria Infirmary, Newcastle upon Tyne

Graham R. V. Hughes MD FRCP
Reader in Medicine and Head of Rheumatology Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London

O. F. W. James MA FRCP
Reader in Medicine (Geriatrics) and Consultant Physician, University of Newcastle upon Tyne, Freeman Hospital, Newcastle upon Tyne

D. G. Julian MA MD FRCP FRCPE FRACP
Professor of Cardiology, University of Newcastle upon Tyne, Freeman Hospital, Newcastle upon Tyne

Maurice H. Lessof MA MD FRCP
Professor of Medicine, Guy's Hospital Medical School, London

B. E. C. Nordin MD FRCP DSc
Senior Research Fellow and Clinical Professor, Royal Adelaide Hospital, Adelaide, South Australia

M. Peacock MB FRCP
Assistant Director of Mineral Metabolism Unit and Honorary Consultant Physician, Leeds General Infirmary, Leeds

T. B. Stretton MB FRCP
Consultant Physician, Manchester Royal Infirmary, Manchester

Mark J. Walport MA MRCP
Registrar in General Medicine and Rheumatology, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London

J. M. A. Whitehouse MA MD FRCP

Professor of Medical Oncology, Southampton University; Director, Wessex Regional Oncology Service, Southampton General Hospital, Southampton

Robert Wilkinson BSc MD FRCP

Senior Lecturer in Medicine, University of Newcastle upon Tyne; Consultant Physician, Department of Nephrology, Freeman Hospital, Newcastle upon Tyne

Christopher J. Williams DM MRCP

Senior Lecturer in Medical Oncology and Honorary Consultant Physician, University of Southampton CRC Medical Oncology Unit, Southampton General Hospital, Southampton

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Endocrinology

R. Hall

DISEASES OF THE HYPOTHALAMUS

Hypothalamic disease is rare and its clinical manifestations are often non-specific; hence it is easily overlooked when a diagnosis is being sought. A wide variety of diseases may affect the hypothalamus either directly or indirectly (Table 1.1).

Table 1.1 Diseases of the hypothalamus

Congenital
GH deficiency with or without other deficiencies
LH and/or FSH deficiency with anosmia (Kallman's syndrome) or without anosmia
Isolated deficiencies of TSH or ACTH
Laurence-Moon-Biedl syndrome (polydactyly, mental retardation, retinitis pigmentosa and hypogonadism)

Tumours
Hypothalamic
Craniopharyngiomas
Germinomas
Sphenoidal ridge meningiomas
Gliomas of the optic chiasm
Other cerebral tumours
Secondary deposits
Lymphomas
Pituitary
Suprasellar extension of pituitary tumours

Infectious diseases
Encephalitis
Meningitis (tuberculous or bacterial)
Syphilis

Granulomatous diseases
Sarcoidosis
Histiocytosis X
Multi-system granulomas

Vascular disease
Post-partum hypopituitarism
Carotid and other aneurysms
Subarachnoid haemorrhage
Pituitary apoplexy

Structural
Secondary to internal hydrocephalus from any cause, e.g. aqueduct stenosis in neurofibromatosis, colloid cysts, ependymomas

Iatrogenic
Radiation or neurosurgical treatment of pituitary lesions
Nasopharyngeal irradiation
After prolonged steroid or thyroid hormone medication

Trauma
After head injury (usually with fractured base of skull)

Functional
Anorexia nervosa, starvation, emotional deprivation syndromes

Clinical features

Hypothalamic disease presents either as a result of the effects of the local lesion or as hypopituitarism.

Local effects

Infiltrative or expanding local lesions may cause headaches and field defects differing from those of a primary pituitary lesion, because pressure on the chiasm from above usually causes an initial inferior quadrantic temporal hemianopia. Behavioural, functional and autonomic abnormalities may mimic a wide variety of psychiatric disorders.

Appetite disorders are common, usually leading to obesity or, more rarely, profound weight loss. However, the great majority of obese patients are not suffering from any detectable organic disease of the hypothalamus, although an 'endocrine cause' is often suspected. The most gross example of 'hypothalamic obesity' is seen in the Prader Willi syndrome of voracious appetite, gross obesity, mental retardation, hypogonadism, diabetes mellitus, and small hands and feet. In the equally rare Laurence–Moon–Biedl syndrome, obesity and mental retardation are associated with retinitis pigmentosa and extra digits. Sleep disorders are not uncommon, with hypersomnia or altered sleep rhythm. Sexual behaviour may be disturbed, with loss of libido or promiscuity, and puberty may be either precocious or delayed. Precocious puberty in boys is usually organic and points to a lesion in the region of the pineal. Loss of thirst sensation is common in patients with expanding hypothalamic lesions and is particularly dangerous if the patient has already developed diabetes insipidus. Gross hypernatraemia, sometimes fatal, can occur because of uncompensated water loss, and plasma sodium values up to 200 mmol/l may be recorded. Disorders of temperature control are easily overlooked. The patient may develop hypothermia or hyperthermia, or poikilothermia in which the body temperature fluctuates with that of the environment. Emotional behaviour may be immature, inappropriate, aggressive or retarded and is often a cause of great distress to the relatives. Motor activity may be grossly decreased and the inactivity contributes to the development of obesity. Memory defects may be profound: defects of short-term memory result from involvement of the mamillary bodies.

Endocrine effects

Hypothalamic disease may reduce the synthesis or transport of the prolactin-inhibiting factor dopamine and lead to hyperprolactinaemia and its various sequelae (*see* p. **6**). Apart from prolactin deficiency, hypothalamic lesions cause hypopituitarism of varying severity. Diabetes insipidus could be better classified as a local effect, as it results from damage either to the magnocellular neurones of the supraoptic nucleus in the hypothalamus or to the supraoptico-hypophysial tract. The commonest clinical presentation of hypothalamic disease is diabetes insipidus associated with hypogonadism in a patient with a normal pituitary fossa. It should be stressed that primary pituitary disease does not itself cause diabetes insipidus unless there is suprasellar spread or there has been surgical or radiotherapeutic intervention.

Diagnosis

Diagnosis consists of defining the local lesion or syndrome and characterising the extent, if any, of hormone deficiency. Formal visual-field charting may suggest hypothalamic disease and indicate its location and rate of extension. Skull X-rays may be normal, or show distortion or erosion of the posterior clinoids, pineal or

aberrant calcification. CT scans with and without intravenous contrast medium may outline a tumour. Metrizamide cisternography can be helpful in delineating the extent of a lesion (Hall K et al 1980) and a combination of CT scanning after intrathecal administration of the contrast medium is also useful. Air encephalography is less pleasant for the patient but can provide valuable information. Cerebral arteriography is now less often required but may demonstrate tumour extension or vascular blushes and exclude aneurysms.

The search for extracranial evidence of a systemic disease may yield clues to the diagnosis. For example, a pneumothorax occurring in a patient with a hypothalamic disorder suggests an underlying eosinophilic granuloma. Pulmonary infiltration may be seen in eosinophilic granulomas or sarcoidosis. Chromosomal anomalies can occur in some patients with germinomas. Cutaneous manifestations of neurofibromatosis may suggest a diagnosis of hydrocephalus from aqueduct stenosis.

Sometimes all diagnostic manoeuvres fail and, if there is evidence of an expanding hypothalamic lesion, neurosurgical exploration may be required with biopsy of any suspicious tissue or correction of internal hydrocephalus by shunting.

Treatment

Obviously, treatment of the disease will depend on the cause. Hormonal deficiencies are corrected as in hypopituitarism. Some tumours, such as craniopharyngiomas, may be amenable to excision or decompression; others, such as germinomas, may be radiosensitive. Chemotherapy may be of use in lymphomas and histiocytosis X. Sarcoidosis may respond to corticosteroid medication in some cases.

PITUITARY ADENOMAS

Pathology

Modern techniques of electron microscopy and immunocytochemistry have allowed eight distinct types of anterior pituitary cell adenomas to be defined (Table 1.2).

Table 1.2 Types of pituitary adenoma (Kovacs & Horvath 1979)

Cell type	Frequency (%)
Growth hormone	21
Prolactin	32
Mixed growth hormone, prolactin	6
Acidophil stem cell	3.5
Corticotroph	13
Thyrotroph	0.5
Gonadotroph	1.0
Undifferentiated	23

Clinical features

Pituitary tumours may present as a result of hypersecretion of one or more hormones, as hypopituitarism from compression of the normal pituitary tissue or pituitary stalk by the adenoma, or as a result of local expansion within the fossa or into the infra-, para- or suprasellar regions. A detailed discussion of the clinical features and routine endocrine investigations is provided in Hall R et al (1980).

Radiological investigation of pituitary tumours

Lateral and anteroposterior views of the fossa demonstrate the size and extent of the tumour. Intrasellar lesions produce enlargement of the fossa with erosions of its bony outlines. A double contour of the floor of the fossa may be caused by uneven downward expansion but is more often attributable to an inadequate radiological technique ('a poor lateral') or to a normal variant in the shape of the fossa. It is now apparent that many so-called minor abnormalities of the fossa are, in fact, normal variants and do not signify the presence of a pituitary tumour. Many radiologists doubt the advantage of detailed sellar tomography which involves a significant dose of radiation.

Computerised tomography (CT scanning) is of great value in the neuroradiological investigation of pituitary lesions. Axial (horizontal) plane scans can demonstrate a suprasellar extension which may show enhancement after intravenous contrast medium (Conray). Coronal or semicoronal scans give an even better demonstration of the extent of the lesion. The water-soluble contrast medium, metrizamide, can be run into the basal subarachnoid cisternae and around the brain after introduction by the lumbar route. The suprasellar cisterna can be identified easily and lateral radiographs of this area will demonstrate all the structures shown by pneumoencephalography. The technique is simpler than others and the side effects fewer and less severe so that serial examinations are possible. An empty sella is clearly shown by this technique. A metrizamide cisternogram can be combined with a CT scan — a metrizamide CT cisternogram in both the axial and coronal planes provides a three-dimensional appreciation of the extent of the lesion. Using the new generation of CT scanners it is now possible to demonstrate microadenomas a few millimetres in diameter within the pituitary fossa.

Angiography is not often required in the investigation of pituitary tumours although some surgeons prefer to know the precise location of the carotid arteries before embarking on pituitary surgery.

Growth-hormone-secreting adenomas

GH-secreting adenomas produce a wide variety of clinical manifestations leading to acromegaly in adults and gigantism (with some features of acromegaly) if the condition develops before fusion of the epiphyses. Gigantism is now very rare, making up less than 1% of the syndromes of GH excess. Estimates of the incidence and prevalence of acromegaly have been presented in a study from the north-east of England (Alexander et al 1980). The annual incidence appears to be close to three cases per million and the prevalence of diagnosed cases up to 40 per million. The study showed that in men there was a significant increase in the risk of death from cardiovascular, cerebrovascular and malignant diseases whereas in women there was excess mortality from cerebrovascular disease only; these findings are similar to those reported by Wright et al (1970).

Diagnosis

Even when the clinical features are obvious, GH oversecretion must be confirmed by measurements of GH during a standard glucose tolerance test. In normal subjects GH levels should fall to <4 mU/litre (<2 ng/ml). Radiological enlargement of the pituitary fossa is detectable in at least 90% of cases. If surgical ablation or yttrium-90

implantation is contemplated the upper level of the tumour should be defined by CT scanning or pneumoencephalography. When active therapy is not contemplated and the visual fields are normal, invasive neuroradiological procedures may be withheld. Secretion of other pituitary hormones should be tested. The combination of thyrotrophin-releasing hormone (200 μg), plus gonadotrophin-releasing hormone (100 μg) is convenient to use, bearing in mind that active acromegaly is insulin-resistant. Basal levels of prolactin (PRL) should be measured because there is often associated oversecretion of this hormone: there is some evidence that patients with concomitant GH and PRL hypersecretion respond better to bromocriptine.

The diagnostic problem is usually to decide which patients with rugged features and large hands and feet justify further investigation. Patients who complain of a change in their appearance, especially if this is confirmed by inspection of previous photographs, are worthy of investigation. Other causes of enlargement of the hands include manual work, obesity, hypothyroidism and primary amyloidosis. Enlargement of the feet usually affects their width rather than their length. Enlargement of the tongue may also be complained of in hypochondriasis, hypothyroidism and primary amyloidosis.

Treatment

No treatment can as yet be guaranteed to restore GH levels to normal, to prevent further tumour growth and to avoid hypopituitarism or other local complications. For patients up to the age of 60 years or so with active disease and a tumour confined to the fossa, or with only a small suprasellar extension, the treatment of choice is now trans-sphenoidal hypophysectomy, if a sufficiently experienced surgeon is available. Hypopituitarism is produced in only about one-quarter of the patients because some normal tissue is usually left around the stalk. Cure rates of about 80% can be achieved, as judged by the return of GH levels to normal (Richards & Thomas 1980). If GH levels remain high postoperatively, residual tumour growth can usually be prevented by external radiation in a total dose of up to 4500 rad. Treatment with bromocriptine can then be used to reduce GH levels and to bring about symptomatic improvement until radiation becomes effective.

In specialised centres yttrium-90 implantation can be effective. A dose of 50000 rad is used if the GH level is <100 mU/l and 150000 rad if the level exceeds 100 mU/l. Further implants can be inserted if GH levels are not sufficiently reduced, and small suprasellar extensions can also be treated.

When there is a large suprasellar extension which is inaccessible from the trans-sphenoidal route, transfrontal decompression of the chiasm is performed, followed by external radiation of the residual tumour. Again, bromocriptine can be given to achieve further symptomatic improvement.

When invasive therapy is considered to be inappropriate because of a patient's wishes, age or concomitant disease, medical treatment with bromocriptine, a long-acting dopamine agonist, produces a worthwhile clinical response in at least 75% of cases. Treatment is built up gradually to an average dose of 5 mg four times daily. It has now been shown that, as well as lowering GH levels, bromocriptine can reduce the size of some GH-secreting tumours, although its effect on prolactinomas is more obvious.

It is essential to treat the associated hypopituitarism which can complicate untreated acromegaly or may be an early or late effect of such treatment.

Prolactin-secreting adenomas

Prolactin-secreting pituitary adenomas now appear to be the commonest of the pituitary tumours, although it is still uncertain whether this is attributable to a true increase in frequency, an increased index of suspicion, the ready availability of PRL immunoassays, the advent of an effective therapy such as bromocriptine, or to a combination of these factors. Although PRL-secreting adenomas can be induced by oestrogen medication in animals, there is still no clear evidence that oral contraceptive medication induces prolactinomas, despite the clinical suspicion of this possibility.

Clinical features

Hyperprolactinaemia in women causes a combination of amenorrhoea or oligomenorrhoea, galactorrhoea, infertility, loss of libido and, very occasionally, hirsutism. In men the clinical features may be less obvious: they include impotence, loss of libido, galactorrhoea, oligospermia or azoospermia, reduced prostatic size and semen volume, infertility and a female distribution of body fat. The hypogonadism seen in either sex may be caused partly by pressure of the adenoma on normal pituitary tissue or by PRL blocking the action of gonadotrophins. Galactorrhoea may be detected only by careful expression of the breasts but can be absent even in the presence of very high PRL levels.

Diagnosis

Many drugs and diseases can cause hyperprolactinaemia and the serum PRL level may also be raised in a variety of physiological situations (Table 1.3). Serum for PRL estimation should be taken after 11:00 hours to avoid the effects of the nocturnal increase which can persist into the earlier morning. Although PRL levels rise in response to stress, the effects of stress in routine blood sampling have probably been overestimated. In the appropriate clinical context, if PRL levels are raised (>400 mU/l) the problem is to decide the cause. The higher the PRL level, the more likely is the patient to have a pituitary tumour, although tumours can be found in some patients who have only a modest increase in PRL levels. A lateral skull X-ray should be performed: if this shows a definitely enlarged fossa, the diagnosis is established and the extent of the tumour and secretion of other pituitary hormones must be determined. If the PRL level is raised and the pituitary fossa normal or only 'suspicious', one is faced with what has been termed 'the prolactinoma problem'. Is the hyperprolactinaemia functional or does the pituitary fossa harbour a microadenoma? It has been shown that patients with prolactinomas have an impaired PRL response both to TRH and to dopamine-receptor blockade with metoclopramide or domperidone. Patients with functional hyperprolactinaemia show a normal (several hundred per cent) increase in PRL in response to these stimuli. Patients with macro- or microadenomas secreting PRL also tend to show an exaggerated TSH response to dopamine-receptor blockade. Modern CT scans can sometimes reveal the presence of a microadenoma within the fossa.

Table 1.3 Causes of hyperprolactinaemia

Physiological
Neonatal period
Puberty in girls
Coitus and orgasm
Nipple stimulation
Pregnancy and suckling
Sleep
Stress
Drugs
Dopamine-receptor-blocking agents:
Phenothiazines, e.g. chlorpromazine
Haloperidol
Metoclopramide, sulpiride, pimozide, domperidone
CNS-dopamine depleting agents:
Reserpine
Methyl dopa
Others:
Oestrogens
TRH
Hypothalamic or pituitary stalk lesions
Craniopharyngiomas, gliomas, 'pinealomas'
Granulomas — sarcoidosis, eosinophilic granuloma, TB meningitis
Stalk section following trauma, pituitary surgery, or pressure from a tumour
Pituitary tumours
Prolactin cell
Mixed growth hormone cell/prolactin cell
Acidophil stem cell
Mixed corticotrophin cell/prolactin cell
Miscellaneous
Idiopathic/functional
Hypothyroidism
Chronic renal failure
Ectopic, e.g. from bronchogenic carcinoma or hypernephroma

Treatment

The optimal treatment of prolactinomas has yet to be decided. The problem is to decide whether to employ trans-sphenoidal hypophysectomy, external radiation or bromocriptine, or a combination of these.

It is unlikely that large tumours in association with a markedly enlarged pituitary fossa and very high PRL levels (> 2000 mU/l) can be removed completely by any surgical procedure. In this situation, bromocriptine is the treatment of choice, supplemented by external radiation in some centres. If the tumour is large enough to cause definite but not gross enlargement of the fossa, trans-sphenoidal hypophysectomy is performed in some centres, again supplemented by radiation and bromocriptine if PRL levels remain high postoperatively.

If the pituitary fossa is not enlarged, but neuroendocrine tests indicate the presence of a microadenoma, there is still debate as to whether bromocriptine alone should be used, particularly if the patient's complaint is primarily of infertility, or

whether an attempt should be made to remove the lesion trans-sphenoidally. In patients with suprasellar extensions of the tumour, or recurrence after previous surgery and/or external radiation, bromocriptine is the treatment of choice because there is now clear evidence of shrinkage of the tumour with this drug. The duration of therapy required is uncertain but it is probably wise to check the hormonal activity and extent of the tumour every year.

Bromocriptine has a major role in the management of prolactinomas and there is much to be said for treating all patients with this drug alone. Early side effects consist of nausea, vomiting and syncope; later effects are constipation, nasal stuffiness and Raynaud's phenomenon. It is usual gradually to increase the dose to 2.5 mg 8-hourly over the course of a week or two, to minimise side effects. Initially, half a tablet (1.25 mg) is given in bed at night after a meal, for a few nights; the dose is gradually increased after meals, with the patient sitting or lying at first. Once a dose of 7.5 mg daily has been established, the initial side effects usually resolve and the later ones are rarely troublesome at this dose level. A few patients require doses of up to 20 mg daily but, in general, patients with hyperprolactinaemia are more sensitive to bromocriptine than those with acromegaly.

If pregnancy results from bromocriptine therapy the drug is usually discontinued, although there is no evidence that it causes any damage to the fetus. Because of the small risk (probably about 5%) of tumour extension during the pregnancy, the patient should be seen at monthly intervals for review and visual-field testing, and should be warned to report immediately if she develops headaches or nausea. If tumour expansion does occur during pregnancy it is seldom necessary to resort to surgery: tumour shrinkage can be produced effectively and safely by recommencing bromocriptine.

Corticotroph adenomas

These were discussed in the last edition (Horler & Foster 1978, p. 43) and no further comment is required here.

Thyrotroph adenomas

Raised TSH levels are usually the result of primary thyroid failure. In rare instances, if thyroid failure is prolonged, a feedback thyrotrophin-secreting adenoma may arise and cause enlargement of the pituitary fossa.

Very occasionally, hyperthyroidism, with increased circulating thyroid hormone levels, is associated with a raised serum TSH level. The pituitary fossa is usually enlarged and the disease can be cured by removal of the tumour. A characteristic finding is the presence of raised levels of α-subunits, presumably of TSH, but neither these nor the TSH level rise after thyrotrophin-releasing hormone (TRH).

In the less frequent syndrome of non-tumour TSH-induced hyperthyroidism the α-subunit cannot be detected in the circulation. Most of these patients have had previous destructive therapy to the thyroid. They show a partial TSH response to TRH and some suppression of TSH induced thyroidal radioiodine uptake by triiodothyronine. It is possible that they result from an altered set point for thyroid hormone–TSH interaction and may reflect partial resistance of the thyrotroph to thyroid hormone feedback.

Gonadotroph adenomas

These tumours can also arise from long-standing gonadal failure such as that which occurs in Klinefelter's syndrome or Turner's syndrome. Here, low levels of sex steroids are associated with raised FSH and either raised, normal or low LH levels and enlargement of the pituitary fossa. The tumours are normally responsive to gonadal steroid replacement therapy.

Very occasionally, gonadotrophin-secreting tumours, usually secreting FSH, may arise de novo. In such cases sexual function is often well maintained and the presence of normal-sized testes in a patient with an apparently non-functioning pituitary tumour should lead to measurement of gonadotrophin levels. Some patients may have reduced libido, potency and sexual function and this may, on occasion, result from concomitant hyperprolactinaemia. An attempt should be made to remove the tumour whenever possible.

Multiple endocrine adenoma syndromes

The MEA syndromes consist of associations of endocrine hyperplasia, adenomas or carcinomas which are often familial and inherited in a Mendelian dominant manner, although sporadic cases can occur.

MEA type 1

The tumours and their frequency are shown in Table 1.4. Associations of parathyroid, pituitary and pancreatic adenomas are by far the commonest. Growth hormone cell adenomas are the most frequent pituitary tumour, although probably less than 5% of acromegalics show evidence of MEA 1. Prolactinomas, corticotroph cell adenomas and apparently non-secretory tumours may also be associated. Pancreatic tumours are usually islet-cell adenomas secreting insulin or, less often, gastrin or other pancreatic hormones, but may be non-secretory. It is uncertain whether the association of thyroid adenomas is a real one, for these tumours are common in the general population.

Table 1.4 Multiple endocrine adenoma Type 1

Lesion	% Affected
Parathyroid adenomas and hyperplasia	90
Pancreatic islet adenomas (β and non-ß cells)	80
Pituitary adenomas (functioning and non-functioning)	65
Adrenocortical adenomas	38
Thyroid adenomas	18

The clinical relevance of the MEA 1 syndrome is that any patient with one of the more commonly associated tumours should be asked about other such disease in the family and other relevant clinical manifestations should be sought. A few simple screening tests should be performed: for example, in a patient with hyperparathyroidism, a skull X-ray should be taken to exclude a pituitary tumour, and fasting blood glucose and insulin measured to exclude an insulinoma. Certainly,

whenever lesions in more than one gland are discovered in a patient, all of his first-degree relatives should be screened.

MEA type 2a

This syndrome comprises medullary carcinoma of the thyroid, phaeochromocytomas, commonly bilateral and, more rarely, parathyroid adenomas or hyperplasia. As a result of family screening it has been possible to detect the earliest manifestations of the syndrome, which consist of hyperplasia of the 'C cells' and of adrenal medullary tissue. All patients with medullary carcinoma of the thyroid should be screened for phaeochromocytoma by urinary 4-hydroxy-3-methoxy mandelic acid (HMMA) measurements, although this test is not always sufficiently sensitive to detect small phaeochromocytomas. Similarly, all patients with phaeochromocytomas should be screened, by measurement of basal and stimulated calcitonin, for medullary carcinoma of the thyroid. In families with this type of carcinoma it has also been found necessary to use provocative tests to detect early cases. Calcium infusion tests are helpful: 15 mg Ca^{2+}/kg is given over 4 hours, with basal and 4-hour calcitonin measurements. Injections of pentagastrin (0.5 μg/kg over 5 seconds) causes rapid release of calcitonin within 2 minutes. This is a useful outpatient screening procedure, although the injection may cause faintness and it is best to keep the patient recumbent. Administration of alcohol (50 ml orally in adults and 30 ml in children over the age of five years) leads to release of calcitonin which is detectable at 15 minutes. The patient must be fasting and warned to avoid driving afterwards.

It should be stressed that the majority of patients in most centres, with either medullary carcinoma of the thyroid or phaeochromocytoma, do not suffer from the MEA syndrome and the diseases usually appear to occur sporadically. However, a single family with MEA may produce a large number of affected subjects in a given area.

MEA type 2b

This syndrome consists of medullary carcinoma of the thyroid associated with a variety of somatic abnormalities, which is more often sporadic and less frequently combined with parathyroid or adrenal medullary disease. The somatic changes include a 'Marfanoid appearance', a proximal myopathy, thickened lips, neuromas of the tongue, cornea and eyelids, ganglioneuromatosis of the bowel and pigmentation of the skin. The facial appearance and tongue neuromas are characteristic.

Mixed syndromes

Mixed MEA syndromes can occur, albeit rarely. Patients with acromegaly may have a phaechromocytoma or aldosteronoma. Similarly, a patient with the MEA 2 syndrome who developed the Zollinger-Ellison syndrome has been described.

Tumours of the APUD system

The term APUD indicates 'amine precursor uptake and decarboxylation' — properties common to most peptide-hormone-producing cells. Tumours arising from the APUD system can occur in many different sites because of the wide distribution of such cells. Insulinomas, gastrinomas, vipomas, glucagonomas,