patients could have come to the surgery had a transport system been available.

Reference to Table VII shows that it was the younger patients who the doctors thought could most easily have come to the surgery—over half of the new visits to patients aged under 1 year were made when the patient did not need a home visit; similarly, one-third of all the children did not need a home visit. Of the adults aged over 65 about one-quarter could reasonably have come to the surgery. Of the patients who the doctor thought could have come to the surgery but who asked for a new visit 80% were not in bed compared with only 43% for all new calls. This suggests that the attitude of the doctor in assessing the number of unnecessary calls was not unreasonable.

Of patients making calls between 8 and 10 a.m. only 29% were revisited. Nevertheless, the later the new call the more serious the illness. Hence of patients making calls between 10 a.m. and 8 p.m. 37% were revisited and in the case of patients making calls between 8 p.m. and 8 a.m. as many as 44% were revisited. A parallel increase in hospital admissions became evident the later the time of the call (1.6% of routine morning calls made between 8 and 10 a.m., 6.4% of those between 10 a.m. and 8 p.m., and 16.7% for those between 8 p.m. and 8 a.m.) There is therefore a 1 in 6 chance that a visit carried out between 8 p.m. and 8 a.m. will require the patient's admission to hospital.

The late call rate of 17% found in this survey is almost identical with the 18% found in South Wales by Williams⁵ using similar criteria. Though late calls in general practice are frequently considered to be frustrating and irritating, this survey showed that the conditions were more serious, as an increasing proportion of patients had to be revisited and admitted to hospital the later the calls were received. This would appear to be at variance with the findings of Jacob,⁸ who suggested that the personal characteristics of the adult making the calls was the deciding factor in many late calls rather than the severity of the condition.

Chronic revisits represented a considerable proportion of the visiting load. Their value has often been doubted. There is a danger in labelling chronic patients with a diagnosis, since if new conditions supervene these can be more easily missed. Only 3 out of 10 chronic patients were in bed and 4 out of 10 were not examined. Hence probably many chronic visits do not require much in the way of clinical skill, and these patients need social help as much as medical assistance. Co-operation with the new local authority departments of social service—particularly close liaison of social workers with general practitioners—would undoubtedly improve the overall general standard of care to the

aged and people with chronic disabilities as well as providing more time for the doctor to deal with purely clinical problems.

For patients with chronic disabilities who require clinical supervision the use of transport should be considered, for this can help both patient and doctor. Doctors thought that only 9% of chronic patients could have come to the surgery unaided, but on postulating a minibus service for this purpose the figure increased by a further 36%. The use of a minibus would be particularly valuable in reducing chronic visiting in rural areas. Organizing such a service for patients with acute illnesses would be full of problems—not the least being assessing need—and thus its value for them would be less. Young doctors thought almost twice as many patients revisited could have come to the surgery by minibus than did older doctors.

The number of revisits carried out by nurses was surprisingly low—only 14%. Even more surprising was that they did only 17% of revisits to chronic patients, especially when one remembers that doctors did not examine 40% of their chronic patients on a revisit. Hence probably the full potential of nurses for this work has not yet been achieved and the prophecies of earlier workers^{3, 9} have not yet been fulfilled. Perhaps as well as asking himself why he is revisiting any particular patient the general practitioner should also consider whether he is the most appropriate person to do so.

We wish to thank all participating general practitioners for the care they took in completing somewhat lengthy forms. We also acknowledge the guidance and support of the Practice Organization Committee of the North-East England Faculty of the Royal College of General Practitioners. The survey was supported financially by the Newcastle upon Tyne Regional Hospital Board, and the secretarial burden was borne enlightenedly and well by Mrs. A. Denton.

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Clinical Endocrinology

Pituitary Tumours and Hypopituitarism

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The anterior pituitary gland secretes corticotrophin (ACTH), thyrotrophin (TSH), gonadotrophin, growth hormone, prolactin, and melanocyte stimulating hormone (MSH). It is under the control of the hypothalamus, in which stimulating or

inhibitory factors are synthesized and pass to the gland down the pituitary stalk. One of these, thyrotrophin releasing factor (TRF), has recently been synthesized and its properties are being studied. ACTH regulates cortisol secretion by the adrenal cortex, and also has a direct action on the skin leading to increased pigmentation. TSH stimulates the secretion of thyroxine and tri-iodothyronine by the thyroid gland. The gonadotrophins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), act on the gonads, regulating germ-cell maturation and sex-hormone secretion in both men and

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women. The term luteinizing hormone (LH) is now used for the interstitial cell stimulating gonadotrophin found in men. Growth hormone is secreted in adults as well as children and adolescents, although its role when growth is complete is poorly defined. The actions of prolactin in the human are not properly understood but an excess has been shown in some women with galactorrhoea. MSH leads to darkening of the skin in the same way as ACTH.

Pituitary Tumours

Tumours in or adjacent to the pituitary gland may produce both local and endocrine abnormalities. Of the tumours of the pituitary itself the commonest is the nonfunctioning chromophobe adenoma; less frequent are growth-hormone-secreting, eosinophil adenomas and ACTH-secreting tumours. Craniopharyngiomas usually occur just above the pituitary, and tumours may also occur in the hypothalamus. Other neoplasms may occur in this area, including secondary carcinoma and deposits of lymphoma.

CLINICAL PRESENTATION

Patients may come to the attention of the practitioner on account of local symptoms or endocrine abnormalities—or the pituitary tumour may be an accidental finding during x-ray films taken, for example, because of sinus trouble or suspected fractured skull. In a recent series seen in an endocrine unit the presentation was with local symptoms in 40%, endocrine 57%, and accidental in 3%.

Local Symptoms

The commonest symptom is headache, which is rarely of the traditional bursting bitemporal character. Of much greater localizing value is the bitemporal hemianopia that follows extension upwards of the tumour and pressure on the optic chiasma. The patient will often mention that he walks into people because he has failed to see them coming up on one side. Less common is the development of a squint or oculomotor nerve palsy from lateral extension. Rarely these symptoms may develop suddenly and dramatically, possibly with impairment of consciousness, owing to haemorrhage into a tumour (pituitary apoplexy).

Endocrine Manifestations

As a chromophobe adenoma enlarges and normal pituitary tissue is compressed the production of hormones is reduced. Not all the hormones are affected at the same time. Gonadotrophin is usually the first to be lost, then growth hormone followed by TSH, and ACTH is the last to fail. A growth-hormone-secreting tumour often interferes with gonadotrophin secretion but rarely affects TSH or ACTH. A similar sequence will occur if the tumour is in the hypothalamus or interrupts the pituitary stalk, preventing the hypothalamic releasing factors from reaching the pituitary gland. Lesions above the pituitary are also liable to interfere with the antidiuretic-hormone (ADH) releasing mechanism, with resultant diabetes insipidus.

Failure of gonadotrophin secretion before puberty will result in primary amenorrhoea in a girl or delayed development in a boy. Though a pituitary tumour is a rare cause it should be considered when such cases are being investigated. In an older woman secondary amenorrhoea will result; there are many causes for this, but if it persists for 12 months an x-ray film of the pituitary fossa is advisable. Impotence with loss of libido is a rare presentation of pituitary tumour in a man, but is often admitted when specific questions are asked after the diag-

nosis has been made. A deficiency of growth hormone will be apparent clinically only in children.

A deficiency of TSH will lead to the clinical picture of hypothyroidism. In practice the latter is more commonly due to a primary defect of the thyroid but it is important not to miss the rare case of pituitary myxoedema. A simple screening test is a search for thyroid antibodies because in patients with primary hypothyroidism these are nearly always present in significant titre.

Loss of all anterior pituitary hormones, panhypopituitarism, has sometimes occurred by the time a patient with a pituitary tumour seeks medical advice. The diagnosis is not easy because the condition is rare. The patient will have amenorrhoea or loss of libido and potency, the features of hypothyroidism, general ill health with poor response to intercurrent illness, and loss of body hair. These patients usually have a typical pale smooth skin and rarely acquire a sun-tan. This is due to lack of MSH and the action of ACTH which produces skin pigment.

PITUITARY TUMOURS WITH HYPERFUNCTION

An eosinophil adenoma producing an excess of growth hormone will produce gigantism in adolescence or acromegaly in an adult. Young people are sometimes brought to their doctor because they seem to be growing excessively tall. This is usually genetic, but may be due to an excess of growth hormone and appropriate investigations should be undertaken. Acromegaly is an insidious condition in which the hands and feet enlarge, the nose broadens, and the lower jaw protrudes. Patients rarely go to their doctor complaining of these changes, but the doctor not infrequently notices them when the patient attends for some other reason. Some conditions associated with acromegaly may alert the practitioner to this possibility: diabetes may occur from the action of growth hormone which antagonizes insulin; the patients often have the symptoms of a carpal tunnel syndrome; gross and disabling osteoarthritis of the hip occurs; and rarely there is enlargement of the heart with ultimate cardiac failure.

An ACTH-producing tumour may present with local manifestations but more commonly as Cushing's syndrome. In all patients with this condition where the pathological change seems to be bilateral adrenal hyperplasia, over-production of ACTH must be postulated and careful x-ray films of the pituitary fossa taken. The tumour is usually very small and undetectable at this stage; it may occasionally get bigger if the patient is treated by bilateral adrenalectomy. When this happens the patient's skin becomes deeply pigmented and cranial nerve palsy may occur.

DIAGNOSIS

The first step in the diagnosis of a pituitary tumour is to take x-ray films of the pituitary fossa; this may be enlarged, and there may be erosion of the posterior clinoids or of the wall. Occasionally the presence of a tumour may be suspected from finding a double contour to the floor suggesting that one side is being pushed down into the sphenoid sinus by the tumour. Further information may be obtained by tomography of the pituitary fossa. A craniopharyngioma tends to be situated above the fossa and may erode the clinoid processes and show areas of calcification.

If a pituitary tumour is found or strongly suspected on the x-ray findings a careful recording of the visual fields must then be performed. If there is evidence of field loss, suprasellar extension of the tumour is likely to be present and air encephalography should be undertaken to assess its extent and direction. In patients without a visual field defect, except those who are old or frail, air encephalography is advisable to exclude an upward extension of the tumour.

In patients with pituitary tumours endocrine assessment before treatment is required if there is gigantism or acromegaly

because in these cases the decision about treatment will be influenced by the level of growth hormone. This should be measured in the fasting basal state and, as it tends to vary from day to day in patients with acromegaly, at least three estimations should be made. The upper limit in a normal person is 5 ng/ml. Occasionally higher levels are found but these are readily suppressed by glucose, given by mouth or intravenously. In a mild case of acromegaly the fasting basal level will be 10 to 20 ng/ml, and in a severe one it may exceed 100 ng/ml and will not be reduced by glucose.

TREATMENT

The treatment of a pituitary tumour may be active with surgery or irradiation, or it may consist of giving appropriate replacement therapy for any hormone deficiency. Active therapy is needed for visual symptoms, for suprasellar extension that is likely to produce visual disturbances, and for excess production of growth hormone or ACTH if it is appreciable. Severe headache attributed to expansion of the pituitary fossa may be an indication for treatment but the results are often disappointing. Active treatment is very rarely indicated when the only abnormality is a hormone deficiency, a point discussed later.

There are several types of active treatment to be considered. The transfrontal surgical approach is usually advisable if there is a considerable suprasellar extension with visual disturbance. With lesser degrees of, or without suprasellar extension, a transphenoidal approach is satisfactory provided the paranasal sinuses can be cleared of any infection. If with either of these surgical approaches the tumour is thought to have been incompletely removed or to be invasive, postoperative external irradiation should be considered. An alternative method of treatment is with implantation of radioactive yttrium. This needs special equipment and a skilled operator. It is probably inadvisable if the tumour is extending down into the sphenoid sinus. External irradiation may be used to supplement surgery and is occasionally used alone in patients considered unfit for other forms of treatment. Hormone assays have shown that some tumours do respond to external irradiation but the results are variable and uncertain. Patients undergoing surgical procedures for tumours in the pituitary area should be given full steroid cover.

Recently there have been reports of beneficial responses to the administration of the modified steroid medroxyprogesterone acetate in patients with acromegaly. This drug seems to block the response to the excess of growth hormone but cannot yet be recommended for routine treatment.

Young women with secondary amenorrhoea due to a pituitary tumour present a difficult therapeutic problem. It may be possible to induce ovulation and achieve a pregnancy with gonadotrophin therapy but the pituitary tumour may grow rapidly during pregnancy. In these patients yttrium implantation giving a relatively small dose of irradiation may cause shrinking of the tumour and allow resumption of normal gonadotrophin secretion.

POST-TREATMENT ENDOCRINE ASSESSMENT

Full endocrine assessment is required after operation and in those patients in whom operation is not indicated, to decide what replacement therapy is needed. As in all cases of endocrine hypofunction, dynamic tests of response to stimulation should be used whenever possible.

Most important is the assessment of ACTH production and reserve. If the patient has had steroid cover for any surgical procedure the dose is gradually reduced to prednisone 1 mg eight hourly. Morning and midnight plasma cortisol measurements are then made and if these are normal with a characteristic diurnal variation ACTH production is probably adequate. As a dynamic stimulation test insulin hypoglycaemia may be used.

Provided the blood sugar is reduced below 40 mg/100 ml a significant increase of plasma ACTH and cortisol will be seen if ACTH reserve is adequate. Another test of ACTH reserve is to give metyrapone and measure the urinary total 17-oxogenic steroids, but the result of this investigation is not valid if the patient is on any corticosteroid replacement therapy—for example, with prednisone—at the time.

If ACTH production is significantly reduced, that of the other anterior pituitary hormones is also likely to be affected. It is relatively simple to assess TSH production by measuring the plasma thyroxine level; the protein-bound iodine concentration will be spuriously raised if the patient has had arteriographic studies. It is now possible to stimulate TSH production by giving an intravenous injection of synthetic hypothalamic thyrotrophin releasing factor (TRF) and measuring the plasma TSH level. Loss of growth-hormone production is important only in growing children. A stimulation test must be applied; insulin hypoglycaemia is the most effective, though subcutaneous glucagon, rebound after oral glucose, or a cup of hot Bovril may all be used. Gonadotrophin status in premenopausal women may be assessed on menstrual history. In men loss of libido and impotence may be due to hormone deficiency or the result of psychological disturbances. Measurements of plasma LH or testosterone are helpful in confirming gonadotrophin deficiency.

FOLLOW-UP

Patients with pituitary tumours, whether or not they have received active treatment, should be kept under observation. The visual fields should be checked regularly, together with x-ray films of the pituitary fossa. These observations should initially be made annually and later every two years. The patient's endocrine status should be checked and adequacy of replacement therapy assessed clinically.

Patients with acromegaly also need to have their growth-hormone levels followed. After operation or irradiation, the success of treatment may be judged by fasting basal measurements, made on at least three occasions. Subsequently patients should be reviewed annually with charting of the visual fields, radiographs of the pituitary fossa, and estimations of growth hormone.

Hypopituitarism

The commonest causes of hypopituitarism at the present time are pituitary tumours with or without operation and pituitary ablation for metastatic breast cancer. Nevertheless, there are other causes: pressure due to hydrocephalus; granulomata in the hypothalamus or the pituitary; and a group of patients in whom tuberculous meningitis has led to damage to the pituitary stalk. In some cases of hypopituitarism no cause can be found, though autoimmune "hypophysitis" has been suggested on occasion. Postpartum hypopituitarism is now very rare, probably because severe postpartum haemorrhage is quickly treated and when pituitary necrosis does occur it is soon recognized and treated. The patient who never properly recovered from a postpartum haemorrhage and was not finally diagnosed as having hypopituitarism until many years later, when she became comatose or was admitted to a mental hospital, is now very uncommon. Hypopituitarism of long standing is occasionally still seen in patients who have had pituitary tumours or craniopharyngiomas treated surgically and have not been properly followed up. The clinical features have already been mentioned under the heading of endocrine manifestations, and the appropriate investigation in the section devoted to post-treatment endocrine assessment.

In some cases the pituitary defect may involve only one or two hormones. Isolated gonadotrophin defect is more commonly recognized in boys in whom there is no pubertal development

and a very low plasma LH level; a pituitary tumour must be excluded by radiological investigation. Postpubertal disturbances of gonadotrophin secretion are common in young women and the usual type of secondary amenorrhoea is probably due to failure of the hypothalamus to produce gonadotrophin releasing factor. This usually corrects itself in a matter of months but if secondary amenorrhoea is prolonged a pituitary tumour must be excluded. Isolated deficiency of growth hormone does occur and should be looked for in all children below the third percentile in height.

REPLACEMENT THERAPY

The replacement therapy required in a patient with hypopituitarism, whether due to a pituitary tumour or some other cause, will depend on the trophic hormones that are deficient. For this reason detailed endocrine assessment is required and, as the situation may change, the hormone status must be reviewed regularly.

If there is evidence of ACTH deficiency, replacement therapy is most conveniently given with cortisone or prednisone. Aldosterone production by the adrenal cortex is little affected by loss of ACTH and therefore the glucocorticoid action of prednisone is adequate. The dose will be 3 to 6 mg per day given in divided doses eight-hourly (1 mg tablets of prednisone should be used). Patients on corticosteroid replacement therapy

for hypopituitarism must carry cards indicating that they need this treatment. If they get any fever or intercurrent illness or have to have surgical operations the dose will need to be increased. Vomiting of the tablets necessitates intramuscular injection. It should be noted that if the patient is deficient of ACTH all pituitary trophic hormones are likely to be lacking, but the reverse does not apply. If TSH deficiency is found replacement should be with thyroxine, 0.3 mg daily.

Gonadotrophin deficiency in premenopausal women may be corrected by injections of the appropriate gonadotrophin if pregnancy is desired—but otherwise cyclical therapy with oestrogen-progestogen mixtures may be used to maintain the normal condition of the breasts, uterus, and vagina. If this is not done the patients often complain of dryness of the vagina and dislike of intercourse. Gonadotrophin deficiency in young men who may want children should be corrected by injections of chorionic gonadotrophin with the hope that the addition later of a gonadotrophin with an FSH component will restore spermatogenesis. For older men fluoxymesterone by mouth or injections of long-acting testosterone will restore libido and potency but not fertility.

Children with growth-hormone deficiency who are short and whose epiphyses have not fused may benefit from injections of human growth hormone. It is therefore very important in children with hypopituitarism not to give gonadotrophin or sex-hormone replacement therapy until the maximum growth has been achieved.

Computers in Medicine

Computer Programme to Estimate Recurrence Risks for Multifactorial Familial Disease

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Summary

A computer programme to estimate recurrence risks for multifactorial genetic disease in affected families uses parameters on population prevalence and on heritability of liability of the condition and details of the family history. Information on affected and unaffected relatives (first-degree, second-degree, and third-degree) and on sex or age effects on prevalence and on heritability can all be accommodated by the programme.

Introduction

Many common familial diseases are not inherited in a simple Mendelian manner but may be the result of many genetic and environmental factors, so-called multifactorial inheritance. The recurrence risks for such diseases are not the simple Mendelian ratios and the best available estimates are the empiric risks—the observed frequency of the disease in relatives of affected

patients. In practice, however, these risks may vary with the sex, severity, and age of onset in affected individuals and with the number of affected members in the family concerned. New methods of estimating recurrence risks for multifactorial conditions have been developed,^{1 2} and these can be used in genetic counselling to supplement empiric risks in complex situations. The objects of this paper are to describe a computer programme available for calculating recurrence risks and to demonstrate its use in genetic counselling problems.

Scope

A wide range of possible situations can be covered by the programme. It can accommodate: (1) affected and unaffected relatives; (2) any family history, giving (a) accurate risks within sibships but (b) approximate risks with second-degree and third-degree relatives; (3) differences in prevalence and heritability for different sexes or different severity or age classes for the disease; and (4) risks to future children or risks to an individual conditional on his not being affected so far.

A further development of the programme may allow the use of information on continuous variables associated with a disease (such as blood glucose levels in diabetes or personality scores in schizophrenia) and so improve the accuracy of the risk estimate in a given family.

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