TUMOURS OF THE PITUITARY GLAND - SIX
CASES

INTRODUCTION

The theme of this dissertation is the mode of presentation,
assessment and management of six patients with tumours of the
pituitary gland. Such tumours may be secretory or non-secretory.
Typically secretory tumours present with endocrine abnormalities
due to hypersecretion of a particular hormone, while non-
secretory tumours present with symptoms caused by the expansion
of the lesion in the pituitary fossa, such as headaches, visual
field defects or hypopituitarism. Treatment is by surgery if
there are signs of visual impairment due to optic nerve
compression or if there is internal hydrocephalus. Otherwise
radiotherapy is normally the method of choice. Careful assessment
of pituitary function is necessary and treatment itself may
increase the impairment, compounding the necessity for replacement
therapy. However recently the management of certain of the
secretory tumours has been modified by the introduction of the
drug Bromocryptine.

Of the six cases presented two have secretory tumours and are
discussed in detail. The other four have non-secretory tumours and
illustrate various modes of presentation, and resulting endocrine
deficiences. The assessment of pituitary function is considered
in relation to these cases and finally some aspects of the insulin
hypoglycaemia test are examined in depth.

CASE I - MR ALEXANDER COOK

PRESENTATION

Alexander Cook is a thirty eight year old single man who works on a Norwegian Oil Rig and lives with his parents when on leave. He had no previous medical history when he first presented with recurrent frontal headaches of increasing severity. These were not associated with any visual disturbances but he was aware of an increase in his shoe and glove sizes and in the tightness of a ring which he had worn for many years.

He denied that there had been a change in his facial appearance and was unable to produce any suitable photographs for comparison. However the prominence of his jaw was striking which together with his history was highly suggestive of acromegaly.

General physical examination revealed no other abnormalities and he was normo-tensive with a normal male distribution of body hair and had no detectable visual impairment.

INVESTIGATIONS

The clinical diagnosis of acromegaly was supported by performing an oral glucose tolerance test in which his elevated basal levels of growth hormone were not suppressed by the administration of glucose. However, his glucose tolerance was normal.

Assessment of his visual fields by perimetry revealed no defects but a skull x-ray combined with tomography of the pituitary fossa demonstrated downwards expansion of the sella on the left hand side without any bony erosion suggestive of superior extension of the lesion. Increased thickness of the soft tissues of his hands was shown by x-ray.

Although he had no clinical signs or symptoms indicative of deficiency or hypersecretion of other pituitary hormones, basic screening was performed. Thyroid function, as assessed by protein bound iodine, T3 resin uptake and free thyroxine index was normal. Twenty four hour urinary outputs of 17- hydroxycorticosteroids,

Follicle Stimulating Hormone and Intestitial Cell Stimulating
Hormone were all normal.

MANAGEMENT

In view of the absence of any signs of optic chiasmal
compression the decision was made to treat him with radiotheraphy
rather than surgery. However, at that time, there were current
reports of the successful lowering of Growth Hormone in
acromegalies by Bromocryptine (C.B. 154) and it was decided to
assess the value of this drug prior to using radiotherapy. Before
its commencement and at monthly intervals during Bromocryptine
treatment he was assessed by means of sequential measurements of
hand volume and skin thickness as well as his growth hormone
response in a two-hour glucose tolerance test. The dose of
bromocryptine was initially 2.5 mg every six hours and was increased in
monthly increments to 40 mg daily.

He showed a definite response to this drug with regard to his
growth hormone levels although the basal levels remained above
normal and were not supressed by glucose administration. Despite
this good response he was given conventional high voltage radio-
therapy in November 1976 and was thereafter maintained on
Bromocryptine (40 mg daily).

SUBSEQUENT COURSE AND INVESTIGATIONS

After the course of radiotheraphy he began to complain again
of lassitude, increasing tiredness, frequent headaches and epi-
gastric discomfort and was re-admitted to the Metabolic Unit of
the Western General Hospital for full assessment of his pituitary
function.

Preliminary investigations including a full blood count,
erythocyte sedimentation rate, urea and electrolyte, liver function
tests and lying and standing blood pressure were all within normal
limits. Screening tests for thyroid function and twenty four hour
urinary gonadotrophin levels were also normal. However his plasma
cortisol levels were low and showed a loss of diurnal variation.

In order to determine his functional pituitary reserve, an

insulin hypoglycaemia test was performed and combined with administration of thyrotrophin releasing hormone (TRH). Satisfactory hypoglycaemia was achieved with spontaneous return to normoglycaemia and his plasma cortisol levels rose satisfactorily. Basal growth hormone levels were still elevated but showed a normal pattern of response to insulin. TRH – stimulated TSH release reached normal levels but the response was delayed.

He was discharged home on a lower dose of Bromocryptine (10 mg daily) but was re-admitted at the request of his general practitioner three weeks later with increasing lassitude and postural hypotension. Further investigations included x-rays of his skull, re-assessment of his visual fields by perimetry and a short Synacthen test to exclude primary adrenal cortical deficiency. However these investigations were normal and he had an excellent response to synacthen, reflected by a good post-Synacthen rise in plasma cortisol and a twofold rise in his urinary 17- hydroxycorticosteroid output. There was a slight improvement in the diurnal pattern of his plasma cortisol levels and in the absence of abnormal findings he was discharged home. When reviewed three months later he was feeling extremely well and had no further evidence of deficient pituitary function although his basal growth hormone level was still slightly elevated and was not suppressed by administration of oral glucose.

DISCUSSION OF CASE I

Acromegaly usually results from the presence of a growth hormone secreting pituitary adenoma of eosinophil or mixed cell type. In an adult whose epiphyses have fused it leads to an over growth of all organs, skin, soft tissues and skeleton.

Local expansion of the tumour may cause features common to all pituitary tumours, such as headache which is attributed either to dural traction, or to raised intracranial pressure if there is obstruction to the circulation of cerebrospinal fluid. Visual defects due to chiasmal compression may develop with variable loss of vision in the temporal fields and these may be

asymetrical. Loss of visual acuity and colour vision with optic atrophy may also result if compression is more severe and long standing. Compression or destruction of normal pituitary tissue, the hypothalamus or pituitary stalk may result in deficient secretion of other pituitary hormones and usually affects the gonadotrophins first. However hypogonadism may result from elevated prolactin levels due either to its secretion by tumour cells or to pituitary stalk compression with impaired release of prolactin-inhibitory factor. This is discussed in more detail in relation to Case II.

In addition to these features common to all types of pituitary tumour, acromegaly is associated with certain specific complications apart from its effects on skin and bone. Due to the anti-insulin effects of growth hormone, basal levels of insulin are raised and eventually pancreatic β cell exhaustion may occur resulting in an impairment of glucose tolerance and diabetes mellitus. There is a tendency for hypertension to develop in acromegalics and although the cause of this is unclear it is notably resistant to conventional anti-hypertensive therapy and may be severe. In addition, an unusual type of cardio-myopathy may develop which, in combination with the risks of diabetes mellitus and hypertension, leads to an increased incidence of early death from cardiovascular complications. It has been estimated that untreated acromegalics have approximately twice the normal mortality rate of their age group, mainly as a result of these complications. (Wright et al, 1970). Contributing to the morbidity rather than the mortality from acromegaly is the tendency for the early onset of osteoarthritis to occur, probably due to skeletal deformities.

For the reasons outlined above, early treatment is mandatory and in the past the choice was between surgery and radiotheraphy. Surgery is indicated for those cases with chiasmal compression and visual field defects and often post operative radiotheraphy is required when growth hormone levels are not reduced to normal. Hypopituitarism or diabetes insipidus may follow surgery. Irradiation in cases without visual field defects carries less chance of causing hypopituitarism but the full effects of either

treatment may not be evident for three to four years. (Kanis et al, 1974)

The use of Bromocryptine in acromegaly was suggested after it had been observed that acromegalic patients had a paradoxical response to dopamine agonists. They show a fall in growth hormone levels (Liuzzi et al, 1972), instead of the usual rise. Bromocryptine is a dopamine agonist and well established in the treatment of hyperprolactinaemia. (Besser et al, 1972) It has been shown to reduce growth hormone levels in acromegalics (Thorner et al, 1975) although, as this case illustrates, they rarely fall to the normal range. Bromocryptine's place in the management of acromegaly is at present undefined but it may provide an extremely useful adjunct to conventional therapy. It does have the added advantage of improving the hypogonadism and impotence which results from any coincidental elevation in prolactin levels.

CASE II - MISS DIANE GRAHAM

PRESENTATION

Diane Graham is a twenty five year old unmarried clerkess, who presented at the age of twenty (1972) with primary amenorrhoea. She was of average height and build with well developed secondary sexual characteristics, normal pubic and axillary hair and no signs of hirsuitism. However from the age of fifteen she had been troubled by a spontaneous discharge of milky white fluid from both nipples. Questioning revealed that she suffered from recurrent headaches but had no associated visual symptoms.

PRELIMINARY INVESTIGATIONS

Chromosomnal analysis confirmed that she had the normal female 46 XX configuration. Her visual fields and sense of smell were normal and no pituitary lesion was revealed by x-ray. Gynaecological examination was performed under general anaesthesia and one ovary biopsied. Her external and internal genitalia were of normal appearance although the uterus and ovaries were small. However, the ovarian tissue contained numerous primondial follicles which suggested a lack of gonadotrophin stimulation.

Plasma assays of gonadotrophins and sex steroids were not locally available in 1972 and thus the investigation of her hormonal status was based on their urinary excretion. Her twenty four hour outputs of oestrogens and pregnanediol were well below the normal range for a non-pregnant woman of reproductive age as was her excretion of luteinising hormone. There was, of course, no evidence of impaired renal function and her thyroid function and corticosteroid excretion were normal.

These results suggested hypopituitary hypogonadism and the induction of ovulation was attempted using clomiphene although she had no desire to become pregnant at that time. This drug is thought to act at hypothalamic level by blocking oestrogen receptors and thus induces a rise in FSH and LH levels by interfering with the negative feed back control mechanism. As well as promoting ovulation, it is a test of the integrity of the hypo-

thalamo — pituitary ovarian axis. Diane responded with an excellent rise in her output of total urinary oestrogens, but there was no rise in pregnanediol. She did not menstruate and had no evidence of ovulation or corpus luteum formation. Several further courses of clomiphene failed to induce menstruation or ovulation and she decided not to continue treatment with this drug.

FURTHER INVESTIGATIONS

In 1976, advances in knowledge had enabled her situation to be reassessed. The combination of amenorrhoea, galactorrhoea, low oestrogen levels and lack of response to clomiphene was very suggestive of hyperprolactinaemic hypogonadism which was confirmed when her prolactin level was shown to be very high.

When her skull x-ray was repeated, she was found to have an enlarged pituitary fossa in which tomograms defined a space-occupying lesion on the left side. There was expansion of the fossa and erosion of the dorsum sella and posterior clinoid process on the left, which suggested upward extension of the lesion. However no defect was detected on repeating the assessment of her visual fields.

In the light of these findings, her pituitary function was re-examined. Thyroid function as assessed by PBI, T_3 resin uptake, 4-hour radio iodine uptake and a TRH stimulation test was normal. She had a normal response to insulin with spontaneous reversion to normoglycaemia following hypoglycaemia and normal rises in plasma cortisol and growth hormone levels. Administration of gonado-trophin releasing hormone (LHRH) produced an entirely normal gonadotrophin response, confirming that her hypogonadism was secondary to hyperprolactinaemia rather than to deficiency of pituitary gonadotrophins.

FURTHER MANAGEMENT

The decision was taken to treat her surgically but in the interim she was commenced on bromocryptine. She responded to this with a partial lowering of her prolactin levels and cessation of galactorrhoea. At operation the tumour was removed and histology

showed it to be an eosinophilic adenoma. Surgery presented a particular problem in her case as she was a Jehovah Witness and would not give her permission to have blood transfusion even if the situation became critical. Fortunately this complication did not arise. She was discharged home on a maintenance dose of prednisolone which had been commenced, as is routine, at the time of surgery.

POST OPERATIVE ASSESSMENT

She was admitted to the Metabolic Unit three months post operatively for withdrawal of steroids and assessment of pituitary function. Her blood pressure remained steady and her blood count, electrolyte levels and urinary corticosteroid excretion were also normal. Her plasma cortisol levels were low, but exhibited diurnal variation. Thyroid function tests were normal. A combined pituitary function test was performed after an overnight fast with administration of insulin, TRH and LHRH. The responses to these three hormones were all normal. However, her prolactin level was still considerably elevated and she was recommenced on Bromo-cryptine (40 mg per day).

DISCUSSION

There are two possible mechanisms whereby a tumour in the region of the hypophysis may cause hyperprolactinaemia. Firstly, as in the case of Diane Graham, there may be a prolactin-secreting tumour actually present within the pituitary gland. This may be primarily composed of eosinophilic cells or may be of mixed or chromophobe cell origin (Friesen et al, 1972). The tumours are often very small initially and in this case the onset of the galactorrhoea preceded the appearance of radiological changes in the pituitary fossa by nine years.

The other situation in which hyperprolactinaemia may be associated with a pituitary or hypothalamic tumour is if there is compression of the pituitary stalk or cells producing prolactin inhibitory factor (Turkington, 1972). Unlike other anterior pituitary hormones, prolactin is under predominantly inhibitory

control from the hypothalamus and thus interruption of the hypothalamo-pituitary connections results in hypersecretion of prolactin with hyposecretion of the other hormones.

In the absence of associated gonadotrophin deficiency, elevated prolactin levels cause amenorrhoea by inhibiting the ovarian response to gonadotrophins. Thus oestrogen levels are low and there is an impaired response to clomiphene administration (Jacobs et al, 1976). Bromocryptine has been shown to be very effective at lowering prolactin levels with cessation of galactorrhoea and resumption of ovulation and menstruation. (Thorner et al, 1975b)

In the case of a proven pituitary tumour, Bromocryptine will lower prolactin levels but surgery is usually required when there are signs of chiasmal compression. If the patient is a woman who may wish to become pregnant, surgery or radiotherapy should be performed even in the absence of chiasmal compression as the rapid enlargement of the pituitary during pregnancy may cause a rapid deterioration in vision. (Jacobs and Franks, 1975)

In the absence of subsequent development of hypopituitarism, Diane Graham has a good chance of retaining normal ovarian function and fertility while on Bromocryptine therapy.

CASE III - MISS MARION STARK

PRESENTATION

Marion Stark is a fifty-five year old spinster who presented
to an ophthalmologist on account of a progressive decrease in her
visual acuity over the previous three years. Examination of her
optic fundi revealed temporal pallor of both optic discs and she
had a bilateral upper temporal quadrant visual field defect which
was confirmed on perimetry. Enlargement of the pituitary fossa
was demonstrated by a skull x-ray.

Her general health was good and she had no other symptoms or
signs suggestive of endocrine disease. At that time she was fifty
four years old and menstruation had ceased spontaneously ten years
earlier.

A right frontal craniotomy was performed on 20th July, 1976
and a pituitary tumour removed, It was compressing the optic
chiasma and on histological examination it was found to be a
chromophobe adenoma. She was discharged on the maintenance dose
of corticosteroids which had been begun, as is routine, to cover
her pituitary operation.

POST OPERATIVE ASSESSMENT

Four months after this operation she was admitted to the
Western General Hospital for the withdrawal of her steroid therapy
and assessment of her pituitary function. She had no complaints
other than being aware of impaired vision in the left upper
temporal field which was confirmed clinically.

Her blood pressure, urine and routine haematology and bio-
chemistry were all within normal limits as were the results of
screening tests for thyroid function. However, her twenty four
hour radio iodine uptake was at the lower limit of normal and her
plasma cortisol levels were low, although they did show a little
diurnal variation.

A combined pituitary function test was performed with the

standard doses of insulin (0.1 mg/kg), TRH (200 mg) and LHRH
(50 mg). Hypoglycaemia was achieved but her blood glucose rose
slowly and after ninety minutes was only 2.3 mmol/1. Her basal
plasma cortisol levels were in this instance unrecordable but
they rose satisfactorily after the insulin. Her growth hormone
also rose from an unrecordable basal level, but the response was
sluggish and subnormal. Her TSH response to TRH was similarly
delayed and basal levels of LH and FSH were very low for a woman
of post menopausal age with a minimal response to LHRH. She had
an elevated serum prolactin concentration.

DISCUSSION

These results indicated that she had a degree of impairment
of hypothalamopituitary function but, despite low basal levels of
plasma cortisol and growth hormone, was able to respond to the
stress of insulin – induced hypoglycaemia. It was decided not to
recommence her steroid therapy but to review her at regular
intervals. Her low gonadotrophin levels and raised prolactin level
would not require treatment as she was post menopausal and in the
absence of significant ovarian oestrogen production she is un-
likely to develop galactorrhoea.

CASE IV - ANDREW CRISP

PRESENTATION

Andrew Crisp is a fifteen year old schoolboy, who presented
with a history of intermittent visual impairment over the
preceding three months. He had experienced headaches but these
were not severe and he had no other symptoms.

He was a plump, highly intelligent boy but was well below
the average height for his age and was prepubertal. Visual acuity
was considerably impaired in both eyes and worse on the left with
a pallor of the left optic disc suggestive of optic atrophy.
Assessment of his visual fields by perimetry demonstrated the
presence of a bitemporal hemianopia and very marked constriction
of the left visual field.

Considerable expansion of the pituitary fossa was seen on the
skull x-ray. An EMI scan confirmed the presence of a well defined
lesion in the suprasellar region with some expansion of both
lateral ventricles and the third ventricle, which was indicative
of internal hydrocephalus.

MANAGEMENT

On 28th June 1976 a chromophobe adenoma of the pituitary
gland was removed at operation. It was obliterating the cisterna
chiasmatica and had compressed both optic nerves from below. He
was given the normal steroid cover during and after surgery and
post operatively developed diabetes insipidus which required
therapy with syntopressin.

POST OPERATIVE ASSESSMENT

Four months later he was admitted to the Western General
Hospital for withdrawal of both steroids and Syntopressin com-
bined with assessment of his pituitary function.

He complained of having had little improvement in the vision
of his left eye, but that on the right side had improved. The
left visual field was still markedly constricted. He had not

altered in height and was still prepubertal.

In the ward he remained normo tensive and routine haematology and biochemistry were normal. Screening tests for thyroid function including radio iodine uptake studies were within the normal range but his diurnal plasma cortisol levels were all unrecordable, which suggested ACTH deficiency.

During the course of an insulin hypoglycaemia test he experienced a profound and prolonged fall in blood sugar. This was associated with no detectable rise in either plasma cortisol or growth hormone from their unrecordable levels. His TSH response to TRH was normal but his gonadotrophin levels were low and failed to respond to LHRH. He had a considerably elevated serum prolactin concentration.

DISCUSSION

These investigations confirmed that he had a combined pituitary deficiency of ACTH, growth hormone and gonadotrophins, although TSH secretion was adequate. The very high prolactin level suggests that there is damage to the hypothalamus or pituitary stalk although failure to respond to LHRH indicates that there must also be damage to the pituitary cells themselves.

He was then recommenced on maintenance steroid therapy. Ultimately he will require induction of puberty with HCG and he will never achieve his expected height. It is also unlikely that he will regain the vision in his left eye. The clinical implication of his raised prolactin level is uncertain.

CASE V -- MRS ELIZABETH AITKEN

PRESENTATION

Mrs Aitken originally presented at the age of thirty two,
sixteen months after the birth of her first child, with lethargy,
anorexia and vague headaches. She had not resumed menstruation
but no details have been recorded about her lactation history.
Examination of her visual fields had demonstrated bilateral upper
temporal field defects but x-ray of her pituitary fossa was
normal. However, an EMI scan outlined a cystic lesion in the
region of the hypophysis. A combined pituitary function test done
at that time confirmed the clinical diagnosis of hypopituitarism.

A right frontal craniotomy was performed and a large supra-
sellar cyst aspirated. Post operatively she developed diabetes
insipidus, requiring pitressin therapy.

SUBSEQUENT ASSESSMENT

Six months later she was admitted to the Metabolic Unit in
March 1975 for further assessment. She was on maintenance doses
of cortisone, thyroxine and using DDAVP twice daily. The latter
is a synthetic analogue of vasopressin which is administered intra-
nasally and acts for longer than the older preparations such as
Pitressin tannate in-oil and Syntopressin.

Her complaints on admission were persisting secondary
amenorrhoea and loss of libido. She had no galactorrhoea and on
examination, apart from scanty pubic and axillary hair, there were
no physical abnormalities. Her visual fields were undiminished
when tested by confrontation and her optic fundi were normal.

All the above three drugs were stopped on admission, in
preparation for pituitary function assessment. Her plasma cortisol
levels were low and did not show diurnal variation. Following the
administration of insulin, LHRH and TRH, she had a normal hypo-
glycaemic response with a spontaneous return to euglycaemia
although her cortisol levels remained unrecordable throughout the
test. However, she had a definite, although subnormal growth

hormone response. Her subnormal gonadotrophin levels were un-
altered by LHRH but she did respond normally to TRH. Her serum
prolactin level was measured, but unfortunately the result is
not recorded in her case records.

During twelve hours of water deprivation. her plasma
osmolarity rose above normal and she showed an inability to
concentrate her urine, indicating the need for combined therapy
with DDAVP in addition to corticosteroids. Oestrogen replacement
therapy may also be required.

CASE VI — MR EDWARD BOYLE

HISTORY

Mr Boyle originally presented in 1970, at the age of 52, with
peristent frontal headaches of increasing frequency. He was un-
aware of any visual upset and his visual fields were not restricted.
X-ray examination showed expansion of the pituitary fossa and a
pituitary biopsy was performed via the trans-sphenoidal route,
confirming the presence of a chromophobe adenoma. In view of the
absence of signs of optic nerve compression he was treated with
radiotherapy.

SUBSEQUENT PRESENTATION AND INVESTIGATION

In April 1977 he was admitted to the Western General Hospital
for reassessment on account of tiredness, mental slowness, poor
concentration, cold intolerance, constipation, impotence and loss
of libido. His shaving frequency had declined to once weekly,
whereas he had formerly shaved twice or thrice daily. He was on
no medications apart from antacids for a radiologically diagnosed
duodenal ulcer.

On examination, he was obese and mentally slow. His skin was
pale and soft and he had no pubic, axillary or body hair. Optic
fundi and visual fields were normal but it was noted that his knee
jerks showed delayed relaxation.

X-ray of his skull showed"considerable expansion of the
boundaries of the pituitary fossa by an intra-fossa mass."
Routine haematology was normal but serum electrolytes showed him
to have an elevated potassium level although his sodium
concentration was normal. Blood urea was slightly elevated and
his creatinine clearance was correspondingly low.

His plasma cortisol levels were very low and showed no
diurnal variation but PBI, T_3 resin uptake and free thyroxine
index were, surprisingly, within the normal range. A combined
pituitary function test was performed which evoked a normal
cortisol response although growth hormone was unrecordable. LHRH

stimulation failed to produce a gonadotrophin response which confirmed the clinical impression that he was gonadotrophin deficient. The results of four hour radio iodine uptake studies and the TRH stimulation test were not available and the decision to commence thyroxine will depend on these results.

The x-ray appearance is suggestive of progression of the tumour and his symptoms are too delayed to be a direct effect of the radiotherapy. In addition to appropriate replacement therapy more definitive treatment may be required, although unless signs of visual field involvement develop, surgery will probably not be necessary.

ASSESSMENT OF PITUITARY FUNCTION

There are a number of factors which should be considered when using hormone assays based on peripheral plasma and urine samples to assess pituitary function.

These hormones are relatively unstable in blood at room temperature. Thus the plasma must be separated and frozen as quickly as possible. A good example is the plasma ACTH assay, concerning which Dr J. G. Radcliffe of the Radioimmunoassay Unit, Glasgow issues the following instructions:-

1) At lease 10 mls of blood should be taken into a plastic syringe and put into a cooled heparinised plastic container (e.g. in an ice bucket).

2) The sample must be centrifuged as soon as possible (within 20 minutes of sampling) in a refrigerated centrifuge (4°C).

3) The plasma (at least 5 ml) should be transferred to a polystyrene tube and deep frozen (at least 20°C) immediately.

The time from sampling to deep freezing should be less than 45 minutes.

However, how often is this protocol vigorously followed in the ward situation where blood samples may be left for up to two hours or more before being centrifuged and then the plasma is slowly frozen in the freezing compartment of the ward fridge. Such sources of error are probably inevitable but should always be considered when an unexpected result is obtained, though it would be helpful if the relative stabilities of the various hormones were more widely appreciated.

The secretion of the pituitary hormones fluctuates considerably over the course of a twenty four hour period. Growth hormone and prolactin may be released in bursts during the resting state and particularly in the early hours of sleep. Stress and the fasting state of the individual have considerable influence on

their rate of secretion. Thus, a single plasma sample is unlikely
to reflect the overall output of these hormones and serial sampling
over the course of several hours is more representative. It is
unfortunate that methods for the estimation of these pituitary
hormones in urine are not readily available, for these would give
a good index of total daily output, providing that their renal
clearance was relatively constant.

Pituitary function can also be assessed in terms of the out-
put of hormones from the target glands. Thus, in centres where
ACTH estimations are not readily available, the response of the
adrenal cortex in terms of plasma cortisol or its excretory
products, urinary 17- hydroxycorticosteroids, is effectively used
to assay ACTH secretion, provided that there is no adrenal gland
pathology. Twenty four hour urinary 17- hydroxycorticosteroid
output is a good index of adrenal cortisol secretion, so long as
certain drugs are withheld for twenty four hours before and during
the collection periods. These drugs include various antihyper-
tensives, barbiturates, tranquillisers, diuretics and other drugs
which interfere with the assay. ACTH secretion characteristically
shows a diurnal variation over the twenty four hour period,
reaching a peak in the early morning and a trough in the late
evening. Loss of this diurnal variation in plasma ACTH or cortisol
concentration may be the first sign of Cushing's disease. This
emphasises the point that, if it is intended to use single plasma
samples for diagnosis or to compare patients and the effects of
therapy then they should be collected under as near identical
conditions as possible. (e.g. at 08^{00} hours before breakfast and
at midnight)

Gonadotrophin secretion in women of reproductive age is
normally cyclical and can only be reliably interpreted in relation
to menstrual status. Thus weekly sampling is performed over a six
week period in the investigation of amenorrhoea or infertility and
the levels of the target ovarian hormones (i.e. ovarian steroids)
measured as well as gonadotrophins.

Suspected hyper or hyposecretion of pituitary hormones is
investigated by means of dynamic tests. If hyperfunction is

suspected, supressive tests which examine the negative feedback
control mechanism are employed, such as the use of dexamethasone
to inhibit ACTH secretion and the administration of glucose to
suppress growth hormone secretion. The latter was used in the case
of Alexander Cook, as the absence of a fall in growth hormone level
is diagnostic of acromegaly.

If pituitary hypofunction is suspected the lesion may be
within the anterior pituitary itself or at hypothalamic level.
Administration of the appropriate hypothalamic releasing factor will
test the ability of the pituitary cells to release their hormone,
such as the use of TRH and LHRH in the combined pituitary function
test. Stimulation at the hypothalamic level may be achieved by
removing its negative feedback inhibition.

One example is the use of metyrapone which blocks the 11-β
hydroxylase enzyme in the adrenal cortex, thus lowering circulating
cortisol levels. This leads to stimulation of ACTH secretion by
removal of the inhibitory effect of cortisol on the hypothalamus.
Administration of Clomiphene blocks oestrogen receptors in the
hypothalamus and thus reduces oestrogen feedback inhibition.

As well as being of considerable diagnostic value, such tests
have a vital role to play in the management of patients with
pituitary disease. For example, the failure of Andrew Crisp to
respond to LHRH indicated that he would not achieve puberty
spontaneously and would ultimately require therapy with gonado-
trophins. Diane Graham's inadequate response to Clomiphene may be
of therapeutic as well as of diagnostic value for it has shown
that this drug will not induce ovulation in her case.

Insulin hypoglycaemia is a particularly useful dynamic test
and before discussing its results in these six patients, I propose
to consider its physiological basis in some detail.

THE INSULIN HYPOGLYCAEMIA TEST

The insulin hypoglycaemia test measures the response of the hypothalamic – pituitary axis to the stress of hypoglycaemia. Insulin is injected intravenously with the dose being adjusted according to the subject's body weight. Half hourly samples of blood are withdrawn through an indwelling cannula and assayed for blood glucose, cortisol and growth hormone. The stress is considered adequate only if blood glucose falls below 2.2 mmol/l, at which level there are associated systemic effects such as sweating, pallor and tachycardia (Greenwood and Landon, 1966).

The test does not distinguish between pituitary and hypothalamic disorders as the stress is believed to act at the level of the hypothalamus but it does give an estimate of the ability of the hypothalamo–pituitary axis to respond to stress.

An individual who has been hypophysectomised shows a marked hypersensitivity to the hypoglycaemic action of exogenous insulin with a profound fall in blood glucose and a slow return to the base line levels. This insulin hypersensitivity is also seen after a meal rich in carbohydrate, when secondary hypoglycaemia occurs following clearance of the glucose load from the blood. It is most important that any individual who is suspected of having deficient pituitary reserve is very carefully supervised during the course of an insulin hypoglycaemia test, or the profound prolonged hypoglycaemia may lead to coma or convulsions. Thus it is common practice to give a smaller dose of insulin (0.1 mg/kg rather than 0.15 mg/kg) when pituitary deficiency is suspected.

It is interesting to consider the basis of this insulin hypersensitivity which is usually assumed to be due to the absence of ACTH and corticosteroids.

Insulin appears to be the only hormone responsible for lowering the blood glucose level, while several hormones act in different ways to counteract the effects of insulin and raise blood glucose levels. Insulin is thought to act by enhancing the uptake

of glucose by peripheral tissues and by the hepatic cells in which it is stored as glycogen.

As blood sugar levels fall in the fasting state there is rapid secretion of adrenaline and glucagon which both activate the hepatic enzyme glycogen phosphorylase, leading to release of stored glucose. This mechanism, which counteracts hypoglycaemia, is backed up by the release of growth hormone and ACTH. Growth hormone appears to inhibit glucose uptake by peripheral tissues while enhancing the mobilisation of free fatty acids from adipose tissue which acts as an alternative metabolic substrate. It also acts on hepatic cells and promotes glucose release.

Adrenal glucocorticoids, under the control of ACTH from the anterior pituitary, also decrease peripheral glucose utilisation, while enhancing glucose production from non-carbohydrate precursors through gluconeogenetic pathways. They also promote hepatic glycogen deposition, thereby ensuring that, during prolonged stress, these reserves are not exhausted. Glucocorticoids also facilitate and enhance the hyperglycaemic effects of both glucagon and adrenaline. (Ramey and Goldstein, 1957)

It is not established which, if any single one, of these hyperglycaemic agents is predominantly responsible for the rapid return to euglycaemia after insulin administration in normal subjects and why insulin hypersensitivity follows hypophysectomy. However current opinion considers that the loss of either growth hormone (Altszuler, 1974) or adrenaline (Wurtman et al, 1972) is responsible for this latter phenomenon. However, both glucagon and adrenaline are powerful hyperglycaemic agents and at first sight one would not expect them to be influenced by hypophysectomy.

De Bodo and Altzuler (1958) in a detailed review of the subject compared the effects of insulin in hypophysectomised dogs with those which had been adrenalectomised. At doses of insulin between 0.08 and 0.25 mg/kg, both sets of dogs were hypersensitive to insulin. However, using a small dose of insulin (0.025 mg /kg) the adrenalectomised dogs responded with spontaneous return to normoglycaemia, while the hypophysectomised dogs were still insulin

hypersensitive. Furthermore they showed that in the absence of corticosteroids, there was failure of both adrenaline and glucagon to raise blood glucose levels due to an impairment of their action at hepatic level. They were able to abolish the insulin hypersensitivity of hypophysectomised animals by administration of maintenance doses of growth hormone. These observations have been supported by later workers and Altszuler (1974) concludes that the insulin hypersensitivity seen after hypophysectomy is due to the loss of growth hormone as well as ACTH.

However Wurtman and Pohorecky (1972) have a very different explanation which they often quote as an introduction to their work on the corticosteroid dependence of the adrenal noradrenaline methylating enzyme. They have good evidence that phenylethanolamine –N-methyl transferase (P.N.M.T.), the enzyme which catalyses the N-methylation of noradrenaline to produce adrenaline, is dependent for its action on the presence of adrenal glucocorticoids. Anatomically the venous drainage of the cortex passes through the medulla, bathing its cells with blood containing an extremely high concentration of glucocorticoids (one hundred fold greater than that present in the general circulation). Hypophysectomised dogs have adrenal cortical atrophy and have been shown to have low acitivty of PNMT and low outputs of adrenaline. Maintenance doses of corticosteroids do not result in the return of this enzyme's activity as the blood bathing the medulla will merely contain systemic levels of these steroids. Only massive systemic doses of corticosteroids give a sufficient intra-adrenal concentration to result in an increase in the activity of PNMT.

In their review, Wurtman et al postulate that it is the absence of adrenaline that is responsible for insulin hypersensitivity as only this hormone could be released and act quickly enough to explain the rapid return to normoglycaemia seen in the normal subject. They do not regard the role of growth hormone to be important, claiming that its release and action would be too slow. They never mention glucagon which has been shown to have both a rapid release and a rapid blood glucose mobilising effect. (Sawin, 1969) Furthermore they do not discuss the dependence of adrenaline and glucagon on adequate levels of corticosteroids
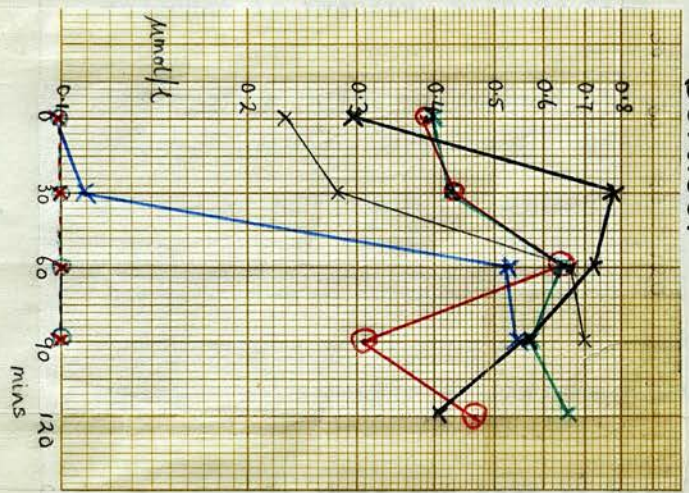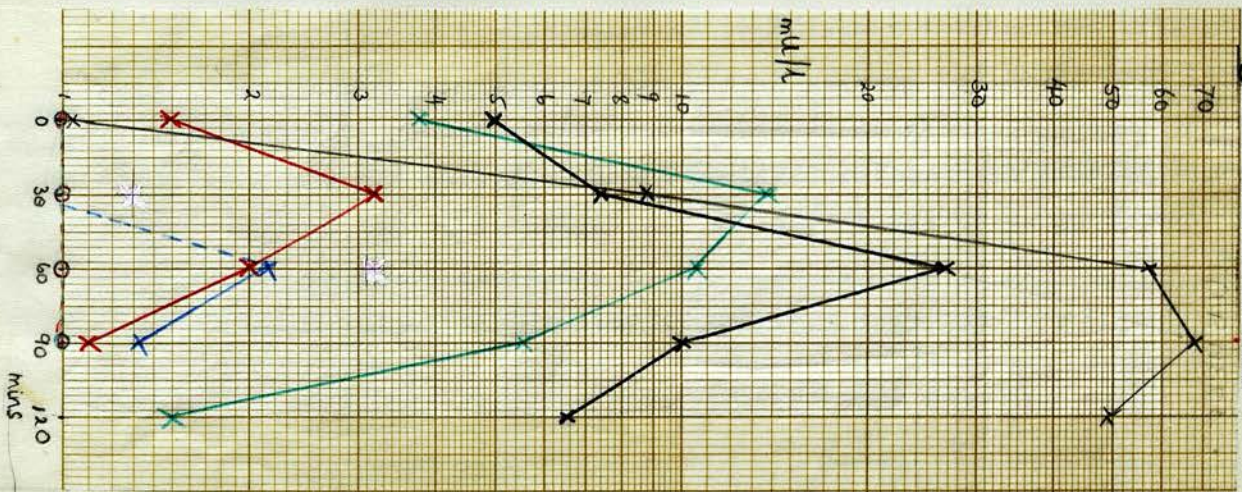
THE INSULIN HYPOGLYCAEMIA TEST

Glucose — mmol/l — mins

Cortisol — μmol/l — mins

Growth Hormone — mU/l — mins
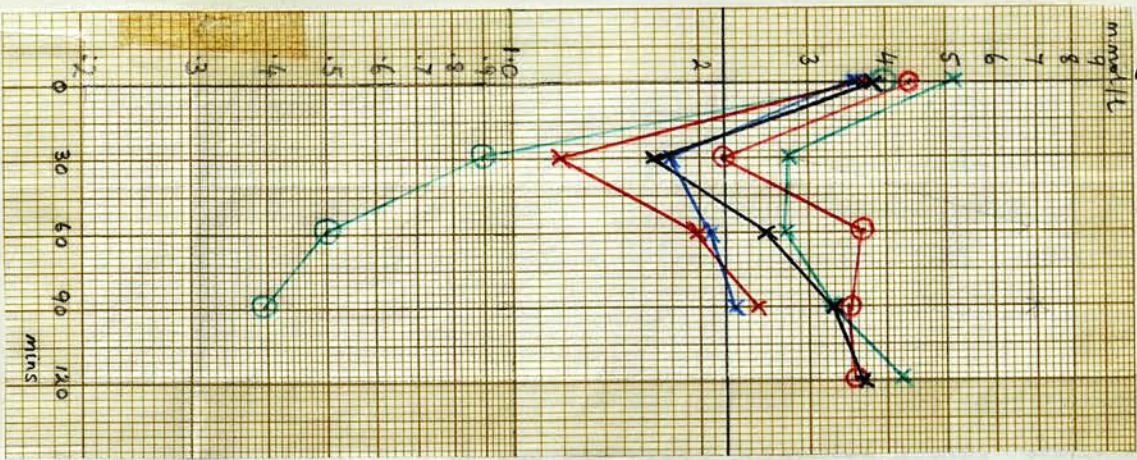
A. COOK
D. GRAHAM
E. AITKEN
M. STARK
A. CRISP
E. BOYLE
CONTROLS (6 volunteers)

Levels were unrecordable
(ie. below limits of Assay)

Edinburgh
May 1977

for their hyperglycaemic action.

More evidence is required before these arguments can be resolved. It would be interesting to examine in more detail the response to insulin of hypophysectomised patients who are kept on their maintenance steroid dose and thus should have a normal peripheral responses to adrenaline and glucagon.

I shall now consider the findings of the insulin hypo-glycaemia test in the six cases presented above. Their results, as compared with those of six controls, are plotted graphically.

Andrew Crisp experienced a profound, prolonged hypoglycaemic response to insulin, with no rise in either plasma cortisol or growth hormone levels and will probably need steroid replacement therapy for life. Elizabeth Aitken, whose basal plasma cortisol levels were low with a loss of the normal diurnal variation, failed to produce a cortisol response to an adequate fall in her blood glucose level. However she did have a prompt, albeit sub-normal, growth hormone response and returned spontaneously to euglycaemia, which supports the view that growth hormone is very important in counteracting the hypoglycaemic action of insulin.

Marion Stark was slow to return to normoglycaemia and exhibited a markedly impaired growth hormone response although her plasma corticol response at one hour was adequate. However her basal plasma cortisol levels were low, but showed a normal diurnal variation and as her pituitary appeared to respond adquately to stress, steroid replacement therapy was withheld. Once again the glucose and growth hormone responses seem to be related. Edward Boyle had unrecordable diurnal plasma cortisol levels but showed a normal cortisol response to insulin hypo-glycaemia. This emphasises the importance of using dynamic tests of pituitary function, rather than relying on estimations of the basal output of pituitary and target hormones.

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