Volume I: Research Component

PSYCHOLOGICAL FUNCTIONING FOLLOWING SURGERY FOR PITUITARY DISEASE

Karen Treece

A thesis submitted to
The University of Birmingham
for the degree of
Doctor of Clinical Psychology

Department of Clinical Psychology
School of Psychology
The University of Birmingham
April 2007

ABSTRACT

A long-term, multi-centred, case controlled, follow up study of patients who had been treated for pituitary tumours with transsphenoidal surgery (TSA) was conducted. Transsphenoidal surgery is the "Gold Standard" treatment for removal of pituitary tumours (Royal College of Physicians 1997). Patients had received surgery between 1998 and 2002. Pituitary patients were compared to controls on psychosocial functioning measures. Impaired levels of psychosocial functioning had been observed in pituitary patients before surgery and three months after surgery, but this had resolved one year after surgery (Treece et al 2005).

The aim of this follow up study was to determine whether or not the resolution in psychosocial functioning observed one year after surgery had been maintained at long-term follow up (4-8 years after surgery). Patients who had completed the prospective study were approached. Thirty-two pituitary surgery patients and nineteen control surgery patients completed measures of psychosocial functioning. The levels of psychosocial functioning between the two groups were not significantly different at long-term follow up ($p<0.05$). Normalised levels of psychosocial functioning measured in pituitary patients one year after surgery, remained at long-term follow up. Transsphenoidal surgery to remove pituitary tumours was not detrimental to psychosocial functioning between four and eight years after surgery.

OVERVIEW

This thesis was submitted to the University of Birmingham for the degree of Doctorate of Clinical Psychology. It represents both research and clinical work carried out during the course.

Volume I of the thesis is the research component, which consists of two papers: a review paper and an empirical paper.

The review paper examines the effects of pituitary disease and its treatments on neuropsychological functioning. It briefly explains the incidence and effects of pituitary disease, the reasons for treating pituitary disease, the evolution of treatments, and what is regarded as a successful outcome. Studies which examine neurocognitive function in patients who have received surgery or radiotherapy for the removal of pituitary tumours are reviewed.

The empirical paper examines the effects of surgery for pituitary disease on psychosocial functioning and health related quality of life. This was a long-term, case controlled, follow-up study of patients who had pituitary tumours surgically removed between 1998 and 2002. The findings of the study suggest that the normalisation of psychosocial functioning that was observed at twelve months after surgery, has been maintained at long-term follow up (between four and eight years after surgery). Clinical implications are considered, and future directions for research are discussed.

The final section of Volume I is a set of appendices containing information relevant to the research papers but not recorded within them. This information includes an executive summary, information and consent forms, ethical approval, additional analysis and instructions to authors for journal submission.

Volume II of the thesis is the clinical component, which consists of five clinical practice reports completed during the course. These reflect some of the work carried out on clinical placement. These reports are as follows: A case formulation of a woman with severe obsessive compulsive disorder. An audit and service evaluation in a CAMHS setting. A case study of assessment and treatment of anger in a young man with a diagnosis of autistic spectrum disorder. A single case experimental design study, of the treatment of depression and anxiety, in a 65 year-old man. A case study of a neuropsychological assessment of a girl with hydrocephalus.

ACKNOWLEDGEMENTS

I would like to thank my supervisors Professor Nadina Lincoln and Dr Christopher Jones for their support during the planning and completion of the research presented in this volume.

I would like to thank Mr Iain Robertson, Mr David Parker and Professor John Wass for allowing me to recruit their patients to this study.

I would also like to thank all the patients who kindly took part in this study.

CONTENTS

GLOSSARY OF TERMS

Acromegaly – a condition caused by the over production of the pituitary hormone – growth hormone.

Adenoma – a tumour which is not life threatening, neither malignant nor metastatic.

Adenomectomy – surgical removal of an adenoma.

Control Group – a group of participants who have been recruited to a study in order to compare group performances on standardised measures. (Referred to as **CG** in this thesis.)

Control Group – Chronically Ill Control Group – Chronically ill control groups are usually recruited from GP surgeries or hospital settings. The rationale for having a chronically ill control group is to control for the effects of illness or illness behaviour. It is most important to have strict inclusion and exclusion criteria, and to select the type of chronic illness within the control group with care. (Referred to as **CG-I** in this thesis.)

Control Group – Healthy Control Group – Healthy control groups are often recruited from university populations (students or staff). This may introduce bias if intelligence or cognition are being measured by the study, because a university population should have a higher average IQ level than the "normal" population. (Referred to as **CG-H** in this thesis.)

Control Group – Surgical Control Group – Surgical control groups are normally recruited from hospital settings. They are used in research studies in order to control for the effects (on cognition) of recovery from anaesthesia and from surgery. They also improve the validity of measurements of mood and anxiety because both the surgical group and the control group are being subject to anxiety provoking surgical procedures. (Referred to as **CG-S** in this thesis.)

Craniopharyngioma – a tumour which grows close to the pituitary gland but does not originate from it. It can be classed as a true tumour and may become malignant or metastatic, it has a far poorer prognosis than a pituitary adenoma.

Cushings Disease – a condition caused by the over production of the pituitary hormone adrenocorticotrophic hormone (ACTH) which results in high levels of cortisol freely circulating in the blood stream.

Functioning pituitary tumour – a pituitary tumour which mimics the pituitary by producing pituitary hormones.

Gray – a unit of radiotherapy treatment.

Gross cognitive decline – severe impairment of cognitive functioning. A severe reduction in the person's usual level of cognitive functioning,

Global cognitive decline – impairment of cognitive functioning across all cognitions, ie memory, perception, language, executive functioning.

Hypogonadism – underdevelopment of primary and secondary sexual characteristics caused by an underproduction of sex hormones (gonadotrophs); follicle stimulating hormone (FSH), and luteinizing hormone (LH).

Hyperpituitarism – higher than normal levels of pituitary hormones.

Hypopituitarism – lower than normal levels of pituitary hormones.

Mass effect – the occlusion of a structure, or the structure's function by the presence of a body (or mass) next to it (in this case an adenoma).

Macroadenoma – an adenoma which is greater than 10 mm in diameter.

Microadenoma – an adenoma which is less than 10 mm in diameter.

Non-functioning pituitary tumour – an adenoma which produces no pituitary hormones.

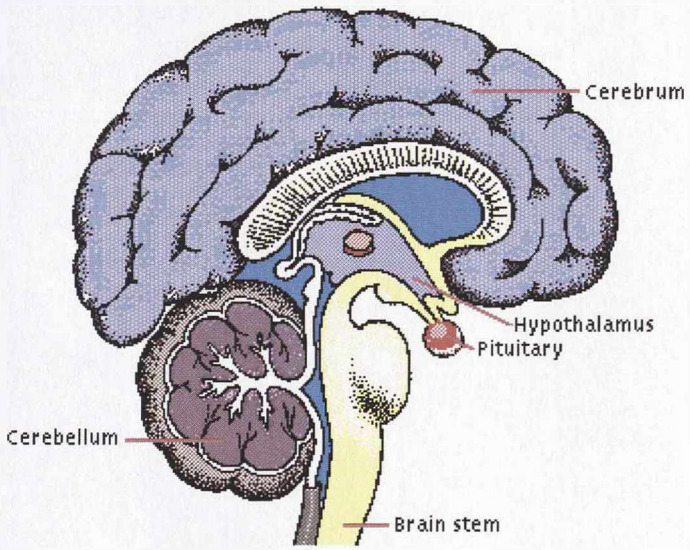
Panhypopituitarism – a complete absence of pituitary hormones.

Pituicytes – cells of the pituitary gland, these can be of different types depending on the pituitary hormone which is produced by the cell. Eg. growth hormone producing pituicyte.

Pituitary – a ductless endocrine gland situated at the base of the brain within a bony pocket (the sella tursica), which produces many hormones that regulate other endocrine glands and bodily functions. It is the most important endocrine gland of all, and is known as the "conductor of the endocrine orchestra".

Pituitary Gland Position (midsagittal view of the brain).

http://www.thehormoneshop.com/images/pituit1.gif (accessed 3rd September 2007, 15.25 pm)



Pituitary adenoma – an abnormal, excessive growth of the cells of the pituitary. Often removed in order to restore the correct hormonal balance or to relieve mass effects. Can also be called a pituitary tumour, or be referred to as pituitary disease. Pituitary adenomas are not life threatening if treated.

Pituitary fossa – the bony pocket which the pituitary sits in, also called the sella turcica.

Pituitary hormones – the hormones which are released from pituitary gland.

Pituitary tumour – an abnormal, excessive growth of the cells of the pituitary. Often removed in order to restore the correct hormonal balance or to relieve mass effects. Can also be called a pituitary tumour, can also be referred to as pituitary disease. Pituitary tumours are not life threatening if treated, they have life shortening hormonal effects if left untreated.

Prolactinoma – a pituitary adenoma which produces prolactin. This causes an excess of prolactin which in turn suppresses the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH).

Radiotherapy – Arc radiotherapy – radiotherapy delivered from a single source, giving the full dose, normally given on a single occasion, the source may travel around the target area in an arc. (Referred to as RT1 in this thesis.)

Radiotherapy – Bifrontal radiotherapy – Two field radiotherapy, with one beam projecting through each frontal lobe. (Referred to as RT2 in this thesis.)

Radiotherapy – Bilateral radiotherapy – Two field radiotherapy, with one beam projecting through each temporal lobe. (Referred to as RT2 in this thesis.)

Radiotherapy – Conventionally fractionated three field radiotherapy – (occasionally referred to as conventionally fractionated, external beam, three field radiotherapy) - radiotherapy which is delivered in small doses, from three sources, over an extended period of time. In the case of pituitary tumours a typical modern radiotherapy dose is 42 Gray, which is broken down into 25 daily doses, each daily dose is approximately 1.8 Gray. This dividing of the dose is known as the fractionation. The radiotherapy is delivered in three fields, ie. each daily dose is further broken down into three beams, two delivered through the temporal lobes, and one delivered frontally along the midsagittal line. (Referred to as RT3 within this thesis.)

Radiotherapy – Two field radiotherapy – radiotherapy delivered from two sources, positioned so that the full dose is delivered to a single point, normally given on a single occasion with each beam delivering half the dose. (Referred to as RT2 in this thesis.)

RT1 – radiotherapy delivered from a single source, normally given on a single occasion. The source may arc, or remain stationary.

RT2 – radiotherapy delivered from two sources, positioned so that the full dose is delivered to a single point, normally given on a single occasion with each beam delivering half the dose. In the case of RT2 to the pituitary it could be given bilaterally – penetrating both temporal lobes before concentrating on the pituitary, or bifrontally – penetrating both frontal lobes before concentrating on the pituitary.

RT3 – conventionally fractionated three field radiotherapy – radiotherapy which is delivered in small doses, from three sources, over an extended period of time. In the case of pituitary tumours a typical modern radiotherapy dose is 42 Gray, which is broken down into 25 daily doses, each daily dose is approximately 1.8 Gray. The dose takes about 5 minutes to administer each day. The dividing of the dose is known as the fractionation. The radiotherapy is delivered in three fields, that is to say each daily dose is further broken down into three beams, one delivered through each temporal lobe, and one delivered along the midsaggital line.

Transcranial pituitary surgery – the removal of a pituitary adenoma, via the transcranial approach. A flap of bone is removed in the temporal area, the tough membranes are penetrated and moved aside. The Sylvian fissure is opened (between the temporal lobe and the lateral area of the frontal lobe. The temporal lobe is pulled aside, and the frontal lobe is lifted, both are held in position. The pituitary is approached from above and the adenoma surgically removed. (Referred to as **TC** in this thesis.)

Transfrontal pituitary surgery – the removal of a pituitary adenoma, via a frontal approach. An flap of bone is removed from above the bridge of the nose, (roughly 10cm x 6cm), the tough membranes are penetrated and moved aside. The frontal lobes are pushed aside and held in position. The pituitary can then be approached from above and the adenoma surgically removed. (Referred to as **TF** in this thesis.)

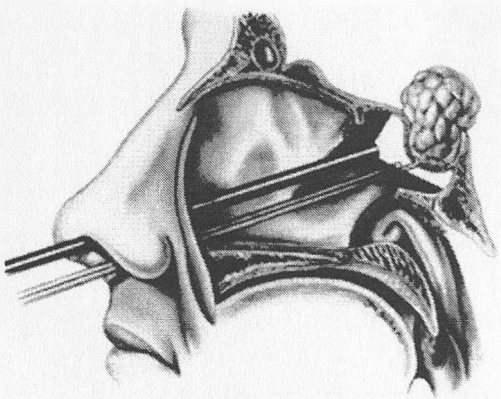
Transsphenoidal – through the sphenoid sinus

Transsphenoidal adenomectomy – removal of a pituitary adenoma through the sphenoid sinus, using an endoscope containing a light source, a camera and surgical tools. See below for illustration of transsphenoidal pituitary surgery using the nasal route rather than the sublabial route (below the upper lip and above the upper tooth margin). Either approach is acceptable, the sublabial is thought to be more useful if the patient has a small nose.

(Referred to as **TSA** in this thesis.)

Transsphenoidal Pituitary Surgery – Transsphenoidal Adenomectomy

(www.drjho.com/399d7a60.jpg) (accessed 3rd September 2007, 14.02 pm)



In the example above, the surgical instruments are introduced through the nostril, then a area of bone is removed from the anterior aspect of the sphenoid sinus (see dotted line), then the sella tursica is approached (highlighted in yellow), an aperture is made in the sella tursica and the pituitary is accessed from below. The surgical instruments are used to remove the tumour.

Sella tursica – the bony pocket at the base of the skull which encases the normal pituitary gland, also known as the pituitary fossa. (Highlighted in yellow above).

Neuropsychological Functioning In Patients Treated For Pituitary Tumours With Surgery – A Review Of The Literature

Pituitary tumours, although usually regarded as benign, are treated because of the detrimental effect they have on the endocrine system and the mass effects they exert on adjacent structures (Guinan, Lowry, Stanhope, Lewis & Kopelman, 1998). Treatment is measured as successful if the mass effects are normalised and the pituitary is rendered neither hyper nor hypo functioning (Laws & Thapar, 1995). This can necessitate the use of surgery, radiotherapy or medical interventions, or any combination of the three. Treatment frequently leaves the patient in need of life-long hormone replacement therapy. The majority of the research papers about treatments of pituitary disease concentrate on the effectiveness of treatments with regard to the removal of mass effects and normalisation of endocrine function, (Crossen, Garwood, Flatstein & Neuwelt, 1994; Duffner et al., 1985; Grattan-Smith, Morris, Shores, Batchelor & Sparks, 1992; McCord et al., 1997; Plowman, 1999; Roman & Sperduto 1995). Few studies are concerned with the effects of treatments on neuropsychological functioning (Grattan-Smith et al., 1992; Guinan et al., 1998; McCord et al., 1997; Page, Hammersley, Burke, & Wass, 1997; Peace et al., 1997; Peace, Orme, Padayatty, Godfrey & Belchets, 1998; Plowman, 1999; Noad, Narayanan, Howlett, Lincoln, & Page, 2004; Treece, 2005).

It has been recognised since the 1950s that patients with pituitary tumours can suffer severe cognitive decline if left untreated (White & Cobb, 1955). It was suggested that this was caused by invasive supra-sellar extensions causing mass effects within the brain and interfering with normal functioning (Lishman, 1987). Kahn and Crosby (1972) proposed that these cognitive deficits

were resolved following surgical removal of the tumour, but Peace et al. (1997) stated that there had been few systematic attempts to investigate the resolution of deficits.

Radiotherapy treatments have been associated with negative effects on cognitive functioning. It was suggested by Jones (1991) that two field radiotherapy (RT2) caused damage to the temporal lobes and caused cognitive dysfunction. Opposed lateral field radiotherapy (two field, RT2) has been investigated with regards to side effects. Aizenberg et al. (1998) evaluated the efficacy and long term side effects of radiotherapy in patients who had been treated for pituitary tumours. They found that almost 10% of the group who had received opposed lateral field radiotherapy (RT2) developed severe neurological complications after treatment. A further 12% complained of memory problems. Aizenberg et al. (1998) and Jones (1991) suggested that two field radiotherapy should not be used for the treatment of pituitary tumours as the side effects were too damaging.

Opposed lateral field radiotherapy (RT2) was thought to have damaging effects because it was only delivered from two points, and given in large doses. Regimes employing 50 Gray and above are no longer used as the risks of radiation morbidity are increased with larger doses (Chon & Loeffler, 2002). Current radiation treatments for pituitary tumours employ a fractionated dose of radiation given over a period of 7 weeks, the total dose being 45 Gray; it is delivered by external beams from three points (RT3). It was assumed that modern fractionated three field radiotherapy treatment did not cause neuropsychological damage, (Pituitary Foundation, 2000).

Studies of cognitive functioning in patients treated for pituitary disease have demonstrated deficits in the areas of executive functioning (Grattan-Smith et al., 1992; Noad et al., 2004; Peace et al., 1997; Peace et al., 1998) and memory (Grattan-Smith et al., 1992; Guinan et al., 1998; McCord et al., 1997; Peace et al., 1997; Peace et al., 1998; Treece 2005). There has been speculation about the cause of the cognitive dysfunction, with underlying disease process, surgery, and radiotherapy being cited by different studies. In a prospective study Treece, Page, Wass and Lincoln (2003) reported memory deficits in patients with pituitary tumours before they had received surgery to remove the tumour. Guinan et al. (1998) suggested that memory deficits occurred after treatment for pituitary disease. Peace et al. (1997 & 1998) suggested that the cause of cognitive dysfunction was likely to be multifactorial.

This paper briefly describes the effects of pituitary disease, the treatments to remove pituitary tumours, and the studies of neuropsychological functioning in patients who have received treatments to remove pituitary tumours.

1.1 INTRODUCTION

The most common problems of the pituitary gland are benign tumours (adenomas) (Clayton & Wass, 1997). The incidence is low with 20-30 new clinical cases per million population per year (Clayton & Wass, 1997). Pituitary tumours account for 10-15% of all intracranial tumours; (McCord et al., 1997) true malignancy is extremely rare (Guinan et al., 1998).

Pituitary tumours develop when there is excessive growth in the cell tissues of the pituitary gland. The symptoms are wide ranging and include impaired vision, sleep problems, mood and appetite disturbance, headaches, fatigue, sexual dysfunction and diabetes insipidus. Pituitary tumours can be classified as functioning or non-functioning, depending on whether or not they mimic the pituitary and produce hormones. Adenomas can cause hyperpituitarism or hypopituitarism, which is an overproduction or underproduction of pituitary hormones. Pituitary tumours can also exert mass effects on the pituitary and surrounding structures.

Non-functioning pituitary tumours are most prevalent. The mass effect can cause hypopituitarism by compressing normal pituitary tissue and inhibiting the production of pituitary hormones. Hypopituitarism is frequently treated with multiple hormone replacements. Deficits in adrenocorticotrophic hormone (ACTH) and thyroid stimulating hormone (TSH) are life threatening; both can result in coma followed by death if untreated (Jeffcoate, 1993). Deficiency in growth hormone (GH) in children can cause shortness of stature, increase in body fat, muscle weakness and fatigue (Brook & Marshall, 2001). In adults it causes muscle wasting, poor tissue repair and osteoporosis. Hypogonadism is caused by a deficiency in luteinizing hormone (LH) and follicle stimulating hormone (FSH). Children with hypogonadism fail to progress through

puberty (Brook & Marshall, 2001). Adults with hypogonadism may be infertile and unable to conceive. Insufficiency in antidiuretic hormone (ADH) results in diabetes insipidus, with polydipsia and polyurea being the main symptoms.

Functioning pituitary tumours produce the same hormones as the pituitary gland, and results in hyperpituitarism. The hormones produced are directly related to the type of pituicytes within the tumour. Excessive pituitary hormones have wide-ranging effects.

The most prevalent types of functioning pituitary tumour are prolactinomas. Micro-prolactinomas (<10mm diameter) are common and may be present in over 10% of the population (Clayton & Wass, 1997). However they are rarely clinically significant so diagnosis is uncommon (Burrow, Wortzman, Rewcastle, Holgate & Kovacs, 1981). Micro-prolactinomas can cause inappropriate lactation and menstrual disturbance. Macro-prolactinomas (>10mm diameter) may result in mass effects and hyperprolactinaemia. They have more adverse effects and a poorer prognosis than micro-prolactinomas (Jeffcoate, 1993). Hypogonadism (described above) results from hyperprolactinaemia, additionally the risk of osteoporosis is high if this remains untreated (Jeffcoate, 1993).

Cushing's Disease is caused by an excess in ACTH. It is associated with a significant increase in morbidity and mortality even if treated. Symptoms can include psychiatric disturbance, "moon face", obesity, muscle wasting, thin skin and hirsuitism (Jeffcoate, 1986; Jeffcoate, 1993). Over production of GH causes giantism in children, which is a generalised increase in body size and stature. In adults it results in acromegaly which is associated with a two-fold increase in

mortality. Acromegaly is characterised by coarsening of facial features, thickening of soft tissues, enlargement of hands, feet, tongue and jaw, headaches, vision disturbance, sleep apnoea and fatigue. Acromegaly also results in the over growth of internal organs such as the lungs and heart, which accounts for much of the increased mortality rate.

Both functioning and non-functioning pituitary tumours can result in mass effects on surrounding structures. The pituitary gland is situated at the base of the skull, adjacent to the optic chiasm and inferior to the hypothalamus. The mass effects on the pituitary gland are described above. Visual disturbances or bitemporal hemianopia can result from forward extension of pituitary tumours if the optic chiasm becomes occluded. Upward extensions of the pituitary affect hypothalamic functions resulting in sleep disturbances and diabetes insipidus. Further upward extensions into the third ventricle can cause raised intercranial pressure and hydrocephalus. Rapid sideways extensions can compress the third, fourth or sixth cranial nerves, producing opthalmoplegia. Pituitary tumours often cause severe headaches, possibly due to the irritation of nerve endings of the dura mata.

There are three main treatments for pituitary tumours, surgery, radiotherapy and medication (Pituitary Foundation, 2000). The "Gold Standard" treatment to remove a pituitary tumour is transsphenoidal surgery (Clayton & Wass, 1997; Fahlbusch, 1981). However, incomplete resection is common (van Beek et al., 2007), due to the invasive nature of the tumours and the difficulty in distinguishing pituitary cells from pituitary tumour cells (R. Quinton, personal communication, 13th July 2001). Radiotherapy is used as a second line treatment, after surgery (Brada, 2002; Noad et al., 2004) to destroy the remaining tumour cells and arrest the regrowth of

the tumour. Some pituitary tumours, particularly prolactinomas, respond well to medication administered to shrink the tumour.

Transsphenoidal Adenomectomy (TSA) surgery is the "treatment of choice" for the removal of pituitary tumours (Clayton & Wass, 1998; Turner & Wass, 2000). The pituitary is approached through the sphenoid sinus, the tumour is resected and removed through the transsphenoidal route (Couldwell, 2003). The surgical approach is either through the nostril, or below the upper lip and above the tooth margin. This surgery leaves no visible scars. Small tumours can be removed completely, and larger tumours can be debulked using this method. Transsphenoidal surgery is not suitable for large invasive tumours which have reached the third ventricle (Clayton & Wass, 1998).

The transfrontal (TF) approach was the most commonly used surgery for the removal of pituitary tumours for many years. It was considered to be safe and effective and was only replaced with transsphenoidal surgery following the introduction of intraoperative microscopes and the development of effective treatments for infections following surgery (Peace et al., 1998). Transfrontal surgery is more invasive and risky than TSA surgery (Guinan et al., 1998) and is reserved for aggressive tumours in particular macro-prolactinomas which have not responded to medication (Peace et al., 1998).

Horsley developed a transcranial-temporal approach (TC) in the 1890s (Thapar & Laws, 2001). The pituitary was approached temporally through the opened Sylvian fissure. Kraus developed the transcranial-subfrontal surgical route in the early 1900s (Thapar & Laws, 2001). A flap of

cranial bone was removed to expose the frontal lobes, the lobes were lifted aside, and the pituitary was approached from above. Transcranial surgery has since developed into the safer bifrontal craniotomy or transfrontal (TF) surgery, which is a basal frontal interhemispheric approach (Thapar & Laws, 2001).

Each type of surgery described above carries the risk of epilepsy, cerebrospinal fluid (CSF) leak, meningitis, and hypopituitarism (Clayton & Wass, 1998). In addition the transfrontal and transcranial approaches may result in damage to the frontal lobes, and a higher risk of infection (Laws & Thapar 1995). A study by Ahmed et al. (1999) concluded that modern surgery carried out by highly experienced neurosurgeons specialising in pituitary surgery was safe and effective.

Radiotherapy (RT) treatments for pituitary tumours have undergone a period of development. Conventionally fractionated, three field external beam radiotherapy (RT3) is considered the "Gold Standard" therapy for pituitary tumours not cured by surgery (Brada, 2002). It minimises the side effects of nausea, hair loss and skin damage which were recorded following earlier types of radiotherapy, such as single dose (RT1) and two-field radiotherapy (RT2) (Chon & Loeffler, 2002). There was a significant risk of late necrosis of the brain in long term survivors of single dose arc radiotherapy (WHO, 1997). High rates of optic nerve damage were associated with bifrontal two-field radiotherapy (Brada et al., 1993; Harris & Levene, 1976). Plowman (1999) stated that many studies support the conclusion that high dose radiotherapy to pituitary tumours results in radiation damage to the optic chiasm. Research studies from the early 1980s reported rates of delayed cerebral radiation necrosis as high as 14% (Marks, Baglan, Prassad & Blank, 1981; Mikhael, 1980; Sheline, Wara & Smith, 1981). More recent studies have reported

radiotherapy induced vascular damage to the temporal lobes (Abayomi, 2002), and late onset encephalopathy (Rauhut, Stuschke, Sack & Stolke, 2002).

The most modern radiotherapy treatment available for pituitary tumours is steriotactic radiosurgery (SRS), also known as gamma knife surgery. A single fraction of radiotherapy is administered directly to the tumour. However, treatment carries a high incidence of radiation-induced damage to the optic chiasm and temporal lobe (Brada, 2002). Chon and Loeffler (2002) reported higher incidences of oedema and cranial neuropathies than with conventionally fractionated radiotherapy (RT3). Brada (2002) was unable to measure any clear benefits in terms of efficacy following steriotactic radiosurgery (SRS) when compared to conventional radiotherapy (RT3). Steriotactic radiosurgery treatment is more frequently used in the USA than the UK. There is only one UK NHS authority which provides steriotactic radiosurgery (Pituitary Foundation, 2006).

Conventionally fractionated three-field radiotherapy (RT3) without surgery may be the "treatment of choice", but only if the tumour is medication resistant and difficult to reach surgically (Clayton & Wass, 1998), or, surgery is contraindicated (Mahmoud-Ahmed & Suh, 2002). Conventionally fractionated three-field radiotherapy can also be used to reduce a tumour size or to arrest its regrowth (Gittoes, 2003).

Some pituitary tumours respond well to medication (Clayton & Wass, 1998) and eliminate the need for surgery or radiotherapy. Prolactinomas are treated with dopamine agonists, which are highly effective (Brook & Marshall, 2001). These cause the tumour to shrink, relieving the mass

effects and reducing the amount of prolactin secreted. Dopamine resistant prolactinomas are treated with radiotherapy (RT3) or surgery (TSA) (Pituitary Foundation, 2000). Growth hormone producing tumours can be treated similarly in some cases (Pituitary Foundation, 2006).

The "treatments of choice" were established by the Royal College of Physicians in 1997 (Clayton & Wass, 1997), however most of the papers relating to the effects of treatments for pituitary tumours on neurocognitive function include groups of individuals who were treated before 1997 or who received mixed therapies. Only the most recent studies (Noad et al., 2004; Treece 2005) excluded patients who did not receive the treatments of choice.

1.1.1 What could cause cognitive decline in patients treated for pituitary tumours with surgery?

It has been shown that patients treated for pituitary tumours have deficits in cognition when compared to people who do not have pituitary disease (Noad et al., 2004). It is possible that the disease process or the treatments used to remove pituitary tumours damage the frontal lobes and the temporal lobes.

Early studies suggested that patients with untreated pituitary tumours suffered gross cognitive decline (White & Cobb, 1955). More recent studies implied that the deficits may be due to the treatments used to remove the tumours. Jones (1991) hypothesised that cognitive decline was due to radiotherapy treatments, and McCord et al. (1997) questioned the safety of combined treatments (surgery followed by radiotherapy). Almqvist, Thoren, Saaf and Erikson (1986) suggested that cognitive dysfunction may be due to an inadequate supply of pituitary hormones.

Pituitary patients may suffer cognitive decline because of the mass effects of the pituitary tumour on adjacent structures. Pituitary tumours develop very slowly and are often diagnosed late in life. The degree of mass effect is in direct relation to the size of the tumour. They can be large space occupying lesions and extend beyond the hypothalamus and into the third ventricle, and may cause raised intercranial pressure and hydrocephalus, with the associated negative effects on cognitive functioning.

Surgical treatments to remove pituitary tumours could also be the cause of cognitive decline. Transfrontal craniotomy (TF) employs a bifrontal basal interhemispheric approach, where the pituitary is approached from the skull base, along the midsagittal plane below the frontal lobes. The main risks from the craniotomy are frontal epilepsy, CSF leak, meningitis and minor vascular tearing and oedema within the frontal lobes due to the lobe being manipulated during surgery. Transsphenoidal surgery (TSA) is regarded as non-invasive because it approaches the pituitary tumour via the nasal cavity, the sphenoid sinus and pituitary fossa. Transsphenoidal surgery avoids the necessity to open the brain cavity and so reduces the risk of damage to the frontal lobes from infection and disturbance (Pituitary Foundation, 2006). However, transsphenoidal surgery is associated with the risk of post-surgery infection.

In order to reach the pituitary tumour, radiotherapy beams project through areas of brain tissue. These areas of the brain are vulnerable to damaging effects of radiation treatments. Both arc radiation (RT1) and two-field radiotherapy (RT2) were delivered in single treatment sessions. In order for them to be effective at treating the pituitary tumour the doses needed to be large, which resulted in a high risk of damage to brain tissue. Arc radiation was delivered as a single beam

which arced around the anterior aspect of the skull, passing through the frontal lobes and the temporal lobes. Two-field radiotherapy (RT2) was delivered from two positions, each beam delivered half of the full dose, which focussed on the pituitary area. Bifrontal two-field radiotherapy projected through the frontal lobes, opposed lateral two-field radiotherapy projected through the temporal lobes. Conventionally fractionated three field radiotherapy (RT3) is delivered from three points, one frontally along the midsagittal line and the others through the temporal lobes. The total dose (45 Gray) is split into 35 fractions which are given over a seven week period. The three beams concentrate on the tumour and deliver their full dose to the target area. The main dose of radiation follows three narrow pathways, but a large proportion of the temporal lobes and the frontal lobes receive a small dose of radiotherapy with each treatment.

Neuropsychologists have mapped cognitive processes to underlying brain structures, and produced good evidence that different lobes are responsible for different cognitive domains (Lezak, Howieson & Loring, 2004). It would therefore be rational to investigate the effects of treatments on cognition using neuropsychological assessments which assess the functions of the frontal lobe and the temporal lobes.

The cognitive domains which could be affected if the frontal lobes or the temporal lobes were damaged, are intellectual function, executive function, attention and concentration, language function and memory. In order to assess deficits within these domains an extensive battery of neuropsychological tests would be needed. For a list of domain specific assessments which could be utilised to measure deficits in cognition please see Appendix B.1.

1.1.2 The emotional impacts of receiving a diagnosis of a pituitary tumour and the need for neurosurgery.

It is possible that patients who receive a diagnosis of a pituitary tumour would make the assumption that it is a diagnosis of a cancer. The damaging effect of the diagnosis could depend upon how well the diagnosis was given, the level of information the patient received about pituitary tumours at that time, and on individual coping styles. There is a large body of literature which suggests that patients who receive a diagnosis of cancer, suffer from post traumatic stress disorder (PTSD), especially if the diagnosis is delivered in an insensitive manner (Smith, Redd, Peyser, & Vogi, 1999). If the diagnosis and consultation are handled sensitively, patients diagnosed with cancer still take time to adjust, (Northouse & Swain, 1987) and go through a period of reaction to loss. During the period of adjustment, cognitive functioning might be impaired due to the impact of the diagnosis on emotional functioning. Wolf (2003) suggested that low levels of cortisol resulted in memory deficits in patients with PTSD. Following surgery for breast cancer 70% of patients show healthy levels of emotional functioning at 12 months after surgery (Irvine, Brown, Crooks, Roberts, & Browne, 1991), but 30% remained distressed (McGuire et al., 1978). A meta-analysis of coping and adjustment in children with cancer (Aldridge & Roesch, 2007) showed that time since diagnosis was a significant predictor, with those most recently diagnosed showing the poorest levels of coping and adjustment.

It is possible that a diagnosis of pituitary tumour may induce symptoms of depression. Many psychological studies indicate that people who are suffering from depression report severe difficulties with memory (Cohen, Weingartner, Smallberg, Pickar & Murphy, 1982; Sternberg & Jarvik, 1976). Conversely, other studies indicate that there is no association between depression

and impaired memory (Feehan, Knight, & Partridge, 1991). Two meta-analyses investigating this effect (Burt, Zembar & Niederehe, 1995; Christensen, Griffiths, MacKinnon & Jacomb, 1997) found evidence both for and against a link between depression and memory. Burt et al. (1995) stated that "the existing evidence paints an unclear picture of whether an association exists between depression and memory impairment". Christensen et al. (1997) criticised many early studies as methodologically inadequate. A later, robustly designed study by Rohling, Green, Allen and Iverson (2002) stated that patients who self reported as depressed, also self reported difficulties with memory, but (unexpectedly) performed at a normal level on objective neurocognitive measures of memory. Christensen et al. (1997) stated that the influence of depression on other cognitive domains had not been adequately investigated, and Rohling et al. (2002) stated that generalisation to other cognitions may not be valid.

There are no direct research studies examining the emotional consequences of a diagnosis of pituitary tumour and its effect on neurocognitive functioning in patients who have been treated for pituitary tumours with surgery or radiotherapy. Johnson et al. (2003) examined patients who were newly diagnosed with pituitary disease, they found depression in patients with Cushing's, but did not look for an association with neurocognitive functioning. Some studies of treatments for pituitary tumours with surgery or radiotherapy examined neurocognitive functioning and mood (Guinan et al., 1998; Noad et al., 2004; Peace et al, 1997; Treece 2005), but none reported a correlation between high levels of depression or anxiety and poor neurocognitive functioning. Peace et al. (1997) found significant impairment of memory and executive functioning in patients treated for pituitary tumours, but no evidence of anxiety or depression. They stated that memory

impairment was not related to mood. Treece (2005) found no correlation between cognitive impairment and poor psychosocial functioning.

To investigate whether a diagnosis of pituitary tumour requiring surgery adversely effects the performance on neurocognitive tests, due to the impact on emotional functioning, a carefully designed prospective study would be required. Patients who may receive a diagnosis of pituitary tumour would need to be examined on objective measures of cognition and psychosocial function prior to diagnosis. This would create problems of predicting who should be tested, with people who did not subsequently develop a pituitary tumour never being followed up, and others being followed up immediately, or many years later. This would result in unequal timing of baseline measurements. The timing of follow up tests would need to be established, choosing perhaps one month after diagnosis, with additional testing related to the timing of the neurosurgery. A study which tested a large group of participants whose data would never be used (i.e. those who did not develop pituitary tumours) would be unlikely to receive either ethical or R&D approval. An alternative approach may be to examine other bodies of research literature, evidence may be found in research examining the effects of diagnosis and adjustment to breast cancer, brain cancer or injuries to the brain which may cause emotional or neurocognitive dysfunction.

A review study of psychosocial adjustment in women with breast cancer (Irvine et al., 1991) found that the majority of women do not experience long term distress. "Neuroticism" was found to be a predictor of poor psychosocial adjustment, and social support was an important mediator of distress. Irvine et al. (1991) criticised prior studies for lack of objectivity, reliability and validity. Studies of traumatic brain injury (TBI) have found depression to have greater

association with lesion site, litigation and financial compensation than with cognitive deficits (Rohling et al. 2002). Persons who had difficulty coping with stressful events before TBI find it difficult to adjust to the consequences of TBI (Prigatano, 1986). Studies of people who have received whole brain radiation to treat brain tumours, have reported a strong association between large doses of radiotherapy and cognitive decline (WHO, 1997). Other studies investigating head and neck tumours reported vascular damage to the temporal lobes following radiotherapy (Abayomi, 2002), or tumour location (Taphoorn & Klein, 2004) to be strongly associated with neurocognitive decline. There appears to be a lack of studies which address both the impact of diagnosis of a disease on emotional functioning, and the subsequent impact on neurocognitive functioning, this may be because of methodological difficulties.

When a diagnosis of pituitary tumour is delivered, it is essential that this happens in a considered, sensitive manner, the words pituitary adenoma are frequently used rather than pituitary tumour (Pituitary Foundation, 2006). Patients are informed that a pituitary adenoma is an excessive growth of cells within the pituitary gland. They are reassured that there is a very good prognosis, the growth is unlikely to be cancerous, the adenoma can be removed, and hormonal levels will be stabilised (through replacements if necessary). Never the less, the need for neurosurgery to remove a pituitary tumour may be perceived as threatening (Pituitary Foundation, 2006) and it would be normal for a patient to experience some degree of anxiety at the time of diagnosis and surgery (Treece, 2005). The Pituitary Foundation (2006) have recognised that some patients may experience symptoms similar to post traumatic stress disorder after treatment, with fears relating to tumour regrowth, management of disease, and future treatments being expressed. It is essential that patients with a diagnosis of pituitary disease feel well supported (Pituitary

Foundation, 2000). Patients are informed that there are local and regional support groups for people with pituitary disease which are affiliated to the Pituitary Foundation. The patient support groups are called "Pit-Pat" they organise social gatherings, coping with pituitary disease groups, health living groups, advice on benefits, lecture evenings with speakers from the NHS or social services, and an annual conference for people with pituitary disease and the professionals who work with them. The Pituitary Foundation also produces a comprehensive set of leaflets for patients with pituitary disease, these are available, free of charge, to order by post or to download from their web site. In addition the Pituitary Foundation publishes guides for NHS professionals who work with patients with pituitary disease (Pituitary Foundation, 2000 & 2006), the GP Fact File is an excellent introduction to pituitary disease for professionals within the NHS, it is also freely available to members of the general public.

1.2 REVIEW OF THE LITERATURE

1.2.1 Search strategy

The following databases were searched until April 2007, MEDLINE, EMBASE, CINAHL, ISI citation index, ISI Web of Science, Science and Social Science Citation Indexes, PsycInfo. Other strategies to ensure identification of all potentially relevant studies included scanning reference lists of relevant research papers and book chapters, personal communication, and hand searching journals. Literature published directly by the Pituitary Foundation and the Royal College of Physicians was also searched for relevant material. Topics and keywords included in the search were pituitary adenoma, pituitary tumour, pituitary disease, pituitary surgery, transsphenoidal, transphenoidal, TSA, transfrontal, transcranial, radiotherapy, radiation, neuropsychological, neuropsychology, neurocognitive, cognition and cognitive.

The inclusion criteria were as follows;

a. Patients studied must have received (or were about to receive) surgery or radiotherapy to remove a pituitary tumour.
b. The focus of the study must be the effects on cognition.

The exclusion criteria were as follows;

a. Animal studies of cognitive performance following pituitary surgery were excluded.
b. Studies looking at the stabilisation of hormone levels following surgery, without the inclusion of the effects on cognitive aspects were excluded.
c. Studies which focussed on changes in cognition following treatment for pituitary tumours in children were excluded.
d. The focus of the study must not have been the effects of replacing growth hormones on cognition, without surgery or radiotherapy to remove a pituitary tumour.
e. Studies which looked at the effects of surgery or radiotherapy on cognition of different types of tumours were excluded.

The quality criteria were as follows;

a. Standardised objective measures of adult neuropsychological functioning.
b. Good research methodology.
c. Comparisons between groups of patients.
d. The study must be well explained within the research paper.
e. Analysis and treatment of the data must be clearly explained, and robust.

A total of 42 papers were found. After taking into consideration the inclusion and exclusion criteria the following papers were selected as meeting the criteria, Grattan-Smith et al. (1992), Guinan et al. (1998), McCord et al. (1997), Noad et al. (2004), Peace et al. (1997), Peace et al. (1998), Treece (2005) and Van Beek et al. (2007).

After considering the quality criteria the following papers were excluded from the full review; Grattan-Smith et al. (1992), McCord et al. (1997) and Van Beek et al (2007). Grattan-Smith et al. (1992) and McCord et al. (1997) are the recognised foundation papers for research in this area. These two journal articles will be described in a historical context because they were the first studies which attempted to measure the effects of pituitary tumours and their treatments on cognitive function. The research paper by van Beek et al. (2007) did not use objective measures of neuropsychological functioning.

There have been five well designed studies that have reported the effects of surgery or radiotherapy for the treatment of pituitary tumours on neurocognitive function. The results and conclusions of the studies will be reviewed in chronological order. The studies will also be compared in terms of research methodologies, cognitions examined, diversity of treatments, relevance to current practice and recommendations for future research.

The treatments received by the pituitary patient groups were varied (see Appendix B.2). The alternative surgeries were transfrontal (TF), transcranial (TC), transsphenoidal adenomectomy (TSA), or transsphenoidal hypophysectomy (TSH) (which is the same older nomenclature for TSA). The alternative radiotherapies were single field radiotherapy (RT1) which could be static

or arcing, two field radiotherapy (RT2) which could be bilateral or bifrontal, or conventionally fractionated three field radiotherapy (RT3). Studies included patients who had received single therapies (either surgery or radiotherapy) or combined therapies (surgery plus radiotherapy), some studies included patients who had received medication to shrink tumours, see Appendix B.2 for the details of treatments received by the patients in each reviewed study. All of the reviewed studies utilised objective standardised adult neuropsychological assessments of cognition, these are detailed along with their abbreviations in Appendix B.3. Appendix B.4 enables comparison between the reviewed studies to be made in terms of the neuropsychological assessments utilised.

1.2.2 Comparison of the studies, and design of the review

Although there are relatively few studies in this area, difficulties were encountered when trying to compare the results of the studies. These were caused by the diversity of therapies administered, the passage of time since treatment, the composition of the groups studied (both within studies and between studies), and the relevance to current practices as recommended by the Royal College of Physicians. So, because of the wide diversity within this small sample of peer reviewed research papers, and the paucity of prospective studies in this area of research, this is a scoping review, rather than a systematic review or a meta analysis.

1.2.3 Historically important studies

Historically, there were two very important papers which highlighted the need to study the effects of pituitary disease and its treatments on cognitive function. These two papers were by Grattan-Smith et al. (1992) and McCord et al. (1997). Each paper was written following audits of patients who had received treatments to control pituitary functioning. Unfortunately both studies

suffered from severe methodological inadequacies when compared to later robust research papers within this area. Therefore both the paper by Grattan-Smith et al. (1992) and McCord et al. (1997) will be regarded as interesting and thought provoking, but neither will be used as evidence because the results are likely to be confounded.

Grattan-Smith et al. (1992) evaluated the effects of radiotherapy on cognitive functioning in patients treated for pituitary tumours. In a retrospective study, patients treated for pituitary adenomas were compared to chronically ill patients on standardised neuropsychological assessments of cognitive function (see Appendix B.4). The cognitions investigated were executive functioning and memory. There were two groups of pituitary patients, those who had received radiotherapy, and those who had not. Grattan-Smith et al. (1992) found significant differences between the pituitary patients and the controls on tests of memory and executive function, with the pituitary patients performing at a lower level. They found no significant differences between the radiotherapy and non-radiotherapy pituitary patients on tests of cognitive functioning. This study by Grattan-Smith et al. (1992) was important because it was the first to employ standardised neuropsychological tests to examine the effects of treatment for pituitary disease on cognitive function. However, good study design and research methodology were not evident, the exclusion criteria were not robust, the control group was poorly selected, and the study and data were not explained well within the research paper.

The second historically important paper was by McCord et al. (1997). The long-term outcome and sequelae of patients who had received radiotherapy as a treatment for pituitary tumours was investigated. The main purpose of the study was to examine how well pituitary function was

controlled by radiotherapy. Outcome measures included mortality, tumour control, hormone levels, effects on vision, neurocognitive function, life satisfaction and affective symptoms. McCord et al. (1997) found that the patients who had received the combined therapy of surgery followed by radiotherapy were more likely to report problems with memory than either of the single therapy groups (surgery or radiotherapy). No significant differences in life satisfaction or affect were found between the three groups. McCord et al. (1997) concluded that neurocognitive sequelae may be different between treatment groups and that symptoms resulting from radiotherapy to the pituitary region were inadequately studied. However, this study was not methodologically strong, it employed a self designed questionnaire to measure cognition, life satisfaction and affect, there was bias in the selection of patients, groups were not compared for equality, and the examination of psychological characteristics appeared to be an "ad hoc" addition to the medical audit.

These two papers highlighted the need for further robust studies in this area with very clearly defined patient groups and a strong methodological design.

1.2.4 Review of the study findings

All retrospective studies may expect to attract criticism because of their study design, however the retrospective studies reviewed below demonstrated far greater design integrity than the historical papers, these studies will be reviewed in full (Peace et al., 1997; Peace et al., 1998; Guinan et al., 1998; Noad et al., 2004), along with the only prospective study in this research area (Treece, 2005).

Peace et al. (1997) conducted a retrospective study of patients who had been treated for pituitary disease. They compared 36 pituitary tumour patients and 36 healthy control group patients (CG-H). The two groups were matched for gender, age and years of education. Eighteen pituitary patients received surgery followed by radiotherapy (S+RT), nine patients received surgery only (S), and nine patients received neither surgery nor radiotherapy, but received medication - either dopamine agonists or hormone replacement therapy to treat the pituitary disease (Med). Of the 27 patients who had received surgery, 14 received transsphenoidal surgery (TSA) and 13 received transfrontal surgery (TF). All participants were tested on a battery of neuropsychological assessments, see Appendix B.4.

Peace et al. (1997) focussed their investigations on measures of executive function and attention, the rationale being that deficits in these areas had been reported in children with pituitary disease (Ryan, Johnson, Lee & Foley, 1988; Siegel & Hopwood, 1986). They also included measures of memory in response to the findings of White & Cobb (1955) who had studied patients with untreated pituitary disease. When pituitary patients were compared to the control group patients, there were significant differences on all four measures of executive function, and one measure of memory. The pituitary patients performed at a lower level than the controls.

Many sets of analyses were performed with the pituitary patients being split into different treatment groups for comparisons. Impairments in memory and executive function were seen in the combined treatment (S+RT) group, and the surgery group (S), but not in the medication group of pituitary patients (Med). There were no significant differences between the combined treatment group and the surgery group. There were no significant differences between those who

had received radiotherapy (S+RT) and those who had not (S or Med). There were no significant differences between those who had transfrontal surgery (TF) and those who had TSA surgery. However there were significant differences between those who had received pituitary surgery (S+RT or S) and those who had not (Med) on three tests of memory.

Peace et al. (1997) concluded that patients treated for pituitary disease suffered from cognitive dysfunction, and the reasons for cognitive dysfunction were likely to be multifactorial, with neurosurgery and hormone imbalance having effects. Peace et al. (1997) called for further investigation in this area.

Peace et al. (1998) conducted a study of cognitive dysfunction in patients with pituitary tumour who had been treated surgically or medically, with or without radiotherapy. They compared three groups of pituitary disease patients to a healthy control group; each group contained 23 subjects. The pituitary groups were transfrontal surgery (TF), transsphenoidal surgery (TSA) or medication only (Med). All participants were tested on standardised assessments of cognitive functioning. Peace et al. (1998) used the same set of neurocognitive assessments in this study as they had in their earlier study (1997). For the full list of neurocognitive assessments see Appendix B.4.

The four groups were compared; 43% of the transfrontal, 30% of the transsphenoidal and 21% of the medically treated pituitary patients had three or more neuropsychological test scores below the 10^{th} percentile; only 4% of the controls shared this level of deficit. Memory and executive function impairments were found in the two surgical groups (TF, TSA). The transfrontal patients were found to have more severe impairments than the transsphenoidal group. When the surgical

patients were split into those who had received radiotherapy (S+RT n=25) and those who had not (S n=21), no significant differences on cognitive function were found.

Peace et al. (1998) concluded that patients treated for pituitary tumours were more impaired than healthy controls on measures of cognitive function. They found that patients who were treated surgically for pituitary tumours were more likely to be cognitively impaired than those treated non-surgically. Peace et al. (1998) reported that 43% of the non surgical pituitary group demonstrated mild cognitive impairment. They concluded that not all the cognitive deficits exhibited by pituitary patients could be attributed to the surgical interventions, and suggested that primary disease, or hormone abnormalities and their treatments may be causative. Peace et al. (1998) called for further investigations into the causes of cognitive impairments in this patient group.

Guinan et al. (1998) presented a retrospective case study of two patients who had received treatment for pituitary tumours. One received combined therapy (TSA+RT3), the other surgery only (TSA). Both participants were tested on an extensive battery of neurocognitive assessments, see Appendix B.4. Guinan et al. (1998) found that both showed severe memory impairments when compared to their intact intellectual functioning. Guinan et al. (1998) concluded from the case studies that memory deficits resulted from treatment factors rather than tumour. Although not explicitly stated, this appeared to be a pilot for their retrospective study described below.

Guinan et al. (1998) described a retrospective study of 90 patients who had been treated for pituitary tumours between 1966 and 1993. Patients were assessed on a battery of

neuropsychological assessments (as above) and compared to healthy controls. The pituitary patients were divided into the following five groups. Transfrontal surgery with radiotherapy (TF+RT n=20), transsphenoidal surgery with radiotherapy (TSA+RT n=21), transsphenoidal surgery only (TSA n=21), radiotherapy only (RT n=10) and medication only (Med n=18). A group of healthy controls were also studied for comparison; these were friends and family of the pituitary patients (CG-H n=19). All groups were matched for pre morbid IQ, age and gender.

Guinan et al. (1998) conducted the most extensive investigation of all the retrospective studies reviewed into the cognitive effects of pituitary tumours and their treatments (see Appendix B.4). The cognitions examined were general intellectual functioning, executive functioning, memory, language and speed of mental processing. The full WAIS battery (Wechsler, 1981) was used to assess intellectual functioning, and the full WMS battery (Wechsler, 1987) was used to assess memory function. The results from these two batteries were compared to see if there was decline in memory function in comparison with intact intellectual functioning. The results of their two case studies had provided the rationale for this method. Further comparisons were made with these and other measures to compare the pituitary patients to the control group, and to make internal comparisons with the pituitary patients.

Guinan et al. (1998) found significant memory dysfunction in all pituitary tumour patient groups when compared to the healthy controls. All pituitary groups (except the RT only group) showed significant decline in their general memory when compared to their intact intellectual functioning. Guinan et al. (1998) found no evidence of general cognitive decline (other than memory) in any group. They found no significant differences on memory function between the

different pituitary treatment groups. From this they concluded that surgery, radiotherapy and bromocriptine can all have a deleterious effect on memory.

Overall they concluded that memory deficits occurred after treatment for pituitary disease. They suggested that surgery, radiotherapy, pressure effects or endocrine changes may have contributed. They also concluded that other cognitive functioning remained intact in this patient group. Guinan et al. (1998) proposed a prospective study of newly diagnosed pituitary patients, examining cognitive function before and after treatment.

Noad et al. (2004) conducted a retrospective study of the effect of radiotherapy as treatment for pituitary tumours on cognitive function. They assessed two groups of pituitary tumour patients on a battery of neuropsychological assessments, see Appendix B.4. Patients were included if they had received surgery only (TSA n=38) or surgery plus radiotherapy (TSA+RT3 n=33). In order to assess cognitive decline which would be most likely following radiotherapy Noad et al. (2004) assessed executive functioning, memory and attention, they also included a measure of pre-morbid intelligence. They included assessments which would measure both immediate and delayed memory in the verbal and non verbal domains.

Noad et al. (2004) found that patients who received combined therapy (TSA+RT3) for pituitary tumours performed less well on tests of executive functioning than patients who had received surgery alone (TSA). The study also suggested that patients treated for pituitary tumours had higher levels of cognitive impairment than would be expected in the normal population (Noad et al., 2004). 10% of the normal population would be expected to perform at or below the 10^{th}

percentile on any test of cognitive function. Analysis was performed to compare the findings with those of Peace et al. (1998). Noad et al. (2004) found that there were significantly more combined therapy patients impaired on three or more cognitive assessment tests, than surgery only patients (27% vs 5%). Noad et al. (2004) called for a prospective study in this area.

Treece (2005) conducted a prospective, multi-centre, case controlled study examining the effects of treatments for pituitary tumours on cognitive function. Treece (2005) compared 62 pituitary patients awaiting surgery (TSA) for the removal of pituitary tumours to a surgical control group of 36 ENT patients who were awaiting functional endoscopic sinus surgery (FESS). The two surgical procedures were similar, utilising the same surgical instruments and access route to the sinuses. The FESS procedure did not involve the pituitary gland. Participants were assessed before their surgery, and three months and twelve months after surgery on a battery of standardised neuropsychological assessments (see Appendix B.4). The groups were matched for age, gender and pre-morbid IQ.

Treece (2005) conducted the first prospective study examining the effects of treatments for pituitary tumours on cognitive function. Intellectual functioning, executive functioning, visuospatial functioning, attention, memory and language were all assessed. The study was designed following the publication of the previously reviewed literature (Grattan-Smith et al., 1992; Guinan et al., 1998; McCord et al., 1997; Peace et al., 1997; Peace et al., 1998). The cognitive domains studied, the assessments utilised, and the findings of the previous studies were all taken into consideration within the design of the Treece (2005) study.

Treece (2005) found significant differences between the pituitary group and the control group on measures of memory and visuospatial functioning prior to surgery (Treece, 2005; Treece et al., 2003) and at each assessment point after surgery (Treece, 2005; Treece, Wass, Lincoln & Page, 2004; Treece et al., 2005). The pituitary patients performed at a lower level. There were no significant differences between the two groups on any other measures of cognitive function.

At one year follow up, 54 pituitary group patients and 23 control group patients remained in the study. Seven pituitary patients (TSA) had received radiotherapy (RT3) between 4 months and 12 months following surgery, they became a subset of combined therapy patients (TSA+RT3). The three groups were compared on tests of cognitive function TSA (n=47), TSA+RT3 (n=7), CG-S (n=23). An additional deficit in visual memory was found in the combined therapy group (TSA+RT3). Following analysis to control for different types of tumour aetiology, hormone replacements, and age, the results remained unchanged.

Treece (2005) acknowledged that a randomised controlled trial (RCT) would have been a more powerful design, with patients randomised to radiotherapy after surgery. However it is unlikely that this design would have received ethical approval. Pituitary patients currently receive radiotherapy after surgery if it is thought to be clinically necessary in order to arrest the tumour regrowth by killing off the remaining pituitary tumour cells. Randomisation may deny some of those patients the necessary radiotherapy treatment. Treece (2005) called for further prospective studies in this area.

1.2.5 Review of the study designs

All of the reviewed studies with the exception of Treece (2005) were retrospective in design. Some authors recognised that a prospective study would be a stronger design and called for further prospective investigations to account for the deficits in cognition in the pituitary patients (Guinan et al., 1998; Noad et al., 2004).

Retrospective studies may expect to attract criticism because of their study design, however those retrospective studies by Peace et al. (1997 & 1998), Guinan et al. (1998) and Noad et al. (2004) presented well defined study designs, with strict exclusion and inclusion criteria, as did the prospective study by Treece (2005). These five studies were not audits; they had been designed in advance with the intention of examining cognitive function in patients treated for pituitary tumours.

The reviewed studies by Guinan et al. (1998), Noad et al. (2004), Peace et al. (1997), Peace et al. (1998), and Treece (2005) matched their studied groups for age, gender and pre morbid IQ. In addition most of these studies compared the pituitary patients to control group patients (see Appendix B.2), with the exception of Noad et al. (2004) who compared the cognitive assessments scores to published norms.

Guinan et al. (1998), Noad et al. (2004) and Treece (2005) recruited patients who were in the age ranges 18-70, 18-70 and 18-65 respectively. This was methodologically strong because they employed standardised cognitive assessments designed for the adult population, and facilitated comparisons between studies to be made. This age range would exclude many older patients who

had co-existing dementia. It is possible that other studies (Peace et al., 1997; Peace et al.,1998) employed a similar age range but this was not reported in the research papers.

All of the reviewed studies documented explicit inclusion and exclusion criteria. However, in some studies (Peace et al., 1997 & 1998; Guinan et al., 1998) the reasons behind some criteria were unclear and may have introduced confounders, see below for details.

All aetiologies of pituitary tumour were included in the studies by Guinan et al. (1998) and Treece (2005). Patients were excluded if they received any surgical or radiotherapy treatment more than once by Guinan et al. (1998), Noad et al. (2004) and Treece (2005). Peace et al. (1997 & 1998) and Guinan et al. (1998) explicitly excluded patients with co-existing causes of cognitive decline. These criteria appear to be valid.

Some studies did not include patients with residual field deficits or chiasmal damage following treatment (Guinan et al., 1998; Peace et al., 1998). This may have been a threat to validity as the field deficits were probably caused by the pituitary tumour or its treatments. The inclusion of patients with visual field deficits may have highlighted additional neuropsychological deficits in pituitary patients treated for tumours. Other studies excluded patients with suprasellar extensions of the pituitary tumour (Peace et al., 1997 & 1998). This may also have compromised validity.

Peace et al. (1997 & 1998) included patients with craniopharyngioma which are not true pituitary adenomas and are excluded by other pituitary studies because of this (Noad et al., 2004; Treece et al., 2005). Craniopharyngiomas are not adenomas, they are metastatic tumours with a poor

prognosis (38% survival rate at 5 years post surgery), they originate from a structure adjacent to the pituitary not the pituitary gland itself.

Noad et al. (2004) and Treece (2005) excluded pituitary patients who had not received either transsphenoidal surgery (TSA) or transsphenoidal surgery followed by adjuvent conventional three-field radiotherapy (TSA+RT3). This ensured that all patients in these studies had only received the "Gold Standard" treatments as recommended by the Royal College of Physicians (1997).

From the descriptions of study design, assessments utilised, patient groups and composition of analysis it would be possible to replicate the reviewed studies. However, because of the time spanned by the studies, and the recent development of treatments it is probable that replication would not prove to be useful. Also, in the current research climate, where randomised controlled trials are perceived as the most effective form of evaluation of treatments, it is becoming increasingly difficult for retrospective studies to gain ethical and R&D approval, so most of the reviewed studies would not be replicated.

1.2.6 Diversity of treatments studied

There was great diversity of treatments, both within studies and between studies. When comparisons were made between the whole group of pituitary patients recruited and the control group participants almost all the reviewed studies recruited mixed groups of surgery patients; patients who had received either TF surgery or TSA surgery (Guinan et al., 1998; Peace et al.,

1997; Peace et al., 1998) and mixed groups of radiotherapy patients (RT1 or RT2 or RT3) (Guinan et al., 1998; Peace et al., 1997; Peace et al., 1998).

When comparisons were made between subsets of pituitary patients some studies examined mixed groups of combined therapy patients (TF+RT with TSA+RT) (Peace et al., 1998). Some studies examined individual groups which included single therapy patients with combined therapy patients (S or RT and S+RT), (Peace et al., 1998).

The focus of some studies was radiotherapy (Noad et al., 2004; Peace et al., 1997). The radiotherapy group in the Peace et al. Study (1997) contained patients who had received radiotherapy alone, and patients who had received combined therapy (RT and RT+S). The comparison groups were similarly mixed combining all surgery treatments and medication treatments (TF and TSA and Meds) (Peace et al., 1997) and in some cases including patients who had just been diagnosed and had received no treatment (Peace et al., 1997). The wide diversity of treatment within groups was similar if the focus of the study was surgery rather than radiotherapy. So a person who had received the combined therapies of surgery plus radiotherapy (S+RT) may appear in the radiotherapy group (Peace et al., 1997), the surgery group (Peace et al., 1998), or in a separate combined therapy group (Guinan et al., 1998; Noad et al., 2004; Treece et al., 2005). The studies which compared robust well designed groups were Guinan et al. (1998), Noad et al. (2004), and Treece et al. (2005).

1.2.7 Relevance to current medical practice

In 1997 the Royal College of Physicians published a document which recommended "Gold Standard" treatments for pituitary tumours. They recommended transsphenoidal surgery (TSA) and conventionally fractionated three field radiotherapy (RT3). Bifrontal (RT2) and arc (RT1) radiotherapy are no longer utilised because of the perceived risk (Peace et al., 1998; Plowman, 1999), and transfrontal surgery (TF) is reserved for only the most serious invasive tumours (Peace et al., 1998). Therefore the studies which presented results from patients who were treated for pituitary disease with TSA, RT3, combined therapy (TSA+RT3) or modern medications will impart the most useful information to current research literature leading to evidence based medicine.

The findings from most of the reviewed studies (Guinan et al., 1998; Peace et al., 1997; Peace et al., 1998) did not generalise to modern day practices because of their retrospective nature, and the investigation of treatments which are no longer utilised. Studies which compare transfrontal surgery plus radiotherapy (TF+RT) to transsphenoidal surgery plus radiotherapy (TSA+RT) (Guinan et al., 1998; Peace et al., 1998) are of limited relevance to modern day practices because these surgeries (TSA or TF) are now used on very different groups of pituitary tumour patient. However, more recent studies would not have existed without these retrospective studies to raise the concept of cognitive deficits in patients with pituitary disease. The two studies that are directly relevant to present clinical practice are Noad et al. (2004) and Treece et al. (2003, 2004, 2005). Both studies only included patients who had received the "Gold Standard" treatments.

1.3 DISCUSSION

Studies which investigated the effects of surgery and radiotherapy on cognition in patients with pituitary disease examined similar sets of cognitive domains and used similar assessments to measure these. This enabled comparisons to be made between the findings. These findings can be conveniently divided into three sections. These are, comparisons between patients with pituitary disease and the general population, comparisons between patients who have received different types of treatments for pituitary disease, and, comparisons between patients who have received only the most modern types of treatments for the removal of pituitary tumours. Comparisons between the patients who had received treatments for pituitary tumours and the control group participants was straight forward, as these were two distinct groups of participants. However caution was necessary when comparing the findings within the pituitary groups because of the (already explored) mixed nature of the groups.

1.3.1 Comparisons of patients with pituitary disease to the general population.

Despite the limitations mentioned, each of the studies reviewed has added to the knowledge base in relation to the effects of pituitary tumours and treatments on cognitive function. In order to compare the cognitive functioning in patients who had been treated for pituitary tumours to the general population, comparisons were made between groups of patients treated for pituitary tumours and control groups. (Guinan et al., 1998; Peace et al., 1997; Peace et al., 1998, Treece et al., 2005), or published test norms (Noad et al., 2004). Peace et al. (1997), Peace et al. (1998) and Noad et al. (2004) reported deficits in executive functioning in the pituitary group. Peace et al. (1997), Peace et al. (1998), Guinan et al. (1998) and Treece et al. (2005) reported memory dysfunction in the pituitary group. Peace et al. (1998) and Noad et al. (2004) suggested that

pituitary patients had higher levels of cognitive dysfunction than would be expected in the normal population. No study reported overall gross cognitive decline in any group in relation to pre morbid intellectual functioning. Each study, which reported significant differences in performance between the pituitary group and the control group on tests of neuropsychological functioning, noted that the pituitary patients were operating at a significantly lower level than the control group participants.

Peace et al. (1998) found that almost 33% of all the pituitary patients in the study had three or more neuropsychological test scores below the clinically expected norms; this compared to less than 4.5% of the controls. In a similar analysis Noad et al. (2004) found that 15.5% of the patients treated for pituitary tumours had higher levels of cognitive impairment than would be expected in the normal population. In Noad et al.'s (2004) study 46% of the pituitary patients scored below the 10^{th} percentile on the Rey figure copy, 27% on the Rey figure recall, 20% on Logical Memory, and 30% on the Stroop test.

The findings relating to executive functioning were examined in more detail: Peace et al. (1997) reported significant differences between the pituitary group and the control group on all measures of executive function (Stroop, COWAT, Block Design, Trail Making Test). Peace et al. (1998) reported that the transsphenoidal patients had significantly lower scores on the Block Design. Noad et al. (2004) found deficits in executive functioning on the Stroop Test, which were greater in the combined therapy group than the surgery only group.

In summary, the findings by Peace et al. (1997) appear to be supported by Peace et al. (1998), and Noad et al. (2004). However only Peace et al. (1997) found deficits on multiple tests of executive functioning. Guinan et al. (1998) and Treece et al. (2005) did not find any deficits in executive functioning in the pituitary group when compared to the control group. One would expect to see high levels of cognitive impairment in executive functioning in groups of patients who had received invasive surgery (TF) involving the frontal lobes, or high dose radiotherapy which penetrated the frontal lobes (RT1 or bifrontal RT2). Mass effects from large adenomas or following hydrocephalus could also disrupt the functions of the frontal lobes.

Similar comparisons of study findings can be made in relation to memory. Peace et al. (1997) measured a low performance on the Recognition Memory Tests for Faces within the pituitary group, no other measurements of memory were significantly different. Peace et al. 1998 found significant differences between the pituitary surgery group and the control group on Story Recall (immediate and delayed recall), List Learning (learning, immediate and delayed recall) and Recognition Memory Test for Faces. Guinan et al. (1998) found significant memory dysfunction in all pituitary tumour patient groups when compared to the healthy controls. These were shown on the Recognition Memory Test for Faces, and the WMS-R battery, where the general memory quotient and the delayed memory quotients showed decline in function. Treece (2005) found significant differences between the pituitary group and the control group on List Learning (learning and immediate recall) and RCFT (copy and delayed recall).

In summary most of the studies showed memory deficits in the pituitary group when compared to the control group. The dysfunction was measured in both immediate memory and delayed

memory (encoding and retrieval respectively) and over the verbal and non-verbal domains. One would expect to see deficits in memory functioning in those groups of people who had received high dose radiotherapy which penetrated the temporal lobes (RT1 or opposed lateral RT2) (Grattan-Smith et al., 1992). The temporal lobes would also be damaged in patients who had received the highly invasive transcranial surgery (TC). It is probable that some of the patients who were classified by the studies as having received transfrontal surgery (TF), had actually received transcranial surgery (TC) as these were both surgical approaches utilised in the periods the retrospective studies recruited from (R.C.L. Page, personal communication, April 28, 2003).

1.3.2 Comparisons of patients in different pituitary treatment groups.

Guinan et al. (1998) found no significant differences on any of the neuropsychological assessments between the pituitary patients who had received radiotherapy and those who had not. Guinan et al.'s (1998) finding was supported by Peace et al. (1997 & 1998). Noad et al. (2004) found only one significant difference between the surgical patients (TSA) and those who had combined therapy (TSA+RT3), this was on the STROOP measure of executive functioning. Treece (2005) also found a single significant difference between the combined therapy group and the surgery only group, on a measure of non verbal memory (Recognition Memory Test for Faces).

Impairments of executive functioning and memory were found in the two surgical groups (TSA and TF) by Peace et al. (1997 & 1998). The transfrontal surgery group showed a greater level of decline, however, this may have been due to their significantly longer duration of illness, and the inclusion in this group of all those patients in the study who had Craniopharyngioma. Peace et al.

(1997) also found a significant effect of surgery on memory when comparing surgical patients to those who had been treated with medication, the differences were on List Learning and List Recall, and Recognition Memory Test for Faces.

Guinan et al. (1998) reported significant impairments on measures of memory in the pituitary patients, however she found no significant differences between the groups which had received different pituitary treatments, and therefore concluded that surgery, radiotherapy and medications all have a negative effect on memory.

1.3.3 Findings from studies directly relevant to modern day treatments for the removal of pituitary tumours.

The studies by Noad et al. (2004) and Treece et al. (2005) compared patients who had received the "Gold Standard" treatments for the removal of pituitary tumours. These two studies are directly relevant to the study of the effects of modern treatments for pituitary tumours on cognitive function. The findings could contribute towards evidence based medicine. Neither study exposed gross cognitive decline (ie. decline over all areas of cognition measured) in patients treated for pituitary tumours with surgery or combined therapy (TSA or TSA+RT3).

The specific findings from these two studies have been discussed in the previous two sections. To recap, the retrospective study by Noad et al. (2004) compared two groups of pituitary patients (TSA and TSA+RT3) on tests of neuropsychological functioning. The prospective study by Treece (2005) compared pituitary patients (TSA) to controls (CG-S) on tests of neuropsychological functioning three times over twelve months. At one year after surgery

comparisons were also made between the group of patients who had received combined therapy in that year (TSA+RT3) to the other two groups (TSA and CG-S).

Noad et al. (2004) found a significant difference between pituitary groups on a single test of executive function, with the combined therapy group showing a poorer performance. Significant differences between the two pituitary groups were not found on any other measures of cognition. Noad et al. (2004) found a greater proportion of patients in the combined therapy group were clinically impaired on three or more tests of neuropsychological functioning when compared to the surgery only group (27% vs 5%).

Treece (2005) found that the pituitary group performed significantly worse than the control group on measures of memory and visuospatial functioning at each time point, (pre-surgery, three and twelve months after surgery). In addition those pituitary patients who had received radiotherapy (TSA+RT3) performed significantly worse than the other two groups on a single measure of visual memory. This was the Recognition Memory Test for Faces, an earlier study had reported deficits on this task (Peace et al., 1997), and it was interesting to note that in a longitudinal study this became impaired following radiotherapy (Treece et al., 2005).

Treece (2005) hypothesised that the surgery group would perform at a significantly higher level than the combined therapy group on many tests of cognition. This was not the case. However, the combined therapy group was very small, additional differences may have been found if the groups had been more equal in size. A long term follow up study was recommended because the

full effects of radiotherapy (or surgery) on cognition may express themselves long after treatment.

1.4 CONCLUSIONS

Patients with pituitary disease exhibit deficits in memory and executive functioning when compared to matched controls and published test norms. This indicates a level of damage to the temporal lobes and the frontal lobes. Gross cognitive decline was not reported by any of the reviewed studies. Many of the early studies were not relevant to modern practices. Only a few studies compared patients who had received the "Gold Standard" treatments for pituitary disease. The only prospective study in this area reported memory and visuospatial functioning deficits before surgery, after surgery and following surgery plus radiotherapy. It concluded that surgery did not increase the level of cognitive dysfunction, and that radiotherapy resulted in a small additional negative effect on visual memory. It is not possible to draw any firm conclusions from a set of retrospective studies and only one prospective study which examines the current medical treatments, however it would appear that there is some evidence that surgery does not cause additional cognitive problems. This may inform clinical judgement when deciding on treatment options. Recently there has been a reduction in radiotherapy after surgery for pituitary tumours (Wass, Carson & Bates, 2004), with repeated resection via the transsphenoidal route being favoured by surgeons (Treece, 2005). Treece (2005) noted this reduction within her multi-centre study at Nottingham QMC, Oxford Radcliffe Hospital and Newcastle Freeman Hospital, these are three of the regional centres which specialise in pituitary surgery.

If, when prescribing treatments to remove pituitary tumours, the only factor to be taken into consideration were the effects on cognitive functioning, one may argue that the treatments should not be offered because of demonstrated damaging effects on memory and executive functioning. However, many of the early studies which demonstrated cognitive decline in pituitary patients (Grattan-Smith et al., 1992; Guinan et al., 1998; McCord et al., 1997; Peace et al., 1997; Peace et al., 1998) included patients who had received treatments which are recognised to be damaging and highly invasive (Brada et al., 2002; Guinan et al., 1998; Plowman, 1999) such as transfrontal surgery and two field radiotherapy. The recommended "Gold Standard" treatments (RCP, 1997) now exclude two field radiotherapy and reserve transfrontal surgery for only a very small group of pituitary tumours (Peace et al., 1998). In addition, the advantages of having received the treatments for the removal of pituitary tumours in terms of medical recovery from pituitary disease are enormous. If the treatment is successful at normalising pituitary hormones, those people who were suffering from acromegaly experience vast changes, their previously thickened skin and enlarged soft tissues return to near normal status. This results in the person's appearance being normalised, they no longer look as if their hands, nose, ears, tongue and feet are "too large". The internal organs reduce to a more normal size, breathing becomes easier and blood circulation improves. These both result in the person feeling more able to take part in normal activities of daily living, quite often patients who were previously unable to work because of their extreme fatigue are able to return to paid employment. Life expectancy is improved to near normal. People with cured acromegaly are routinely offered maxilofacial surgery to reduce the size of the jaw, this further increases the normalisation of appearance.

Similar arguments for the improvement in health status and longevity can be applied to people who have received treatments to remove tumours which cause Cushing's Disease, infertility due to hypogonadism, or hypopituitarism. These all result in an improved health status, and improvements in quality of life. So clearly the improvement in health status must be considered as highly important as well as the effects on cognitive functioning. If the studies of modern treatments to remove pituitary tumours had revealed gross cognitive decline (i.e. severe reduction in cognitive functioning over many cognitive areas) following either surgery or radiotherapy then this would be an extreme finding and would need to be taken into consideration when planning treatments – but as the only prospective study in this area (Treece, 2005) found deficits in memory prior to surgery, and only slight further deficit after radiotherapy this would not appear to be the case. Treece (2005) found no deficits in cognitive functioning in any of the other areas of cognition measured (at any point in time).

Frequently, pituitary tumours can be diagnosed and present for many years before treatment is thought to be necessary by the monitoring endocrinologist or neurosurgeon. The decision to operate is made if the pituitary tumour is exerting mass effects on surrounding structures, or if the patient's hormonal status becomes highly abnormal. At that point, if the person were to be denied the opportunity of having the tumour removed they may risk losing their sight from occlusion of the optic nerve, or of dying quickly because of insufficiency of pituitary hormones. In the longer term, lives may be shortened if patients with pituitary disease have an excess of pituitary hormones. In the case of patients with acromegaly increased mortality is caused by the enlargement of the internal organs which grow too large for the skeleton, then breathing and blood circulation become impaired.

The study by Treece (2005) only followed the patients with pituitary disease for a period of 12 months, from before their surgery for the removal of a pituitary tumour, to 12 months after their surgery. It is possible that the "Gold Standard" treatments (RCP, 1997) for the removal of pituitary tumours are as damaging to cognition as the previously used invasive treatments, this may become evident over time. Conversely, it is also possible that improvements in cognitive functioning may be seen over time, which could be due to the long term effects of normalisation of pituitary hormone levels either naturally following the removal of the tumour, or because of hormone replacement therapies. Therefore, in order to assess the full effects of the modern "Gold Standard" treatments for the removal of pituitary tumours a long term follow up study of this patient group would be recommended.

In addition, further prospective studies looking at cognitive functioning in newly diagnosed patients with pituitary disease may highlight the effects that hormonal status have upon cognitive functioning, these studies should also consider the effects upon psychosocial functioning in this patient group. If a large scale prospective study was able to demonstrate poor cognitive functioning or psychosocial functioning in patients with pituitary tumours, then additional clinical psychology or neuro-rehabilitation services may be offered to these patients. Similarly, if a large scale prospective study was able to demonstrate resolution of cognitive or psychosocial deficits after treatments to remove pituitary tumours then earlier interventions (surgery or radiotherapy) may be considered necessary.

Current medical evidence supports a conservative approach to intervention, employing regular monitoring of tumour state, with intervention triggered by pathology of hormonal status, tumour

growth, pregnancy or other clinical signs which would alter the evaluation of intervention risk. If an improvement in cognitive functioning were reported following surgical or radiotherapy interventions then earlier treatments may be considered to exploit this additional benefit.

In conclusion, currently there is no substantial evidence to indicate cognitive effects should be taken into account when considering the need for surgical or radiotherapy treatments to remove pituitary tumours. However, further prospective studies in this area are required to evaluate the modern "Gold Standard" treatments fully, and to assess their long term effects. Further studies should be multi-centred, prospective longitudinal studies which exercise greater methodological rigour in all areas. Data from a single prospective study examining current treatments, and a small series of retrospective studies examining mixed treatments, is insufficient to support a definitive conclusion either way.

1.5 REFERENCES

Abayomi, O.K. (2002). Pathogenesis of cognitive decline following therapeutic irradiation for head and neck tumours. *Acta Oncologia, 41,* 346-351.

Ahmed, S., Elsheikh, M., Stratton, I.M., Page, R.C.L., Adams, C.B.T., & Wass, J.A.H. (1999). Outcome of transsphenoidal surgery for acromegaly and its relationship to surgical experience. *Clinical Endocrinology, 50,* 561-567.

Aizenberg, C., Woimant, F., Lepage, E., Seret-Begue, D., Candiloros, H., & Virally-Monod, M. (1998). Long-term evaluation of postoperative radiotherapy efficacy and side effects in patients with pituitary adenomas. *International Conference on Endocrinology. The Endocrine Society.* 1-24.

Aldridge, A.A., & Roesch, S.C. (2007). Coping and adjustment in children with cancer. A meta-analytic study. *Journal of Behavioural Medicine, 30,* 115-129.

Almqvist, O., Thoren, M., Saff, M., & Erikson, D. (1986). Effects of growth hormone on mental performance in adults with growth hormone deficiency. *Psychoendocrinology, 11,* 347-352.

van Beek, A.P., van den Bergh, A.C.M., van den Berg, L.M., van den Berg, G., Keers, J.C., Langendijk, J.A., & Wolffenbuttel, B.H. (2007). Radiotherapy is not associated with reduced quality of life and cognitive function in patients treated for nonfunctioning pituitary adenoma. *International Journal of Radiation Oncology Biology and Physics, 68, 986-991.*

Brada, M., Rajan, B., Traish, D., Ashley, S., Holmes-Sellors, P.J., Nussey, S., & Uttley, D. (1993). The long term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clinical Endocrinology, 38,* 571-578.

Brada, M. (2002). Pituitary radiotherapy – do the new therapies have particular advantages. Society for Endocrinology –Training. University of Reading, July 2002. www.endocrinology.org/sfe/training/ss02/ss02_bra.htm

Brook, C.G.D., & Marshall, N.J. (2001). *Essential endocrinology. The hypothalamopituitary axis.* (4th ed.). (pp 34-56) Oxford: Blackwell Science Limited.

Burrow, G.N., Wortzman, G., Rewcastle, N.B., Holgate, R.C., & Kovacs, K. (1981). Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. *New England Journal of Medicine, 304,* 156-158.

Burt, D.B., Zembar, M.J. & Niederehe, G. (1995). Depression and memory impairment: A meta-analysis of the association, its pattern and specificity. *Psychological Bulletin, 117,* 285-305.

Chon, B.H., & Loeffler, J.S. (2002). Efficacy and risk for radiotherapy for pituitary tumours. *The Endocrinologist. 12,* 525-530.

Christensen, H., Griffiths, K., MacKinnon, A., & Jacomb, P. (1997) A quantitive reivew of cognitive deficits in depression and Slzheimer's type dementia. *Journal of the International Neuropsychological Society, 3,* 621-651.

Clayton, R.N., & Wass, J.A.H. (1997). Pituitary Tumours. Recommendations for service provision and guidelines for management of patients. Consensus statement of a working party. *Journal of the Royal College of Physicians of London, 31,* 628-636.

Clayton, R.N., & Wass, J.A.H. (1998). Pituitary Tumours. Recommendations for service provision and guidelines for management of patients. *British Journal of Neurosurgery, 12,* 285-287.

Cohen, R.M., Weingartner, H., Smallberg, S.A., Pickar, F., & Nurphy, D.L. (1982). Effort and cognition in depression. *Archives of General Psychiatry, 145,* 164-167.

Couldwell, W.T. (2004). Transsphenoidal and transcranial surgery for pituitary adenomas. *Journal of Neuro-Oncology, 69,* 237-256.

Crossen, J.R., Garwood, D., Flatstein, E., & Neuwelt, E.A. (1994). Neurobehavioural sequelae in cranial irradiation in adults: A review of radiation induced encephalopathy. *Journal of Clinical Oncology, 12,* 627-642.

Duffner, P.K., Cohen, M.E., Vorhess, M.L., MacGillivray, M.H., Brecher, M.L., Panahon, A., & Gilani, B.B. (1985). Long term effects of cranial irradiation on endocrine function in children with brain tumours. A prospective study. *Cancer, 56,* 2189-2193.

Edwards, C.R.W. (1986). *Endocrinology.* London: William Heinemann Medical Books Ltd.

Fahlbusch, R. (1981). Surgical treatment of pituitary adenomas. In C. Beardwell & G.L. Robertson (Eds.), *Clinical Endocrinology 1. The Pituitary.* (pp. 76-105) London: Butterworths.

Feehan, M., Knight, R.G., & Partridge, F.M. (1991). Cognitive complaint and test performance in elderly patients suffering depression or dementia. *International Journal of Geriatric Psychiatry, 6,* 287-293.

Gittoes, N.J.L. (2003) Radiotherapy for non-functioning pituitary tumours – when and under what circumstances. *Pituitary, 6,* 103-108.

Grattan-Smith, P.J., Morris, J.G.L., Shores, E.A., Batchelor, J., & Sparks, R.S. (1972). Neuropsychological abnormalities in patients with pituitary tumours. *Acta Neurologica Scandinavica, 86,* 626-631.

Green, J. (2000). *Neuropsychological evaluation of the older adult: a clinical guidebook.* London: Academic Press.

Guinan, E.M., Lowy, C., Stanhope, N., Lewis, P.D.R., & Kopelman, M.D. (1998). Cognitive effects of pituitary tumours and their treatments: two case studies and an investigation of 90 patients. *Journal of Neurology, Neurosurgery and Psychiatry, 65,* 870-876.

Harris, J.R., & Levene, M.B. (1976). Visual complications following irradiation for pituitary adenomas and craniopharyngiomas. *Radiology, 120,* 167-171.

Irvine, D., Browne, B., Crooks, D., Roberts, J., & Brown, G. (1991). Psychosocial adjustment in women with breast cancer. *Cancer, 67,* 1097-1117.

Jeffcoate, W.J. (1986). The adrenal glands. In C.R.W. Edwards (Ed.), *Endocrinology.* (pp. 62-82) London: William Heinemann Medical Books Ltd.

Jeffcoate, W.J. (1993). *Lecture notes on endocrinology.* (5th ed.). Oxford: Blackwell Scientific Publications.

Johnson, M.D., Woodburn, C.J., & Vance, M.L. (2003). Quality of life in patients with pituitary adenoma. *Pituitary, 6,* 81-87.

Jones, A. (1991). Radiation oncogenesis in relation to the treatment of pituitary tumours. *Clinical Endocrinology, 35,* 379-397.

Kahn, E.A., & Crosby, E.C. (1972). Korsakoff's syndrome associated with surgical lesions involving the mammillary bodies. *Neurology, 22,* 117-125.

Laws, E.R.(Jr.), & Thapar, K. (1995). Surgical management of pituitary adenomas. *Bailliere's Clinical Endocrinology and Metabolism, 9,* 391-405

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological Assessment.* (4th ed.). Oxford: Oxford University Press.

Lishman, W.A. (1987). *Organic psychiatry: the psychological consequences of cerebral disorder.* (2nd ed.). Oxford: Blackwell.

Luria, A.R. (1976). *The neuropsychology of memory.* New York: John Wiley.

Mahmoud-Ahmed, A.S., & Suh, J.H. (2002). Radiation therapy for Cushing's disease: A Review. *Pituitary, 5,* 175-180.

Marks, J.E., Baglan, R.J., Prassad, S.C., & Blank, E.F. (1981). Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *International Journal of Radiation, Oncology, Biology and Physics, 7,* 243-252.

McCord, M.W., Buatti, J.M., Fennell, E.M., Mendenhall, W.M., Marcus, R.B., Rhoton, A.L., Grant, M.B., & Friedman, W.A. (1997). Radiotherapy for pituitary adenoma: long-term outcome and sequelae. *International Journal of Radiation, Oncology, Biology and Physics, 39,* 437-444.

McGuire, G.P., Lee, E.G., Bevington, D.S., Kuchemann, C.S., Crabtree, R,J., & Cornell, C.E. (1978). Psychiatric problems in the first year after mastectomy. *British Medical Journal, 1,* 963-965.

Mikhael, M.A. (1980). Dosimetric considerations in the diagnosis of radiation necrosis of the brain. In H.A. Gilbert & A.R. Kagan (Eds.), *Radiation damage to the nervous system.* (pp. 59-91). New York: Raven Press.

Noad, R.F., Narayanan, K.R., Howlett, T., Lincoln, N.B., & Page, R.C.L. (2004). Evaluation of the effect of radiotherapy for pituitary tumours on cognitive function and quality of life. *Clinical Oncology, 16,* 233-237.

Northouse, L.L., Swain M.A. (1987). Adjustment of patients and husbands to the initial impact of breast cancer. *Nursing Research, 36,* 221-225.

Page, R.C.L., Hammersley, M.S., Burke, C.W., & Wass, J.A.H. (1997). An account of the quality of life of patients after treatment for non-functioning pituitary tumours. *Clinical Endrocrinology, 46,* 401-406.

Peace, K.A., Orme, S.M., Padayatty, S.J., Godfrey, H.P.D., & Belchetz, P.E. (1998). Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transsphenoidal surgery or medication. *Clinical Endocrinology, 48,* 391-396.

Peace, K.A., Orme, S.M., Thompson, A.R., Padayatty, S.J., Ellis, A.W., & Belchetz, P.E. (1997). Cognitive dysfunction in patients treated for pituitary tumours. *Journal of Clinical and Experimental Neuropsychology, 19,* 1-6.

Pituitary Foundation. (2000) *Pituitary disease. Fact file for general practitioners. Fact sheets.* Bristol: Author.

Pituitary Foundation. (2006). *Fact file for medical professionals.* Retrieved January 10 2007, from www.pituitary.org.uk/content/view/53/ author

Plowman, P.N. (1999). Pituitary adenoma radiotherapy – when, who and how? A review. *Clinical Endocrinology, 51,* 265-271.

Prigatano, G.P. (1986). Personality and psychosocial consequences of brain injury. In. Author (Ed.), *Neuropsychological rehabilitation after brain injury.* (pp. 29-49) Baltimore: John Hopkins University Press.

Rauhaut, F., Stuschke, M., Sack, H. & Stolke, D. (2002). Dependence of the risk of encephalopathy on the radiotherapy volume after combined surgery and radiotherapy of invasive pituitary tumours. *Acta Neurochirurgica, 144,* 37-46.

Rohling, M.L., Green, P., Allen, L.M., & Iverson, G.L. (2002). Depressive symptoms and neurocognitive test scores in patient passing symptom validity tests. *Archives of Clinical Neuropsychology, 17,* 205-222.

Roman, D.D., & Sperduto, P.W. (1995). Neuropsychological effects of cranial irradiation: current knowledge and future directions. *International Journal of Radiation, Oncology, Biology and Physics, 31,* 983-998.

Royal College of Physicians. (1997) *Consensus statement of a working party. Recommendation for service provision and guidelines for management of patients.* London: Author.

Ryan, C., Johnston, S., Lee, P. & Foley, T. (1988). *Cognitive deficits in short statured adolescents with growth hormone deficiency.* Poster presented at the meeting of the American Psychological Association Convention. Atlanta. GA.

Sheline, G.E., Wara, W.M., & Smith, V. (1980). Therapeutic irradiation and brain injury. *International Journal of Radiation, Oncology, Biology and Physics, 6,* 1215-1228.

Siegel, P.T., & Hopwood, N.J. (1986). The relationship of academic achievement and the intellectual functioning and affective conditions of hypopituitary children. In B. Stabler & L. Underwood (Eds.), *Slow grows the child.* (pp 57-72). New Jersey: Lawrence Erlbaum.

Smith, M.Y., Redd, W.H., Peyser, C., & Vogi, D. (1999). Post-traumatic stress disorder in cancer: A review. *Psycho-oncology, 8,* 521-537.

Sternberg, D.E., & Jarvick, M.E. (1976). Memory functions in depression. *Archives of General Psychiatry, 33,* 219-224.

Taphoorn, M.J.B., & Klein, M. (2004). Cognitive deficits in adults with brain tumours. The Lancet, Neurology, 3, 159-168).

Thapar, K., & Laws E.R.(Jnr.) (2001). Pituitary Surgery. In K. Thapar, K. Kovacs, B.W. Scheithauer & R,V, Lloyd (Eds.), *Diagnosis and management of pituitary tumours.* (pp 225-246). New Jersey: Humana Press.

Treece, K.A. (2005). *The effects of treatments for pituitary tumours on cognitive function and quality of life. A prospective study.* Unpublished thesis submitted to the University of Nottingham for the degree of Master of Philosophy.

Treece, K.A., Narayanan, K., Wass, J.A.H., Karavitaki, N., Parker, D., Howlett, T., James, A., Quinton, R., & Page, R.C.L. (2005). A prospective study of cognitive function in patients with

pituitary tumours requiring surgery. Presentation of baseline and 3 month and 12 month follow up results. *Endocrine Abstracts, 10,* 52.

Treece, K.A., Page, R.C.L., Wass, J.A.H., & Lincoln, N.B. (2003). The effect of pituitary tumours on cognitive function. A prospective study. Presentation of baseline results. *6th European Congress of Endocrinology, Abstract Book, 6,* 157.

Treece, K.A., Wass, J.A.H., Lincoln, N.B., & Page, R.C.L. (2004). The effect of pituitary tumours on cognitive function. A prospective study. Presentation of baseline and initial follow up results. *Endocrine Abstracts, 7,* 115.

Turner, H.E., & Wass, J.A.H. (2000). Modern approaches to treating acromegaly. *Quarterly Journal of Medicine, 93,* 1-6.

Wass, J.A.H., Carson, M.N., & Bates, P.R. (2004). The changing patterns of presentation and treatment of acromegaly in the UK as reflected by the UK National Acromegaly Database. *Endocrine Abstracts, 7,* 125.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale – Revised.* New York: Psychological Corporation.

Wechsler, D. (1987). *Wechsler Memory Scale – Revised.* San Antonio: Psychological Corporation.

White, J.C., & Cobb, S. (1955), Psychological change associated with giant pituitary neoplasms. *Archives of Neurology and Psychiatry, 74,* 383-396.

WHO Working Group on Radiation Therapy in Cancer. (1997) *Radiotherapy in cancer management – a practical manual.* London: Chapman & Hall Medical.

Wolf, O.T. (2003). HPA axis and memory. *Best Practice & Research in Clinical Endocrinology and Metabolism, 17,* 287-299.

Long-Term Outcomes Of Psychosocial Functioning In Patients Treated For Pituitary Tumours With Surgery.

Abstract

A long-term, multi-centred, case controlled, follow up study of patients who had been treated for pituitary tumours with transsphenoidal surgery (TSA) was conducted. Transsphenoidal surgery is the "Gold Standard" treatment for removal of pituitary tumours (Royal College of Physicians, 1997). Patients had received surgery between 1998 and 2002. Pituitary patients were compared to controls on psychosocial functioning measures. Impaired levels of psychosocial functioning had been observed in pituitary patients before surgery and three months after surgery, but this had appeared to resolve one year after surgery (Treece, 2005).

The aim of this follow up study was to determine whether or not the resolution in psychosocial functioning observed one year after surgery had been maintained at long-term follow up (4-8 years after surgery). Patients who had completed the prospective study were approached. Thirty-two pituitary surgery patients and nineteen control surgery patients completed measures of psychosocial functioning. The levels of psychosocial functioning between the two groups were not significantly different at long-term follow up ($p<0.05$). Normalised levels of psychosocial functioning measured in pituitary patients one year after surgery, remained at long-term follow up. Transsphenoidal surgery to remove pituitary tumours was not shown to have detrimental effects on psychosocial functioning between four and eight years after surgery.

2.1 INTRODUCTION

The Royal College of Physicians recommended transsphenoidal adenomectomy (TSA) and conventional three field fractionated radiotherapy (RT3) as the "Gold Standard" treatments for the removal of pituitary tumours in 1997 (Clayton & Wass, 1998). Since that date these two treatments have been used singly or in combination as treatment to remove pituitary tumours, and to prevent tumour regrowth (Pituitary Foundation, 2006). The reason for the formal introduction of recommended "Gold Standard" treatments was to prevent more damaging and invasive treatments being used in the routine treatment of small and medium sized, easily reached pituitary adenomas. Some surgeons had resisted the change from transfrontal or transcranial surgery to transsphenoidal surgery; so formalisation of recommended practices was necessary (J.A.H. Wass, personal communication, 25th February 1999). The earlier more invasive treatments (transfrontal surgery, transcranial surgery and radiotherapy treatments in large doses) are now reserved for only the largest most invasive tumours of the pituitary (Peace, Orme, Padayatty, Godfrey, & Belchetz, 1998), these could be aggressive, quick growing pituitary tumours reaching as far as the third ventricle.

It is important to examine the effects of the newly recommended treatments (McCord et al., 1997), in case they are found to be just as damaging as the previous more invasive treatments (Treece, 2005). To date, the long-term effects of these "Gold Standard" treatments on psychosocial functioning in patients who have been treated for pituitary tumours has not been examined (Treece, 2005).

It is known that some of the effects of treatments for pituitary tumours are expressed many months or even years after the treatments have been received (Armstrong et al., 2002; Brada et al., 1993; Turner & Wass, 2000). This is particularly the case for the effects of radiotherapy on the expression of pituitary hormones (Plowman, 1999; Turner & Wass, 2000). The levels of hormones are monitored carefully following radiotherapy treatment, if the hormone levels fall to a dangerously low level then hormone replacement therapy is commenced (Royal College of Physicians, 1997). Secondly, the long term effects of modern pituitary surgery (TSA) have not been examined, it is possible that damaging effects are expressed at long term after treatment. If this was the case, then the resolution of poor psychosocial functioning which was observed at twelve months after surgery may have been reversed at long term follow up.

When the original prospective study by Treece (2005) was designed, Wass (of Clayton & Wass, 1997 & 1998) and Page (of Page, Hammersley, Burke & Wass, 1997) were consulted. It was agreed that the prospective study would examine affect (anxiety and depression), health related quality of life, and general well-being, in patients who required transsphenoidal surgery for the removal of pituitary tumours before surgery and at three months and 12 months after surgery. It was also agreed that these patients would be followed up at 5 years and 10 years after surgery to look for long-term effects. The prospective study was designed and commenced in 1998. This current long-term study is the 5 year follow up of the prospective study, (because it was necessary for this study to fit into a DClinPsy training programme the follow up time for individuals was between 4 years and 8 years). A 10 year follow up study is planned to commence in November 2008 and to continue until November 2012, where the actual time of testing will be exactly 10 years after surgery, (this is assuming sufficient research funding is

forthcoming, and the study is granted ethical and R&D approval). The original prospective study also examined cognitive functioning in patients who required surgical treatment for pituitary tumours but that is not reported upon within this document.

A study of psychosocial functioning in patients who had been treated for pituitary tumours with transsphenoidal surgery was conducted. Many patients with pituitary tumours feel generally unwell, and report a wide range of symptoms (Clayton & Wass, 1998) including poor quality of life (Page et al., 1997; Dekkers et al., 2006) and psychosocial functioning (Treece, 2005). Patients with pituitary disease routinely receive treatments to remove the tumours and to relieve the symptoms. There have been a few retrospective studies examining the psychosocial functioning in patients who have been treated for pituitary tumours, these have reported conflicting results (Guinan, Lowry, Stanhope, Lewis, & Kepelman, 1998; Noad, Narayanan, Howlett, Lincoln, & Page, 2004; Page et al., 1997; Peace et al., 1997a; Peace et al., 1997b). There has been a single prospective study in this area which reported deficits in psychosocial functioning before surgery with resolution of dysfunction at one year follow up (Treece, 2005). Studies to investigate the long-term effects of modern treatments for the removal of pituitary tumours on psychosocial functioning are important to assess the efficacy of treatments over time.

It has recently been recognised that standardised measures of health related quality of life and psychosocial functioning should be used to evaluate health-care interventions (Asadi-Lari, Tamburini & Gray, 2004; Bowling, 1997). The QALY (Quality Adjusted Life Years), a recently developed measurement of effectiveness of health-care interventions has been based on an arithmetic product of life expectancy after treatment, and a measure of the quality of life for the

remaining years of life following treatment. The QALY produces an index number for the treatment it is applied to, this allows for comparison to be made between alternative treatments (Feeny, 2005). This measurement will be applied to new treatments and services offered to patients by the NHS now and in future years. It will also be used to evaluate existing treatments, and help build research knowledge to support evidenced based medicines.

For the specific investigation of psychosocial functioning in health research, a battery which included measurements of anxiety, depression, social functioning, mental functioning, psychological functioning, health related quality of life, life satisfaction and inner personal state, would be comprehensive. The measurements used in this study cover all of the above. Measures of economic status and occupational status are also known to impact, but many health research studies do not collect this data (Fayers & Hays, 2005). However, the effects of economic status and occupational status can be counterbalanced in research studies by the inclusion of a control group recruited from the same back ground population. This study includes such a control group.

2.1.1 Do patients with pituitary tumours have a poor level of psychosocial functioning?

There are many different types of pituitary disease resulting from tumours of the pituitary, not all are treated with surgery or radiotherapy (Pituitary Foundation, 2006) some are treated with inhibiting medications or hormone replacements and others are monitored carefully for change. Some tumours receive combination treatments. The quality of life in patients with pituitary disease has been the subject of study for many years (Dekkers et al., 2006; Peace et al., 1997b). Studies are normally restricted in the types of patients recruited according to the area of interest of the endocrinologists. It might be expected that the different types of pituitary disease would

have differing impacts on psychosocial functioning. Both hyperpituitarism (over production of hormones) and hypopituitarism (underproduction of hormones) can be caused by pituitary tumours. Some diseases are characterised by the over production of pituitary hormones (Cushing's Disease, acromegaly, hyperprolactinaemia) and others are characterised by the under production of pituitary hormones (hypopituitarism, growth hormone deficiency, hypogonadism).

There has also been much debate surrounding the hypothesis that normalisation of pituitary functioning, or adequate hormonal replacement which resulted in near normal levels of pituitary hormones, would result in normalisation of psychosocial functioning. However the evidence in this area is very mixed (Biermasz et al., 2004; Johnson, Woodburn & Vance, 2003; Korali et al., 2003). Some studies showed severe effects of pituitary disease on psychosocial functioning (Lynch et al., 1994) and others showed no negative effects at all (Degerbald et al., 1990; Whitehead et al., 1992).

There is a large "controversial" research literature investigating impairment in psychosocial functioning in growth hormone deficient (GHD) adults (Korali et al., 2003). Korali et al. (2003) criticised the empirical evidence, citing considerable methodological constraints in the available studies. Prospective studies examining GHD patients (before and after replacement therapy) have observed both negative quality of life and positive quality of life before replacement intervention and after intervention. Burman and Deijen (1998) elucidated that patients with pituitary insufficiency have diminished social and societal functioning even when on adequate hormonal replacement therapy. Support for this impression was gathered through studies of young GHD adults who had received growth hormone replacements throughout childhood in order to attain

their predicted stature (Dean, McTaggert, Fish, & Friesen, 1985; Takano et al., 1994). Compared to a reference population higher levels of unemployment and single status were observed by Dean et al. (1985). Another study compared GHD young adults to short normal controls of similar age, greater dependency on parents, lower levels of marriage or partnership, and low status employment with low wages were observed in the GHD pituitary patients (Rikken et al., 1995). Some adult GHD studies reported lack of energy and emotional problems (Burman et al., 1995; McGauley, 1989), social isolation (McGauley, 1989; Rosen, Wiren, Wilhelmsen, Wiklund, & Bengtsson, 1994) and reduced capacity to work (Rosen et al., 1994). Others found no impairments in these functions at all (Degerblad et al., 1990; Deijen, de Boer, Blok, & van der Veen, 1996; Page et al., 1997; Korali et al., 2003; Whitehead et al., 1992). A recent placebo controlled trial examined the effects of withdrawing growth hormone replacement treatment from severely GHD deficient patients (McMillan et al., 2003). Those who continued to receive replacements functioned more highly on measures of general health, energy levels and physical ability than patients who received the placebo.

Cushing's disease is characterised by abnormally high levels of cortisol (Sonino & Fava, 1998) and results in high levels of circulating corticosteroids. The symptoms are wide ranging but include disfiguring factors such as increased weight, bruising, skin atrophy and "moon face", which may lead to a poor body image. The symptoms also include emotional lability, high levels of anxiety and a proneness to depression. Many researchers (including Cushing, 1913) have suggested that psychiatric traumas and stressful life events may be causal to this form of pituitary disease (Mazet, Simon, Luton, & Bricaire, 1988). Studies have found high levels of depression (54% to 64%) in patients with Cushing's disease (Haskett, 1985; Kelly, Kelly, & Faragher, 1996;

Sonino & Favia, 1998). Other researchers have reported elevated levels of irritability associated with the depression (Starkman, Schteingart, & Schork, 1986). Significant improvements in psychological distress and depressive symptoms have been reported following treatment of Cushing's disease (Kelly et al., 1996; Korali et al., 2003). Surgery, radiotherapy and steroid inhibitors all being shown to be effective (Dorn et al., 1997; Jeffcoate, Silverstone, Edwards, & Besser, 1979; Kelly et al., 1996; Sonino, Fava, Belluardo, Girell, & Boscaro, 1993; Starkman et al., 1986). Johnson et al. (2003) reported poor psychosocial functioning in patients with untreated Cushing's over a wide spectrum of measures. Compared to healthy controls Sonino, Bonnini, Boscaro and Fava (2006) found higher levels of anxiety, depression and psychotic symptoms in treated Cushing's patients. Heald et al. (2004) obtained similar results a few years earlier with a retrospective cohort of "cured" Cushing's patients, reporting poor psychosocial functioning.

Acromegaly results from the overproduction of growth hormone by the pituitary. Observable features of excessive GH are thickening and growth of soft tissues (skin, nose and ears), excessive perspiration, and enlargement of the hands, feet and jaw. Excessive GH also accounts for abnormal growth and functioning of internal systems. Following "cure" of acromegaly soft tissues diminish and perspiration normalises, but some debilitating features persist (Biermasz et al., 2004). In 1998 Furman and Ezzat noted that few clinicians or research studies had examined psychosocial functioning in conjunction with growth hormone excess, the quantity of research has since increased marginally (Biermasz et al., 2004; Sonino, Scarpa, Paoletta, Fallo & Boscaro 1999). Ezzat (1992) noted that patients with acromegaly suffer from poor self-esteem, body image distortion, social withdrawal and poor interpersonal functioning. She also commented that depression impeded recovery. A few research studies have found loss of initiative and

spontaneity with mood swings (Richert, Eversman, & Fahlbush, 1983) and loss of libido (Hutler & Lundberg, 1994) in patients with acromegaly. Johnson et al. (2003) reported impairment in physical function in patients with untreated acromegaly. Two recent studies of patients with "cured" acromegaly (Biermasz et al., 2004; Rowles et al., 2005) reported that radiotherapy was associated with a poorer quality of life. This was despite long-term biochemical cure of GH excess (Biermasz et al., 2004).

Prolactinomas are the most common of all pituitary tumours. They result in the over production of prolactin (hyperprolactinaemia). This acts on the gonadal axis and can result in hypogonadism. Patients with hyperprolactinaemia frequently present with emotional dysfunctions (Sobrinho, 1998). These include loss of libido, irritability, loss of interest in favoured activities, and a high prevalence of depressed mood (Sobrinho, 1998). Johnson et al. (2003) supported this partly with her reports of impaired mental health functioning in patients with untreated prolactinomas. Research has shown some relief of symptoms following surgery for the removal of tumour (Rothchild, 1985) but Sobrinho (1998) stated that symptoms frequently persisted. Female sexual function and libido are restored if prolactin is returned to normal levels (Swerdloff & Wang, 1998). Sexual function is more impaired in males than in females with excess prolactin, because normal testicular function is disrupted. Results of treatment are unpredictable, but Ciccarelli, Guera, Roas, and Milone, (2005) reported normalisation of testicular function following treatment with Cabergoline, which restored the previously measured low levels of quality of life to near normal.

Hypopituitarism is generalised underproduction of pituitary hormones, if left untreated this can result in coma and death. Hypopituitarism can occur if a non-functioning pituitary tumour is exerting mass effects on the pituitary and occluding hormone production. It also occurs acutely following pituitary apoplexy (Jeffcoate & Birch, 1986), and can occur after treatments to remove pituitary tumours if the pituitary is damaged during treatment (Clayton & Wass, 1998). Levels of pituitary hormones are monitored carefully after surgery or radiotherapy and if there is insufficiency the hormones are replaced with supplements (Clayton & Wass, 1998). Panhypopituitarism is a total lack of pituitary hormones, this is treated with life long hormone replacement. Psychosocial symptoms of hypopituitarism include; depression, apathy, irritability, negativism and loss of libido (Meyers, 1998). More serious mental health problems have also been associated with panhypopituitarism including delusions, mania and paranoia (Meyers, 1998). In a later study Korali et al. (2003) found no significant effect of pituitary insufficiency on psychopathology. Johnson et al. (2003) reported impairments on both physical and mental health measures in patients with untreated non functioning adenomas. According to Cohen, Becan and Adams (1984) resolution of many symptoms occurred following replacement therapy. However, Dekkers et al. (2006) reported significantly impaired psychosocial functioning in patients who had been successfully treated for non-functioning pituitary tumours with replacement therapies. They reported symptoms including fatigue, reduced motivation, role limitation and reduced activity (Dekkers et al., 2006).

A recent prospective study (Johnson et al., 2003) looked at the effects of pituitary tumours on psychosocial functioning in newly diagnosed patients. Patients with pituitary disease had significantly lower psychosocial functioning than a control group. There were different levels of

impairment aligned with different pituitary tumour types. Patients with Cushing's were the most impaired, showing dysfunction in all areas measured. Impairments were observed on both mental and physical measures in patients with non functioning adenomas. Patents with acromegaly experienced limitations in physical functioning, and those with prolactinoma showed dysfunction on mental measures. Johnson et al. (2003) concluded that untreated pituitary tumours have a significant effect on psychosocial functioning.

In summary, the debate putting forwards the hypotheses that disturbed levels of pituitary hormones cause disturbances in psychosocial functioning, and that normalisation of those disturbed levels result in resolution of psychosocial functioning are inconclusive. There have been studies which have shown no significant effect of disturbed levels of hormones on psychosocial functioning (Korali et al., 2003) and others which have shown significant effect (Biermasz et al., 2004; Johnson et al., 2003). There is also conflicting evidence for resolution of poor psychosocial functioning after "cure" of pituitary disease or normalisation of pituitary functioning (either naturally or through hormone replacements), (Biermasz et al., 2004; Dekker et al., 2006). Nevertheless, as elucidated by Korali et al. (2003) much of the research employed inadequate methodologies, and Treece (2005) stated that many studies investigated retrospective samples of patients who had received treatments that are no longer recommended as good practice (TF, RT1, RT2). Even those studies which classified themselves as prospective, in that they looked at patients before and after replacement therapies (Biermasz et al., 2004), included patients who had received earlier therapeutic interventions (the exception to this was Johnson et al. (2003), which was truly prospective).

2.1.2 What are the emotional consequences of pituitary disorders

The emotional consequences of pituitary disorders are wide ranging. There are many studies which report high levels of anxiety in patients with treated or untreated pituitary tumours (Heald et al., 2004; Jeffcoate et al., 1979; Johnson et al., 2003; Mazet et al., 1988; Sonino et al., 2006). A greater number of studies recognise depression as a major problem for patients with pituitary disease, (Dorn et al., 1997; Ezzat, 1992; Haskett, 1985; Heald et al., 2004, Jeffcoate et al., 1979; Johnson et al., 2003; Kelly et al., 1996; Meyers, 1998; Sobrinho, 1998; Sonino & Favia, 1998; Sonino et al., 1993; Sonino et al., 2006; Starkman et al., 1986). Other researchers have also reported low self esteem (Ezzat, 1992; Johnson et al., 2003), social isolation (Ezzat, 1992; McGauley, 1989; Rosen et al., 1994), and poor body image (Ezzat, 1992; Jeffcoate et al., 1979) as problematic.

Pituitary disease frequently results in hormonal changes which will have a direct or indirect effect on affect. People with Cushing's disease have high levels of circulating cortisol, this results in a quickening of the heart rate and produces the physical symptoms of anxiety. Excess cortisol is also thought to adversely act upon the amygdala (responsible for the emotional interpretation of memories) resulting in higher levels of anxiety and emotional lability. A person with Cushing's disease may also notice marked changes in their bodily appearance. Their symptoms include obesity, excessive facial and bodily hair, "moon face", muscle wasting and bruising. These changes can result in low self esteem (Johnson et al., 2003), poor body image and social isolation (Ezzat, 1992), this could impact upon mood. The Pituitary Foundation (2006) reported that altered body image is particularly stressful for women with Cushing's Disease and it can be a major cause of depression when it affects relationships. There are many studies reporting high

levels of depression (Dorn et al., 1997; Haskett, 1985; Heald et al., 2004, Jeffcoate et al., 1979; Johnson et al., 2003; Kelly et al., 1996; Sonino & Favia, 1998; Sonino et al., 1993; Sonino et al., 2006; Starkman et al., 1986) or anxiety (Heald et al., 2004; Jeffcoate et al., 1979; Johnson et al., 2003; Mazet et al., 1988; Sonino et al., 2006) in patients with Cushing's disease.

Similarly, people with over production of growth hormone resulting in giantism (in children) or acromegaly (in adults) may suffer from a poor body image and social isolation (Ezzat, 1992) resulting in heightened levels of anxiety or depression. Adults who produce excessive growth hormone via a functioning pituitary tumour suffer from slowly developing bodily changes. Their facial features gradually coarsen, the soft tissue of the lips, tongue, nose and ears become thickened and enlarged. Patients' hands and feet also enlarge, and the person takes on the appearance of someone whose skin is too large for their body. Patients with acromegaly may suffer from low self esteem and poor body image which in turn may result in social isolation and depression (Ezzat, 1992). The Pituitary Foundation (2006) acknowledged that dysmorphophobia is suffered by patients with acromegaly or giantism, and recommend supportive intervention programs. "Changing Faces" (www.changingfaces.org.uk) runs a series of courses for children and adults, to help deal with changes in body structure, improve self esteem and reduce social anxiety and depression. They also offer courses to professionals who work with patients with disfiguring conditions.

Children who produce too much growth hormone suffer from a generalised increase in body stature (giantism), they become much larger than their peers. In addition, if untreated, children with excess GH may not produce sufficient sex hormones to progress through puberty. Giantism

and failure to mature sexually could both lead to teasing and bullying in the school environment, which is associated with depression, anxiety and suicidal ideation (Fekkes, Pijpers, Fredriks, Vogels & Verloove-Vanhorick, 2006; van der Wal, de Wit, & Hirasing, 2003).

Producing insufficient levels of pituitary hormones can also increase the risk of poor emotional functioning. Children who are growth hormone deficient (GHD), are abnormally short in stature, this may lead to teasing and bullying at school, with an increased risk of depression and suicidal ideation (van der Wal et al., 2003). Some studies have found elevated levels of social isolation (McGauley, 1989; Rosen et al., 1994), unemployment (Dean et al., 1985) and capacity to work (Rosen et al., 1994) in GHD adults. These side effects of growth hormone deficiency, in particular long term unemployment, may be co-morbid with anxiety and depression (Annsseau et al., 2007; Crisp, 2007).

Prolactinomas can result in infertility and sexual dysfunction in adults due to the suppression of gonadotrophic hormones. Excessive prolactin suppresses the follicle stimulating hormone and results in a lack of viable ova or sperm. The emotional consequences of sexual dysfunction or infertility are enormous, patients often present with depression (Sobrinho, 1998), and feelings of inadequacy (Pituitary Foundation, 2000). Changes in levels of sexual activity (reduction or absence) may lead to relationship problems (Pituitary Foundation, 2006) which in turn may lead to depression (Ezzat, 1992).

Large pituitary tumours, which are either functioning or non-functioning, can result in mass effects on the surrounding structures. The most frequently diagnosed mass effect is a reduction

in the visual fields, caused by occlusion of the optic chiasm. The effects of the occlusion can range from partial loss of colour vision, to complete loss of vision. It would be reasonable to expect the degree of distress suffered by the patient, to be directly related to the degree of loss of vision, with those people effected by gross vision loss to be most susceptible to depression. Fitzgerald and Parkes (1998) reported that when people within the general population suffered loss of vision they reacted with fear, frustration and grief, and that 85% developed persistent clinical depression.

General symptoms of pituitary tumours, such as headaches, poor sleep, and fatigue can also increase the risk of anxiety and depression due to general feelings of ill health and lethargy. Many pituitary tumours result in a reduction in participation of activities of daily living and employment due to fatigue, according to Frese and Mohr (1987) unemployment leads to depression, reduced hope and financial problems. Overall, the emotional costs of living with an untreated pituitary tumour are great, failure to treat may result not only in poor physical health, but also in poor emotional and mental health.

2.1.3 Why is it important that treatments to remove pituitary tumours do not have a negative effect on psychosocial functioning?

Pituitary tumours are not considered to be acutely life threatening (they are rarely metastatic), but if untreated they increase long-term mortality (Clayton & Wass, 1997). Pituitary tumours are usually removed in order to restore normal hormonal functioning, that is to prevent over production of hormones, or to treat underproduction of hormones, and to relieve the pressure symptoms of the tumour on adjacent structures (Guinan et al., 1998). Patients who have received

surgery to remove pituitary tumours have a good prognosis, and the treatments are regarded as medically effective (Plowman, 1999). Therefore it is essential that the treatments given to patients with pituitary disease do not impinge on their psychosocial functioning and increase the risk of anxiety or depression because the survival times following surgery are comparable to patients who have never had pituitary disease. If the treatments did result in a poor psychosocial outcome the consultants prescribing the treatments would have to consider this risk when deciding between different interventions.

2.1.4 Review of the previous psychosocial studies

There have been a number of studies which have investigated the effects of surgery for the treatment of pituitary tumours on psychosocial functioning. Those which have used standardised measures of psychosocial functioning are reviewed below. (Please also see footnote).

The majority of the studies were retrospective; only the most recent one by Treece (2005) was prospective. Some of the reviewed studies examined the effects of treatments on psychosocial functioning and neuropsychological functioning (Guinan et al., 1998; Noad et al., 2004; Peace et al., 1997a; Treece et al., 2005). The study by Page et al. (1997) examined psychosocial functioning in patients who had been treated for pituitary disease with the "Gold Standard" treatments. The paper by Peace et al. (1997b) only examined psychosocial functioning, but the

Footnote: See Appendix C.1. for a comprehensive review of the previous studies which investigated psychosocial functioning in patients who had received surgery to remove pituitary adenomas, including details of inclusion and exclusion criteria, surgery, radiotherapy and outcomes in the different groups studied.

sample of patients included in that study seemed to be the same cohort as appeared in their study of cognitive dysfunction following treatments for pituitary disease (Peace et al., 1998).

In a case controlled, retrospective self report study Page et al. (1997) explored psychosocial functioning in patients who had received treatments for the removal of pituitary tumours. They compared pituitary surgery patients (TSA) to control surgery patients (CG-S) on measures of health related quality of life and well-being. The two groups were matched for age and gender. Page et al. (1997) found no significant differences in psychosocial functioning between the patients who had received surgery for pituitary tumours and a matched surgical control group. Page et al. (1997) conducted additional analysis to compare subgroups of pituitary surgery patients to the control group. When comparing patients who had been treated for pituitary disease with the combined "Gold Standard" therapy of TSA followed by conventional three field fractionated radiotherapy (TSA+RT3) to the control group, they found that the pituitary group had a significantly worse General Well Being Schedule (GWBS) total score, and Short Form 36 (SF-36) mental health score than the control group. Page et al. (1997) concluded that there may be an effect of radiotherapy on quality of life in patients treated for pituitary disease, and that further research should be conducted in the area. This was a well designed case controlled study with clear inclusion and exclusion criteria. All pituitary patients in the study received the "Gold Standard" treatments for pituitary disease (see Appendix C.2) as recommended by the Royal College of Physicians (Clayton & Wass, 1997). Standardised measures of psychosocial functioning were utilised. This study influenced the design and the research aims of both the Noad et al. study (2000) and the Treece study (2005).

Peace et al. (1997a) conducted a case controlled retrospective study of psychosocial functioning in patients who had been treated for pituitary tumours. They compared a group of pituitary patients to healthy controls on measures of anxiety and depression. The two groups were matched for gender, age and years of education. The group of patients treated for pituitary disease was very diverse, some had received surgery only, others had received surgery plus radiotherapy and a small number had been treated with medication only (see Appendix C.2). When the pituitary patient group were compared to the healthy control group (CG-H) no significant differences in psychosocial functioning were found. Peace et al. (1997a) concluded that the cognitive deficits that had been observed in the pituitary patients were not related to mood. When Peace et al. (1997a) made comparisons between subsets of pituitary patients they found no significant differences on measures of psychosocial functioning between the different subsets of pituitary patients. This study utilised standardised measures of psychosocial function. Adequate details of surgical treatments received by each patient were recorded so the pituitary group could be divided into subsets. The type of radiotherapy treatments received was not specified, so it is impossible to draw conclusions from this study that would be applicable to modern day practices in the treatment of pituitary tumours. This study added to the research knowledge in this area and provided a basis for further investigations into this patient population.

Another retrospective case controlled study by Peace et al. (1997b) investigated the effects of treatments for pituitary tumours on psychosocial functioning. Peace et al. (1997b) compared three groups of pituitary disease patients to healthy controls on measures of anxiety, depression, social adjustment and health. The control group was comparable to the pituitary groups for gender, age and years of education. The three pituitary groups had received transfrontal surgery,

transsphenoidal surgery, or medication only (Med). More than half of the pituitary surgery patients (TF or TSA) had also received radiotherapy (type not specified, but likely to be mixed between RT2 and RT3, and possibly RT1). A relative or friend of each pituitary patient also completed questionnaires relating to the patients' social adjustment. Peace et al. (1997b) found the TSA group and the Med group rated themselves as being more depressed, anxious and having poorer social adjustment, than the TF group or the healthy controls. Close informants rated each pituitary group as having poor social adjustment. Peace et al. (1997b) concluded that the patients who had received TF surgery were unaware of any social difficulties because of lack of insight caused by the invasive frontal surgery, so realistic self-appraisal was unlikely. They noted that the patients with the most serious disease, and greatest mean duration of illness were present in the TF group. Peace et al. (1997b) stated that this highlighted the problems of using self report measures with certain groups of patients. They further suggested that self report measures of mood and health should only be used in conjunction with standardised objective measures or questionnaires completed by close informants. This was a retrospective study, it did not specify the type of radiotherapy received by the pituitary patients. The pituitary group included patients with craniopharyngioma (in the transfrontal group). Craniopharyngioma is not a true pituitary adenoma. It emanates from a structure adjacent to the pituitary gland and it is frequently cancerous, resulting in poor prognosis. Peace et al. (1997b) dismissed the self reports of those patients in the TF group, assuming they lacked insight – without performing further assessments to confirm this. The treatments received by each surgery group were diverse, probably including outdated radiotherapy, there was also a number of confounding factors and therefore the results of this study are of limited value to modern day practices.

In a case controlled retrospective study Guinan et al. (1998) investigated the effects of pituitary tumours and their treatments on psychosocial functioning. They compared five groups of patients who had been treated for pituitary tumours (between 1966 and 1993) to a healthy control group (CG-H). They utilised standardised measures of anxiety, depressions and health related quality of life, (see Appendix C.2). The five treatment groups were; transfrontal surgery with radiotherapy (TF+RT), transsphenoidal surgery with radiotherapy (TSA+RT), transsphenoidal surgery only (TSA), radiotherapy (RT), and bromocriptine (Med). The groups were matched for age and gender. Guinan et al. (1998) found no significant differences between the patients who had been treated for pituitary tumours and the matched control group on any psychosocial measures. This was a large well designed retrospective study, which employed standardised measures of psychosocial functioning, and strict exclusion criteria. Comprehensive details of the treatments received by each pituitary patient were collected to allow them to be divided into groups. Guinan et al. (1998) did not specify the types of radiotherapy received by the pituitary patients. Therefore the relevance to present clinical practice was limited because of the advances in treatments over the past forty years.

Noad et al. (2004) conducted a retrospective study which investigated the effects of treatments for pituitary tumours on psychosocial functioning using measures of mood, health related quality of life and psychological well-being. Two groups of pituitary tumour patients were compared, a surgery only group (TSA) and a surgery plus radiotherapy group (TSA+RT3), on measures of psychosocial functioning. These two treatments are the modern "Gold Standard" treatments for pituitary tumours as recommended by the Royal College of Physicians (Clayton & Wass, 1997). Noad et al. (2004) established that patients who received combined "Gold Standard" therapies

(TSA+RT3) for pituitary tumours reported poorer health related quality of life than patients who had received surgery alone (TSA). There are a number of criticisms regarding the design of this study. It was retrospective, the patients received their treatments up to ten years before recruitment, there was no control group, and pituitary patients with Cushing's disease were excluded. However, this was a pilot study to see if dysfunction could be measured in pituitary patients, and a prospective study (Treece, 2005) followed on from it. The patients compared had received the modern "Gold Standard" treatments and as such the findings of this study were applicable to current medical practices. This study contributed to the evidence base for treatments for pituitary disease.

In a case controlled, multi-centre, prospective study Treece et al. (2005) investigated the effects of treatments for pituitary disease on psychosocial functioning. They compared a group of pituitary patients awaiting surgical removal of pituitary tumours (TSA) to a control group of ENT patients who were awaiting functional endoscopic sinus surgery. Treece et al. (2005) utilised standardised measures of psychosocial functioning to measure anxiety, depression, psychological well-being and health related quality of life. The participants were assessed at three time points, before surgery, three months after surgery and 12 months after surgery. The groups were comparable for age, gender and IQ. Both the pituitary group and the control group received the "Gold Standard" surgical treatments for their respective illnesses. A surgical control group was used to control for the effects of surgery and recovery from anaesthesia. Strict exclusion criteria were enforced. Pituitary patients with adenomas of all aetiologies were included, those patients with craniopharyngioma were excluded. Treece et al. (2005) found significant differences on measures of psychosocial functioning between the pituitary group and the control group before

surgery and at three months after surgery, with the pituitary patients having a poorer level of psychosocial function than the control group. Significant differences were found before surgery on the General Well-Being Schedule with the control group rating themselves as more "well" than the pituitary group ($p<0.05$). On the GHQ28, the pituitary group also rated themselves as having higher levels of social dysfunction than control group ($p<0.01$) before surgery. At three months after surgery the pituitary group were found to be significantly more depressed than the control group on the Hospital Anxiety and Depression Sale (HADS). They also rated themselves as having lower levels of social functioning, and higher levels of limitations within their physical and mental roles than the control group at three months after surgery, these were all significant at <0.05. However, at twelve months after surgery there were no significant differences on any measure of psychosocial functioning between the patients who had received surgery for the removal of pituitary tumours and the surgical control group. This indicated that the psychosocial functioning in the pituitary group had returned to normal levels one year after surgery to remove pituitary tumours. There was a significant difference in the "rate of change in health" between the pituitary group and the control group at one year after surgery; the pituitary patients had noticed a greater improvement in health than the control group in the year following surgery.

A recent study by van Beek et al. (2007) examined psychosocial functioning in patients successfully treated for non functioning pituitary adenomas. They investigated patients who had received surgery (TSA or TF) with or without radiotherapy. They reported that combined therapy (TSA+RT or TF+RT) was not associated with reduced quality of life in patients who had been treated for non functioning pituitary adenomas and were on adequate replacement therapies.

In 1997 the Royal College of Physicians recommended "Gold Standard" treatments for the removal of pituitary tumours (Clayton & Wass, 1997). These were transsphenoidal surgery (TSA) for the removal of tumours, and, if clinically necessary, conventionally fractionated three-field radiotherapy (RT3) to prevent tumour re-growth following surgery (Clayton & Wass, 1998). Due to the retrospective nature of the majority of the studies, more than half of the papers reviewed included patients who had received treatments which are no longer recommended for pituitary tumours, this makes the findings of those papers of little value to the research literature for evidence based medicine. However, the papers have contributed to the overall research debate and have inspired further investigations.

In summary, three studies found significant differences in levels of psychosocial functioning between some sub-groups of patients who had been treated for pituitary tumours and comparable control groups (Page et al., 1997; Peace et al., 1997b; Treece et al., 2005). Three studies found no significant differences in psychosocial functioning between the whole groups of pituitary patients and the control groups (Guinan et al., 1998; Page et al., 1997; Peace et al., 1997a). Two studies found significant differences when they compared psychosocial functioning in pituitary patients who had received different therapies (Noad et al., 2004; Peace et al., 1997b). Two studies found no significant differences in psychosocial functioning when they compared pituitary patients who had received different therapies (Guinan et al., 1998; Peace et al., 1997a). Treece et al. (2005) measured a resolution to normal levels of psychosocial functioning over the 12 month period following pituitary surgery. Van Beek et al. (2007) found no additional deficits in psychosocial functioning in pituitary patients who had received radiotherapy after pituitary surgery.

The research studies which included only those patients who received the "Gold Standard" treatments will be the most useful in informing the debate relating to evidence based medicine, these were; Noad et al., 2004; Page et al., 1997; Treece et al., 2005.

2.1.5 Aim of the study

The long-term effects of the "Gold Standard" treatments for the removal of pituitary tumours (TSA & RT3) on psychosocial functioning has not been studied. It is important to examine the effects of these newly recommended treatments, in case they are found to be just as damaging as the previously used more invasive treatments. It is thought that damaging effects may be expressed at long term after treatment. If this was the case, then there would be serious clinical implications, and the resolution of poor psychosocial functioning which was observed at twelve months after surgery may not be observed at long term follow up.

This long-term outcome study was a follow up of a prospective, multi-centre, case controlled study looking at the effects of surgery for pituitary tumours on psychosocial functioning (Treece, 2005). Patients with pituitary disease and ENT surgical controls had received similar surgery between 1998 and 2002. The pituitary group patients were found to have a significantly poorer level of psychosocial functioning than the control group patients at baseline (before surgery) and at three months after surgery. At 12 months after surgery the observed differences in psychosocial functioning were no longer significant (Treece, 2005). This indicated a resolution of the poor psychosocial functioning which was present before surgery and at three months after surgery. It also indicated that the pituitary surgery caused no decline in psychosocial functioning at 12 months after surgery. The aim of the current study was to investigate whether or not the

normalised level of psychosocial functioning which was observed at twelve months after surgery had been maintained at long-term follow up in the group of patients who had received pituitary surgery.

2.2 METHOD

2.2.1 Design

This was a between groups, repeated measures design.

2.2.2 Participants

Those participants who were in the previous prospective study (Treece, 2005) at 12 months following surgery were assessed for eligibility. Patients who had completed measures of psychosocial functioning at that stage were eligible. Patients' Consultants and GP practices were contacted to confirm survival details, current addresses and telephone details. The surviving, contactable sample were invited to take part in the study.

Both groups had received surgery between 1998 and 2002. The experimental group had received transsphenoidal surgery (TSA) for the removal of a pituitary adenoma. They were recruited prior to surgery from the Nottingham Queen's Medical Centre, and the Oxford Radcliffe Infirmary. The control group had received functional endoscopic sinus surgery (FESS) to correct ENT sinus problems. They were recruited from the Derbyshire Royal Infirmary before surgery. The groups were comparable for age, gender and pre-morbid IQ.

2.2.3 Procedure

COREC approval to recruit patients to this study was granted by Nottingham Research Ethics Committee 1 in August 2006 (see Appendix C.3). Research and Development approval was granted by Nottingham University Hospitals NHS Trust, Oxford Radcliffe Hospitals NHS Trust

and Derby Hospitals Foundation Trust between August 2006 and December 2006 (see Appendix C.4). The University of Birmingham provided sponsorship and indemnity (see Appendix C.5).

Patients were invited to take part in the study by post. They were sent a letter of invitation, two consent forms (one to sign and return, the other to sign and keep for reference), and a patient information sheet (see Appendices C.6, C.7 & C.8). Once the signed consent had been returned to the researcher, the questionnaire packs were sent to the participants for completion and return. Pre-paid self-addressed envelopes were provided for the return of the consent forms and the questionnaires. At the consent stage, patients were asked if they would like to receive the questionnaires by post, or it they would like to answer them verbally. The researcher telephoned those who opted to answer the questionnaires verbally, and the questionnaires were read out to the patient.

The returned questionnaires were checked for missing data. If the questionnaires were incomplete the patient was telephoned and asked if she/he would answer the additional questions. This ensured there were no missing data points in the analysis. Recruitment to the study started in August 2006 and was complete by December 2006. The cut off date for return of the questionnaires was 31st January 2007.

2.2.4 Materials

The battery of psychosocial measures was identical to that used in the previous study (Treece 2005), this allowed for direct comparisons to be made. The psychosocial measures were

presented in a fixed order – Hospital Anxiety and Depression Scale, Short Form Health Questionnaire , General Health Questionnaire, General Well-Being Schedule.

2.2.5 Psychosocial measures

All of the measurements chosen are frequently used in clinical studies and psychosocial research. They are published, validated, reliable, and can be self-administered by the patient. The measures were included to assess mood, health-related quality of life, well-being and inner personal state and psychiatric morbidity. Each of these measurements has been used in previous studies of quality of life in pituitary patients (Noad et al., 2004; Page et al., 1997), Appendix C.9.

2.2.5.1 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) is a 14 item scale, developed to provide a brief state measure of anxiety (7 items) and depression (7 items). It was designed for use in medical out-patient clinics to detect clinical cases of anxiety and depression. The HADS may be used to assess the severity of anxiety and depression, without contamination by reports of physical health (Zigmond & Snaith, 1983). Bjelland et al. (2002) reported high correlation coefficients with other depression measurements (0.62 – 0.73) and anxiety measurements (0.69 – 0.75). The case finding abilities of the HADS were reported as good by Bjelland et al. (2002), with a threshold of 8+ both sensitivity and specificity were in the range 0.70 – 0.90. The HADS is increasingly used in oncology research because of the established lack of effect from physical symptoms (Bowling, 2001).

The patient is requested to rate how she/he has been feeling over the last week. Each item is rated from 0-3, the range for each composite score, anxiety or depression is 0-21, higher scores indicate higher levels of anxiety or depression. This scale generates three possible scores, HADS Anxiety Score (0-21), HADS Depressions Score (0-21) and HADS Total Distress Score (0-42). This study will report all three scores.

2.2.5.2 Short Form Health Questionnaire (SF-36)

The Short Form Health Questionnaire (Ware, Snow, & Kosinski, 1993) is a 36 item scale which is a generic measure of subjective health status, covering both physical and mental health. The SF-36 was developed to be used in population surveys and studies which evaluated the effects of health policy. Its use is frequently recommended as the generic core of disease specific batteries in both the UK and the USA (Ware & Kosinski, 2005).

The following eight dimensions are covered by the SF-36; physical functioning, social functioning, role limitation due to emotional problems, role limitation due to physical problems, mental health, energy/vitality, general health perception, and pain. Items for each of these dimensions are coded, summed and transformed into a scale from 0% (poor health) to 100% (good health). A single item score for change in health over the past year is also obtained.

The eight dimensions listed above are often reported as outcome measures. However, more recently it has become the norm for the results of the SF-36 to be presented as summary scales of physical health status and mental health status, these are known respectively as the Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores (Ware &

Kosinski, 2005). For this study the Physical Component Summary (PCS), the Mental Component Summary (MCS) and the measure in change in health over the last 12 months (CIH) will be reported.

2.2.5.3 General Health Questionnaire 28 (GHQ28)

The General Health Questionnaire 28 (Goldberg, 1978) is a 28-item measure of general psychiatric morbidity. GHQ28 is divided into four sub-scales measuring, severe depression, anxiety and insomnia, social dysfunction and somatic symptoms. It requires patients to rate themselves against their "usual state", with the options typically being "not at all", "no more than usual", "rather more than usual" and "much more than usual".

The GHQ28 was developed as a measure of general psychiatric morbidity, during the 1960s and 70s for use in general practice settings. It is a screening questionnaire to detect verifiable forms of psychiatric illness (Goldberg, 1978b). Updated handbooks are published periodically which contain reviews of applications, reliability and validity studies (Goldberg & Huxley, 1980, Goldberg & Williams, 1988). Bowling (1997) stated that it was probably the most extensively tested scale for reliability, validity and sensitivity to change, with good results. Bowling (2001) also commented that the GHQ28 was the most widely used measure of psychiatric disturbance in the UK, with many international applications. The GHQ28 is frequently used as a comparative measure when validating other measures of psychosocial functioning, Bjelland et al. (2002) used it in their recent validation study of the HADS.

The scoring of the GHQ28 generates four sub-scale scores, which can be combined to give a GHQ28 Total Score. Each sub-scale of the GHQ28 consists of seven questions, each question is scored 0-3. Each sub-scale score can range from 0-21, the GHQ28 Total Score can range from 0-84. A higher score indicates a higher level of distress. This study will utilise the GHQ28 Total Score.

2.2.5.4 General Well Being Schedule

Dupuy developed the General Well Being Schedule (GWBS) for use in the 1971 US Health and Nutritional Examination Survey (HANES) (Dupuy, 1977; Dupy, 1978). It is a multi-dimensional indicator of subjective feelings of well-being and distress. The GWBS is frequently used as a measure of quality of life and outcome of medical care (Hunt & McKenna, 1992), although strictly it is a measure of well-being or inner personal state, rather than a broader measure of quality of life.

The original GWBS was a 68 item measure, but it was reduced to 18 items for use in HANES. The GWBS reflects both positive and negative feelings, without reference to physical symptoms. It includes measures of anxiety, depression, general health, positive well-being, self control and vitality. The present study uses the 18 item version of the GWBS. The patient is requested to rate how they have been feeling over the past month. Each of the first 14 items are rated on a six point scale, the final 4 items use a numbered visual analogue scale ranging from 0 – 10. Lower scores indicate higher levels of distress.

2.2.6 Standardised scoring

All psychosocial measures were scored in accordance with the published guidelines. The demographic data, and psychosocial measure scores were recorded. The data was transferred to SPSS version 15 for analysis of results.

2.2.7 Plan of analysis

The pituitary group and the control group were compared on baseline demographic characteristics. Age and estimated pre-morbid IQ were compared using independent t tests. Gender was compared using Chi Square.

The psychosocial functioning data was analysed to determine whether or not met the assumptions for parametric analysis. Measures of central tendency were observed. Z scores of skewness and kurtosis were calculated. Normality was assessed using Shapiro-Wilk.

A number of patients in each group were lost to follow up. The proportions of loss in each group were unequal, therefore it was necessary to repeat between group analysis of the 12 month outcome data to ensure that the two groups remained equivalent in terms of psychosocial functioning at that point. Comparisons were made using Mann-Whitney U test.

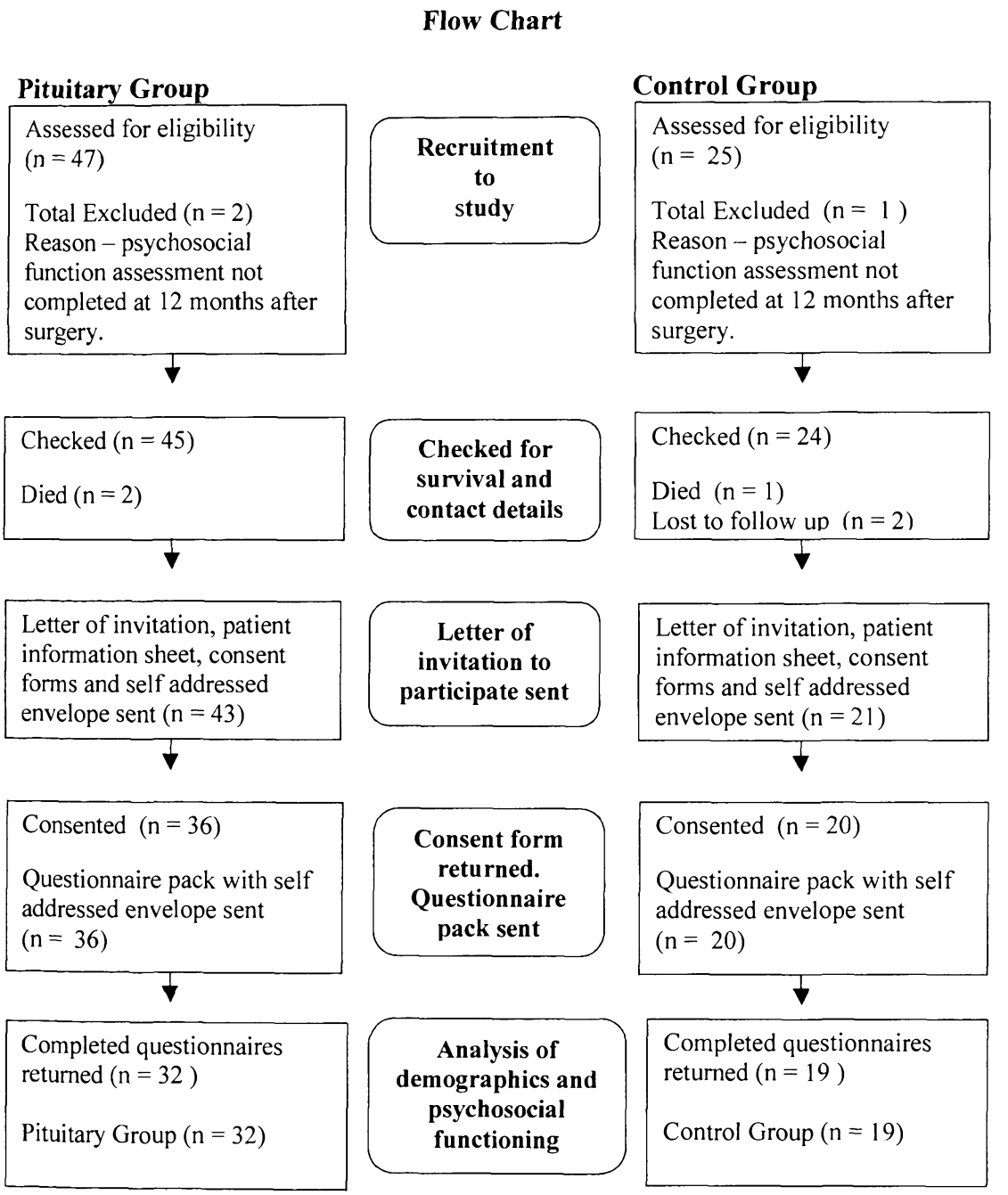
The pituitary surgery group was compared to the control group on tests of psychosocial function at long-term follow up (between 4 years and 7.5 years after surgery). Comparisons were made using Mann-Whitney U test. This was to examine whether or not the improvement in quality of

life, which was measured in the pituitary group at 12 months following surgery, had been maintained.

2.3 RESULTS

2.3.1 Description of the sample

Figure 1.



Forty-seven pituitary surgery patients and twenty-five control group surgery patients were assessed for eligibility for the study. Forty-five from the pituitary group and twenty-four from the control group patients met the criteria, having completed psychosocial assessments twelve months after their surgery. For details of sample recruitment to the study see Figure 1.

Of the participants who met the criteria for inclusion in the study 4.4% of the pituitary group and 12% of the control group were lost to follow up through death or relocation. 15.6% of the pituitary group and 4.2% of the control group did not consent to take part in the study. 8.9% of the pituitary group and 4.2% of the control group did not return the completed questionnaires after consenting to take part in the study. A total of 29% of the pituitary group and 21% of the control group failed to take part in this long-term follow up of the effect of surgery on psychosocial function. Of the sixty-nine participants who were eligible to take part in the study fifty-one participants completed and returned the questionnaires, this is an overall response rate of 74%.

2.3.2 Participant and group characteristics

To determine if there were imbalances between the groups for demographic characteristics, the pituitary surgery group were compared with the control group using t-tests for age and IQ, and χ^2 test for gender (See Tables 1 and 2).

Table 1. Demographic baseline characteristics – age and IQ estimate.

		Pituitary Group (n=32)	Control Group (n=19)	Comparison
Age	Mean	50.56	45.63	t 1.80
	SD	9.88	8.75	df 49
	Min-Max	30-65	27-62	p 0.079
IQ Estimate	Mean	104.06	104.95	t -0.21
	SD	13.33	15.87	df 49
	Min-Max	79-126	70-129	p 0.832

Table 2. Demographic baseline characteristics – gender.

		Pituitary Group (n=32)		Control Group (n=19)		Comparison
Gender		n	%	n	%	
	Men	12	37.5	6	31.6	χ^2 0.18
	Women	20	62.5	13	68.4	p 0.669

There were no significant differences on baseline demographic characteristics between groups.

2.3.3 Tests of normality

All measures of psychosocial functioning were analysed (by group) to determine whether the data met the assumptions for parametric testing (See Appendix C.10). The tests applied for normality were skew, kurtosis and Shapiro-Wilk. Measures of central tendency were observed. Some variables showed a floor effect, while others were multi-modal. The variables were not normal and remained so after transformations. Accordingly non-parametric tests were applied to all the outcome data.

2.3.4 Comparisons between the two surgery groups at 12 months after surgery and at long-term follow up.

The pituitary surgery group and the control surgery group were compared on measures of psychosocial functioning at 12 months after surgery. There were no significant differences between the two groups at this time point, see Table 3. (This confirmed the earlier finding with the full cohort in the prospective study of Treece et al., 2005.)

Comparisons were made between the pituitary surgery group and the control surgery group at long-term follow up. There were no significant differences in psychosocial functioning, see Table 3.

Table 3. Comparisons between groups at 12 months after surgery and at long-term follow up.

Measure	Time	Pituitary Group (n=32)		Control Group (n=19)		U	p
		median	inter-quartile range	median	inter-quartile range		
HAD	12	6.0	4.0-9.0	6.0	4.0-7.0	280	0.638
anxiety	LT	7.0	5.0-8.8	7.0	3.0-8.0	290	0.784
HAD	12	3.5	1.3-6.8	3.0	1.0-6.0	291.5	0.806
depression	LT	3.0	1.0-6.0	2.0	1.0-7.0	293.5	0.836
HAD	12	9.5	6.3-14.8	9.0	6.0-11.0	280	0.639
TOTAL	LT	9.5	6.3-15.8	8.0	5.0-18.0	289.5	0.777
SF-36	12	75.0	50.0-100.0	50.0	50.0– 75.0	225	0.108
CIH	LT	50.0	50.0-75.0	50.0	50.0–50.0	284.0	0.671
SF-36	12	50.7	32.9-56.1	47.9	30.6-53.0	259	0.381
PCS	LT	47.3	34.3-53.9	46.7	34.6-51.6	268	0.483
SF-36	12	53.6	46.1-57.3	55.2	47.4-58.3	267	0.471
MCS	LT	52.1	42.4-56.6	54.6	39.8-59.1	270	0.508
GHQ 28	12	17.0	11.0-23.8	18.0	13.0-21.0	282	0.675
TOTAL	LT	19.0	14.0-29.0	19.0	15.0-32.0	273.5	0.552
GWBS	12	74.5	64.3-90.5	82.0	69.0-87.0	286	0.726
TOTAL	LT	79.0	65.0-89.8	78.0	55.0-89.0	284	0.697

Time 12 = 12 month outcome, LT = Long-term outcome. * = significant at $p<0.05$

There were no significant differences on any measures of psychosocial functioning between the pituitary surgery group and the control group at long-term follow up. This confirms that the resolved levels of psychosocial functioning which were observed at twelve months after surgery had been maintained at long-term follow up.

Footnote For additional analysis please see Appendices C.11 and C.12.
Appendix C.11 Contains within group analysis of psychosocial functioning over time.
Appendix C.12 Contains between group analysis of long-term follow up outcomes in the pituitary surgery group (TSA) and the combined therapy group (TSA+RT3) – which does not appear elsewhere in this thesis.

2.4 DISCUSSION

2.4.1 Summary of findings

This investigation into the long-term outcome of pituitary surgery on psychosocial functioning has shown no detrimental effects. The level of quality of life of pituitary patients has increased over time, from being poorer than a comparable control surgery group at pre surgery, to being not significantly different from it at twelve months after surgery. This was seen as a resolution to normal of a poor level of psychosocial functioning. At between four years and eight years after surgery these patients were examined again in a long-term follow up study. The same measures of psychosocial functioning were utilised so direct comparisons could be made. The psychosocial functioning in the patients who had received surgery for the removal of pituitary tumours, was once again found to be not significantly different from the psychosocial functioning of a comparable control surgery group. This would indicate that the normalised levels of psychosocial functioning which were observed in the pituitary surgery group at twelve months after surgery had been maintained at long term follow up. This also indicated no additional damaging effects of transsphenoidal surgery on psychosocial functioning.

The purpose of this study was to provide some evidence for the proposition that the newly recommended "Gold Standard" treatments for the removal of pituitary tumours do not cause a deterioration in psychosocial functioning long-term after surgery. The purpose was not to demonstrate an improvement in status, but to reconfirm the normalisation of psychosocial functioning (depression, anxiety, general wellbeing, and health related quality of life) which was observed one year after surgery. The normalisation may possibly have been related to the relief of some of the emotional consequences of living with untreated pituitary disease, or the

resolution of the emotional consequences of being diagnosed with a pituitary tumour and the need for neurosurgery. A number of patients who had been diagnosed with Cushing's disease were known to have been "cured" following surgery. One gentleman who had been diagnosed with Acromegaly was memorable because his appearance had normalised greatly by 12 months after surgery, his fatigue had resolved, and he had returned to working full time. Three ladies who had been diagnosed with prolactinomas with mass effects has subsequently conceived following their pituitary surgery. So, the resolution of the symptoms of pituitary disease following surgery to remove pituitary tumours, may contribute to the normalisation of psychosocial functioning due to the relief of the emotional consequences of pituitary disease. Additionally, at long term follow up, patients will no longer be subject to the emotional effects of a diagnosis of pituitary disease or the need for neurosurgery. These perceived threats will have passed, and the (theoretical) associated poor psychosocial functioning should have resolved.

2.4.2 Comparisons with other studies

Investigations into the effects of surgery for pituitary tumours on psychosocial functioning has shown conflicting results (Guinan et al., 1998; Noad et al., 2004; Page et al., 1997; Peace et al., 1997a, Peace et al., 1997b; Treece et al., 2005). Most of the studies were retrospective, and had recruited to the studies between three years (Peace et al., 1997) and thirty years (Guinan et al., 1998) after treatment for the removal of pituitary tumours. The patients in this long-term follow up study received their surgery between 1998 and 2002, which was between four and eight years ago, so these long-term results could be compared to the results of the retrospective studies. The current study found no significant differences in psychosocial functioning between the pituitary surgery group and the control surgery group at long-term follow up. This would appear to be in

agreement with the findings by Page et al. (1998), in the comparison of their whole group of pituitary patients (TSA and TSA+RT3) to their control surgery group. The finding would appear to support similar results from Peace et al. (1997a) and Guinan et al. (1998) who also made comparisons between control groups and groups of mixed therapy pituitary patients, and found no significant differences in psychosocial function.

Some retrospective studies found significant differences between subsets of their pituitary tumour group and their control groups (Page et al., 1998; Peace et al., 1997b). Other retrospective studies found significant differences in psychosocial functioning between alternative subsets of pituitary patients (Noad et al., 2004; Peace et al., 1997b). The current investigation into the effects of surgery for the removal of pituitary tumours has not included patients who have received therapies other than transsphenoidal surgery. This makes it impossible to compare the results to those studies which examine subsets of pituitary patients.

Johnson et al. (2003) examined psychosocial functioning in newly diagnosed pituitary patients of all different aetiologies. It was a prospective study and found poor psychosocial functioning in each subgroup of pituitary patients, and in the sample as a whole. The cohort of patients in this current long-term follow up study, was examined on tests of psychosocial functioning before surgery. These results can be used as a basis for comparison. Like Johnson et al. (2003), Treece et al. (2003) found deficits in the levels of psychosocial functioning before the pituitary patients had received their surgical treatment. However they found no significant differences between patients with different pituitary aetiology after covarying for tumour type, or size (Treece et al., 2003).

2.4.3 Strengths and limitations of the study

This study was well designed. Its strength came from the fact that it was a long-term follow up of a prospective, case controlled, multi-centre investigation. The pituitary group and the control group of patients were from the same background population, so any effects of wealth or employment were controlled for. All patients, both pituitary and control, had received surgery between 1998 and 2002, so the effects of anaesthesia and recovery from surgical intervention were controlled for. The groups were comparable on demographic measures (age, gender and pre-morbid IQ), so could be fairly compared on measures of function. Also analysis of the twelve month data was repeated at long-term follow up because there had been a differential drop out rate between groups. This new analysis only included those patients who completed long-term follow up assessments. The groups were confirmed as being not significantly different on measures of psychosocial functioning at 12 months after surgery. Both groups of patients in this study had received the "Gold Standard" surgical treatments, this means the results from this study will add to the research literature base, and will be relevant to current medical treatments.

It is recognised that the study also has a number of limitations. Ideally this study would have had more participants in each group; there were 32 participants in the pituitary surgery group, and 19 in the control group. Larger groups would have added to the strength of the study. However, both the pituitary group and the control group were true clinical samples, a control group of convenience was not used, unlike many retrospective studies. For post hoc power analysis see Appendix C.13. There was a differential drop out rate between the groups, with 29% of the pituitary group and 21% of the control group failing to fully partake in the follow up study. The reason for this may have been that only those people who had a positive level of psychosocial

functioning agreed to take part in the study. It is possible that the lower response rate in the pituitary group was due to negative effects of pituitary surgery, or continuing pituitary disease – those patients who were still feeling unwell may have felt unable to take part in effortful form filling.

It is not possible to tell whether or not the patients who did not consent to take part in the study were suffering from adverse effects of pituitary disease or surgery, or poor psychosocial functioning.

In many instances there was a dialogue between the participants who consented to the study and the researcher (this was a long term follow up study and the researcher had met each of the participants on three previous occasions). Consented participants who were delayed in returning the completed forms were contacted by telephone, many of them informed the researcher of their current status. Other patients attached notes or letters to their completed questionnaires, and others contacted the researcher directly by telephone. Some patients who had been treated for pituitary disease reported feeling very well, three ladies reported having given birth to healthy babies since their pituitary surgery and were very pleased with their own progress. Two patients reported resolution of their visual deficits, although one failed to return his questionnaire, stating that he was so well now that he did not think the questionnaires applied to him. Other patients, who returned questionnaires, reported additional difficulties related to their pituitary disease, with the continuing need for replacement therapies, or the need for further surgery or radiotherapy. Many patients reported feeling fatigued. Some participants from the control group reported continuing difficulties with sinus problems, others reported feeling very well. Participants from

both groups reported negative life events, one lady had lost her daughter in an accident, a gentleman was caring for his wife who had suffered a stroke, three people had become separated from their partners, two people had been diagnosed with additional illnesses, and two people had lost their elderly pet dogs. In addition, some participants from both groups reported positive life events, a few people had found new life partners, three people had been promoted to very good jobs, some had started new jobs, and others had additional children. From this anecdotal evidence it could possibly be concluded that overall, responders to this study experienced both positive and negative outcomes to their surgery, both positive and negative life events since their surgery, and that there did not appear to be a bias in the type of responder.

There were a few people in each group who consented to taking part in the study, but who did not return the questionnaires. This may have been a problem with the postal system, as many of the invitation letters and questionnaires packs were sent out during December at a time of high demand on the postal services. This could not be avoided because R&D approval for the Oxford patients was granted mid December 2007. A number of completed questionnaires were lost in the post; a few patients reported completing and posting questionnaires, which did not subsequently arrive. Additionally, there may have been an unconscious "researcher effect" on the size of the groups, which effected the percentage response rate in the control group. The researcher telephoned all participants to remind them to return questionnaires that had not been returned. It is possible that the researcher unconsciously made more effort to contact the control group participants because she was aware that the numbers of returned questionnaires was low in the control group.

While recognising the strengths and limitations of this study, it is important to say that this result is encouraging for those patients who have received transsphenoidal surgery for the removal of pituitary tumours. It will add to the research literature and the evidence base relating to the "Gold Standard" treatments for the removal of pituitary tumours.

2.4.4 Clinical implications

Psychosocial functioning in patients who have had pituitary tumours removed surgically appears to be no different to a matched surgical control group at long term follow up. This confirms the 12 months after surgery results.

Currently pituitary surgery is considered successful if the tumour is removed (or debulked), and the hormonal status is stabilised - with replacements if necessary (Plowman, 1999). The burden of the disease and the risks of treatment need to be considered. (The burden of disease was discussed in section 2.1.) Patients are informed of the risks prior to consenting to the surgery. There is a risk of damage to the optic chiasm during surgery, because the surgical instruments are manipulated within the immediate vicinity of the chiasm and accidental occlusion or severing could occur. There is a risk of post operative infection, and CSF leak following the operation, because the meninges are disturbed during the operation. There is a risk of damage to the pituitary gland during surgery which may lead to hypopituitarism or diabetes insipidus following surgery. In addition to these there is the risk of adverse reaction to anaesthetic which accompanies any surgical operation which requires a general anaesthetic. If it had been shown that there was also a risk of depression, anxiety, or poor psychological well-being following

surgery then this additional risk would need to be considered and evaluated before treatment was offered by the consultant, and before the risk was accepted by the patient.

Patients with pituitary disease are thought to be at an increased risk of developing anxiety or depression (Kelly, 1996; Sonino et al., 1998) because of the detrimental effects of hormonal disruption, and additional physical symptoms of pituitary disease. The surgical removal of pituitary tumours is performed in order to relieve these symptoms. Following their study of patients who had just been diagnosed with pituitary disease, Johnson et al (2003) stated that additional services may need to be offered to patients with untreated pituitary tumours, the services suggested included psychiatric evaluation or psychological counselling. However, Korali et al (2003) found no evidence for an increased risk of "mental disorders" in patients with treated or untreated pituitary tumours. Treece (2005) found poor psychosocial functioning prior to surgery and at three months after surgery, but no evidence was found at 12 months after surgery or at long term follow up. Therefore the clinical implications of this current study would appear to point to fewer psychological or psychiatric interventions being necessary following surgical removal of pituitary tumours, with a resolution to a normal level of functioning being maintained at long term after surgery.

Patients with chronic illnesses use a large proportion of National Health Services resources, this is partially because they present at their General Practitioners frequently with queries regarding their illness and require reassurance as well as medication. If in addition to the chronic illness, the patient develops anxiety or depression, the frequency of GP attendance may increase, with a corresponding additional burden on resources and requirement for further treatment. If a surgical

intervention for a chronic illness can reduce either the need for frequent follow up appointments with a hospital consultant or a general practitioner, and reduce the necessity for psychiatric or psychological interventions, then this will result in an overall cost saving to the NHS. Additionally this will result in an improvement in physical health and overall quality of life of the patient which may include improved mood or reduced distress.

2.5 CONCLUSION

The normalisation of psychosocial functioning which was observed at one year after TSA surgery, has been maintained at long term follow up in patients treated for pituitary tumours.

The quantity of research into the long-term effects of pituitary tumours and their treatment is gradually growing. The research literature is being added to as I draw these conclusions (van Beek et al., 2007). Other studies have been proposed, and may be approaching publication. Guinan et al's concluding comments (1998) mentioned a prospective study of newly-diagnosed patients who were going to be assessed before and after surgical and radiotherapy interventions. The quality of research is also improving, with prospective studies becoming the required standard. There is recent prospective evidence to suggest poor psychosocial functioning in pituitary disease patients at the point of diagnosis (Johnson et al., 2003), and prior to surgical interventions (Treece et al., 2003). The current investigation would appear to show that poor psychosocial functioning may have resolved at long-term follow up. This long-term follow up study of the effects of pituitary surgery on psychosocial functioning will contribute towards the research literature, and the evidence base for "Gold Standard" treatments for pituitary tumours. However, it is recognised that this follow up study was relatively small. Further large scale prospective studies are required to fully evaluate "Gold Standard" treatments for pituitary tumours.

In conclusion, it would appear that transsphenoidal surgery to remove pituitary tumours is not detrimental to psychosocial functioning at 12 months after surgery or at long term follow up.

2.6 REFERENCES

Ansseau, M., Fischler, B., Dierick, M., Albert, A., Leyman, S., & Mignon, A. (2007). Socioeconomic correlates of generalized anxiety disorder and major depression in primary care: The GADIS II study (Generalized Anxiety and Depression Impact Survey II). *Depression and Anxiety, 26,* 15-20.

Armstrong, C.L., Hunter, J.V., Ledakis, G.E., Cohen. B., Talent. E.M., Godlstein, B.H., Tochner, Z., Lustig, R., Judy, K.D., Pruitt. A., Mollman, J.E., Stanczak, E.M., Jo, M.Y., Than, T.L., & Phillips, P. (2002). Late cognitive and radiographic changes related to radiotherapy. Initial prospective findings. *Neurology, 59*, 40-48.

Asadi-Lari, M., Tambruini, M., & Gray D. (2004). Patients' needs, satisfaction, and health related quality of life: Towards a comprehensive model. *Health and Quality of Life Outcomes, 2,* 32-47.

Beck, A.T., Rush, A.J., Shaw, B.F., & Emery, G. (1979). *Cognitive therapy of depression.* New York: Guilford Press.

van Beek, A.P., van den Bergh, A.C.M., van den Berg, L.M., van den Berg, G., Keers, J.C., Langendijk, J.A., & Wolffenbuttel, B.H. (2007). Radiotherapy is not associated with reduced quality of life and cognitive function in patients treated for nonfunctioning pituitary adenoma. *International Journal of Radiation Oncology Biology and Physics, 68,* 986-991.

Bjelland, I., Dahl, A.A., Haug, T.T., & Neckelmann, D. (2002). The validity of the hospital anxiety and depression scale: An updated literature review. *Journal of Psychosomatic Research, 52,* 69-77.

Biermasz, N.R., van Thiel, S.W., Pereira, A.M., Hoftijer, H.C, van Hermet, A.M., Smit, J.W.A., Romijn, J.A., & Roelfsema, F. (2004). Decreased quality of life in patients with acromegaly despite long-term cure of growth hormone excess. *The Journal of Clinical Endocrinology & Metabolism, 89,* 5369-5376.

Bowling, A. (1997). *Measuring Health. A review of quality of life measurement scales* (2nd ed.). Buckingham: Open University Press.

Bowling, A. (2001). *Measuring Disease. A review of disease specific quality of life measurement scales* (2nd ed.). Buckingham: Open University Press.

Brada, M., Rajan, B., Traish, D., Ashley, S., Holmes-Sellors, P.J., Nussey, S., & Uttley, D. (1993). The long term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clinical Endocrinology, 38,* 571-578.

Burman, P., Broman, J.E., Hetta, J., Wiklund, I., Erfurth, E.M., Hagg, E., & Karlsson, F.A. (1995). Quality of life in adults with growth hormone (GH) deficiency: Response to treatment

with recombinant human GH in a placebo-controlled 21 month trial. *Journal of Clinical Endocrinology and Metabolism, 80,* 3585-3590.

Burman, P., & Deijen, J.B. (1998). Quality of life and cognitive function in patients with pituitary insufficiency. *Psychotherapy and Psychosomatics. 67,* 154-67.

Cohen, D.L., Becan, J.S., & Adams, C.B.T. (1989). The presentation and management of pituitary tumours in the elderly. *Age and Ageing, 18,* 247-52.

Ciccarelli, A., Guera, E., de Rosa, M., & Milone, F. (2005). PRL secreting adenomas in male patients. *Pituitary, 8,* 39.

Clayton, R.N., & Wass, J.A.H. (1997). Pituitary Tumours. Recommendations for service provision and guidelines for management of patients. Consensus statement of a working party. *Journal of the Royal College of Physicians of London, 31*, 628-636.

Clayton, R.N., & Wass, J.A.H. (1998). Pituitary Tumours. Recommendations for service provision and guidelines for management of patients. *British Journal of Neurosurgery, 12,* 285-7.

Cooper, P., Osborn, M., Gath, D., & Feggetter, G. (1982). Evaluation of a modified self-report measure of social adjustment. *British Journal of Psychiatry, 141,* 68-75.
Crawford, J.R., Parker, D.M., & McKinlay, W.W. (1992). *A handbook of neuropsychological assessments*. Hove: Lawrence Erlbaum Ltd.

Crisp, R. (2007). Depression and occupational disability in five diagnostic groups: a review of recent research. *Disability and Rehabilitation, 29,* 267-279.

Cushing, H. (1913). Psychic disturbances associated with disorders of the ductless glands. *American Journal of Insanity, 69,* 965-990.

Dean, H.J., McTaggart, T.L., Fish, D.G., & Friesen, H.G. (1985). The educational, vocational and marital status of growth hormone deficient adults treated with growth hormone during childhood. *American Disabled Child, 139*, 1105-1110.

Degerbald, M., Almkvist, O., Grunditz, R., Hall, K., Kaiser, L., Knutsson, E., Ringertz, H., & Thoren, M. (1990). Physical and physiological capabilities during substitution therapy with recombitant growth hormone in adults with growth hormone deficiency. *Acta Endocrinologica, 123,* 185-193.

Deijen, J.B., de Boer, H., Blok, G.J., & van der Veen, E.A. (1996). Cognitive impairments and mood disturbances in growth hormone deficient men. *Psychoneuroendocrinology, 21,* 313-322.

Dekkers, O.M., van der Klaauw, A.A., Pereira, A.M., Biermasz, N.R., Honkoop, P.J., Roelfsema, F., Smit, J.W.A., & Romijn, J.A. (2006). Quality of life is decreased after treatment

for nonfunctioning pituitary macroadenoma. *Journal of Clinical Endocrinology & Metabolism, 91,* 3364-3369.

Dorn, L.D., Burgess, E.S., Friedman, T.C., Dubbert, B., Gold, P.W., & Chrousos, G.P. (1997). The longitudinal course of psychopathology in Cushing's syndrome after correction of hypercortisolism. *Journal of Clinical Endocrinology and Metabolism, 82,* 912-919.

Dupuy, H.J. (1977). The general well-being schedule. In N. McDowel (Ed.), (1996) *Measuring health: A guide to rating scales and questionnaires.* (2nd ed.). Oxford: Oxford University Press.

Dupuy, H.J. (1978). *Self representations of general psychological well-being of American adults.* Paper presented at the meeting of the American Public Health Association, Los Angeles, CA.

Ezzat, S. (1992). Living with acromegaly. *Endocrinology Metabolism North America, 21,* 753-760.

Faul, F., & Erdfelder, E. (1992). *GPOWER. A priori, post-hoc, and compromise power analysis for MS-DOS (computer program).* Bonn: Bonn University, Department of Psychology.

Fayers, P., & Hays, R. (Eds). 2005. *Assessing quality of life in clinical trials* (2nd ed.). Oxford: Oxford University Press.

Fekkes, M., Pijpers, F.I.M., Fredriks, A.M., Vogels, T. and Verloove-Vanhorick, S.P. (2006) Do bullied children get ill, or do ill children get bullied? A prospective cohort study on the relationship between bullying and health-related symptoms. *Pediatrics, 117,* 1568-1574.

Feeny, D. (2005). Preferenced-based measures: utility and quality-adjusted life years. In P Fayers and R Hays (Eds.). *Assessing Quality of Life in Clinical Trials* (pp. 405-429). (2nd ed.). Oxford: Oxford University Press.

Fitzgerald, R.G. & Parkes, M. (1998). Coping with loss: Blindness and loss of other sensory and cognitive functions. *BMJ, 316,* 1160-1163.

Frese, M., & Mohr, G. (1987). Prolonged unemployment and depression in older workers: a longitudinal study of intervening variables. *Social Science and Medicine, 25,* 173-178.

Furman, K., & Ezzat, S. (1998). Psychological features of acromegaly. *Psychotherapy and Psychosomatics, 67,* 147-153.

Goldberg, D.P., (1978). *The General Health Questionnaire.* Windsor: NFER-Nelson.

Goldberg, D.P., (1978b). *Manual of the General Health Questionnaire.* Windsor: NFER-Nelson.

Goldberg, D.P., & Huxley, P. (1980). *Mental illness in the community: the pathway to psychiatric care.* London: Tavistock.

Goldberg, D.P., & Williams P. (1988). *A users guide to the general health questionnaire.* Windsor: NFER-Nelson.

Guinan, E.M., Lowy, C., Stanhope, N., Lewis, P.D.R., & Kepelman, M.D. (1998). Cognitive effects of pituitary tumours and their treatments: two case studies and an investigation of 90 patients. *Journal of Neurology, Neurosurgery and Psychiatry, 65,* 870-876.

Haskett, R.F. (1985). Diagnostic categorisation of psychiatric disturbance in Cushing's syndrome. *American Journal of Psychiatry, 142,* 911-916.

Heald, A.H., Ghosh, S., Bray, S., Gibson, C., Anderson, S.G., Buckler, H., & Fowler, H.L. (2004). Long-term negative impact on quality of life in patients with successfully treated Cushing's disease. *Clinical Endocrinology, 61,* 458-465.

Hutler, B., & Lundberg, P.O. (1994). Sexual function in women with hypothalmo-pituitary disorders. *Archives of Sexual Behaviour, 23,* 171-183.

Hunt, S., McKenna, S.P., McEwen, J., Williams, J., & Papp, E. (1981). The Nottingham health profile; Subjective health status and medical consultations. *Social Science and Medicine, 15A,* 221-229.

Hunt, S.M., & McKenna, S.P. (1992). British adaptation of the general well-being index: a new tool for clinical research. *British Journal of Medical Economics, 2,* 49-60.

Jeffcoate, W.J., Birch, C.R. (1986). Apoplexy in small pituitary tumours. *Journal of Neurology, Neurosurgery, and Psychiatry. 49,* 1077-1078.

Jeffcoate, W.J., Silverstone, J.T., Edwards, C.R.W., & Besser, G.M. (1979). Psychiatric manifestations of Cushing's syndrome: Response to lowering of plasma cortisol. *Quarterly Journal of Medicine, 48,* 465-472.

Jenkinson, C., Coulter, A., & Wright, L. (1993). Short Form 36 (SF-36) health survey questionnaire:normative data for adults of working age. *British Medical Journal, 306,* 1437-1440.

Johnson, M.D., Woodburn, C.J., & Vance, M.L. (2003). Quality of life in patients with pituitary adenoma. *Pituitary, 6,* 81-87.

Kelly, W.F., Kelly, M.J., & Faragher, B. (1996). A prospective study of psychiatric and psychological aspects of Cushing's syndrome. *Clinical Endocrinology, 45,* 715-720.

Korali, Z., Wittchen, H.U., Pfister, H., Hofler, M., Oefelein, W., & Stalla, G.K. (2003). Are patients with pituitary adenomas at an increased risk of mental disorders? *Acta Psychiatrica Scandinavica, 107,* 60-68.

Laws, E.R.(Jr.), & Thapar, K. (1995). Surgical management of pituitary adenomas. *Bailliere's Clinical Endocrinology and Metabolism, 9,* 391-405

Lynch, S., Merson, S., Beshya, S.A., Skinner, E., Sharp, P., Priest, R.G., & Johnston, D.G. (1994). Psychiatric morbidity in adults with hypopituitarism. *Journal of the Royal Society of Medicine, 87,* 445-447.

Mazet, P., Simon, D., Luton, J,P., & Bricaire, H. (1988). Syndrome de Cushing; Symptomatologie psychique et personalite de 50 malades. *Nouv Presse Med., 10,* 2565-2570.

McCord, M.W., Buatti, J.M., Fennell, E.M., Mendenhall, W.M., Marcus, R.B., Rhoton, A.L., Grant, M.B., & Friedman, W.A. (1997). Radiotherapy for pituitary adenoma: long-term outcome and sequelae. *International Journal of Radiation, Oncology, Biology and Physics, 39,* 437-444.

McDowell, I., & Newell, C. (1987). *Measuring health – A guide to rating scales and questionnaires.* Oxford: Oxford University Press.

McGauley, G.A. (1989). Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. *Acta Paediatrica Scandanavica, 356(suppl),* 70-72.

McMillan, C.V., Bradley, C., Gibney, J., Healy, M.L., Russell-Jones, D.L., & Sonksen, P.H. (2003). Psychological effects of withdrawal of growth hormone therapy from adults with growth hormone deficiency. *Clinical Endocrinology, 59,* 467-475.

Meyers, C. (1998). Neurobehavioural functioning in adults with pituitary disease. *Psychotherapy and Psychosomatics, 67,* 168-172.

Noad, R.F. (2000). *The effect of radiotherapy as treatment for pituitary tumours on cognitive function and quality of life.* Unpublished thesis, submitted to the University of Nottingham, for the degree of Master of Philosophy.

Noad, R.F., Narayanan, K.R., Howlett, T., Lincoln, N.B., & Page, R.C.L. (2004). Evaluation of the effect of radiotherapy for pituitary tumours on cognitive function and quality of life. *Clinical Oncology, 16,* 233-237.

Page, R.C.L, Hammersley, M.S., Burke, C.W., & Wass, J.A.H. (1997). An account of the quality of life of patients after treatment for non-functioning pituitary tumours. *Clinical Endocrinology, 46,* 401-406.

Peace, K.A., Orme, S.M., Thompson, A.R., Padayatty, S.J, Ellis, A.W., Belchetz, P.E. (1997a). Cognitive dysfunction in patients treated for pituitary tumours. *Journal of Clinical and Experimental Neuropsychology, 19,* 1-6.

Peace, K.A., Orme, S.M., Sebastian, J.P., Thompson, A.R., Barnes, S., Ellis, A., & Belchetz, P.E. (1997b). The effect of treatment variables on mood and social adjustment in adult patients with pituitary disease. *Clinical Endocrinology, 46,* 445-450.

Peace, K.A., Orme, S.M., Padayatty, S.J., Godfrey, H.P.D, & Belchetz, P.E. (1998). Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transsphenoidal surgery or medication. *Clinical Endocrinology, 48,* 391-396.

Pituitary Foundation. (2006). *Fact file for medical professionals.* Accessed 10th January 2007, from www.pituitary.org.uk/content/view/53/ Author
Plowman, P.N. (1999). Pituitary adenoma radiotherapy – when, who and how? A Review. *Clinical Endocrinology, 51,* 265-271.

Richert, S., Eversmann, T., & Fahlbush, R. (1983). Psychopathology, mental functions and personality in patients with acromegaly. *Acta Endocrinologica, 253 (suppl).*

Rikken, B., van Bussbacht, J., le Cessie, S., Manten, W., Spermon, T., Grobbee, R., Wit, J.M. and the Dutch Growth Hormone Working Group. (1995). Impaired social status of growth hormone deficient adults as compared to controls with short or normal stature. *Clinical Endocrinology, 43,* 205-211.

Rosen, T., Wiren, L., Wilhelmsen, L., Wiklund, I., & Bengtsson, B.A. (1994). Decreased psychological well-being in adult patients with growth hormone deficiency. *Clinical Endocrinology, 40,* 111-116.

Rothchild, E. (1985). Psychologic aspects of galactorrhea. *Journal of Psychosomatics, Obstetrics and Gynaecology, 4,* 185-196.

Royal College of Physicians. (1977) Consensus statement of a working party. Recommendation for service provision and guidelines for management of patients. London: Author.

Rowles, S.V., Prieto, L., Badia, X., Shalet, S.M., Webb, S.M., & Trainer, P.J. (2005). Quality of life (QOL) in patients with acromegaly is severely impaired: use of a novel measure of QOL: acromegaly quality of life questionnaire. *Journal of Clinical Endocrinology and Metabolism, 90,* 3337-3341.

Shin, D.C., Johnson, D.M. (1978). Avowed happiness as an overall assessment of quality of life. *Social Indicators Research, 5,* 475-492.

Sobrinho, L.G. (1998). Emotional aspects of hyperprolactinaemia. *Psychotherapy and Psychosomatics, 67,* 133-139.

Sonino, N., & Fava, G.A. (1998). Psychosomatic aspects of Cushing's disease. *Psychotherapy and Psychosomatics, 67,* 140-146.

Sonino, N., Fava, G.A., Belluardo, P., Girelli, M.E., & Boscaro, M. (1993). Course of depression in Cushing's syndrome: Response to treatment and comparison with Grave's disease. *Hormone Research, 39,* 202-206.

Sonino, N., Scarpa, E., Paoletta, A., Fallo, F., & Boscaro, M. (1999). Slow release lanreotide treatment in acromegaly: quality of life. *Psychotherapy and Psychosomatics, 68,* 165-167.

Sonino, N., Bonnini, S., Boscaro, M., & Fava, G.A. (2006). Personality characteristics and quality of life in patients treated for Cushing's syndrome. *Clinical Endocrinology, 64,* 314-318.

Spielberger, D.C. (1983). *Manual for the State-Trait Anxiety Inventory.* Palo Alto CA.: Consulting Psychologists Press.

Starkman, M.N., Schteingart, D.E., & Schork, M.A. (1986). Cushing's syndrome after treatment. *Psychiatry Research, 17,* 177-178.

Swerdloff, R.S., & Wang, C. (1998). Influence of pituitary disease on sexual development and functioning. *Psychotherapy and Psychosomatics, 67,* 173-180.

Takano, K., Tanaka, T., Saito, T., and the Committee for the study group of adult GH deficiency. (1994). Psychosocial adjustment in a large cohort of adults with growth hormone deficiency treated with growth hormone in childhood. *Acta Paediartrica Scandanavica, 399 (suppl),* 16-19.

Treece, K.A. (2005). *The effects of treatments for pituitary tumours on cognitive function and quality of life. A prospective study.* Unpublished thesis submitted to the University of Nottingham for the degree of Master of Philosophy.

Treece, K.A., Narayanan, K., Wass, J., Karavitaki, N., Parker, D., Howlett ,T., Quinton, R., & Page, R. (2005). A prospective follow-up study of cognitive function in patients with pituitary tumours requiring surgery. *Endocrine Abstracts, 10,* 52.

Treece, K.A., Page, R.C.L, Wass J.A.H, & Lincoln, N.B. (2003). The effect of pituitary tumours on cognitive function. A prospective study. Presentation of baseline results. *European Congress of Endocrinology Abstracts, 6,* 157.

Treece, K.A., Wass, J.A.H., Lincoln, N.B., & Page, R.C.L. (2004). The effects of pituitary tumours on cognitive function. *Endocrine Abstracts, 7,* 115.

Turner, H.E., Wass, J.A.H. (2000). Modern approaches to treating acromegaly. *Quarterly Journal of Medicine, 93,* 1-6.

Wade, D.T. (1992). *Measurement in neurological rehabilitation.* Oxford: Oxford University Press, Oxford Medical Publications.

Van der Wal, M.F., de Wit, C.A.M., & Hirasing, R.A. (2003). *Psychosocial health among young victims and offenders of direct and indirect bullying. Pediatrics, 111,* 1312-1317.

Ware, J.E., Snow, K.K., Kosinski, M., & Gandek, B. (1993). *SF-36 Health Survey: Manual and Interpretation Guide.* Boston MA.: The Health Institute, New England Medical Centre.

Ware, J.E, & Kosinski, M.A. (2005). *SF-36 Physical and mental health summary scales: A manual for users of version 1.* (2nd ed.). Lincoln RI.: Quality Metric Incorporated.

Whitehead, H.M., Boreham, C., McIlrath, E.M., Sheridan, B., Kennedy, L., Atkinson, A.B., & Hadden, D.R. (1992). Growth hormone treatment in adults with growth hormone deficiency: Results of a 13 month placebo controlled cross-over study. *Clinical Endocrinology, 36,* 45-52.

World Health Organisation. (1948) Constitution of the World Health Organisation. WHO Basic Documents. Geneva.

Zigmond, A.S., & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67,* 361-370.

Executive Summary – Briefing Document **Appendix A**

Long-term outcomes of psychosocial functioning in patients treated for pituitary disease with surgery.

Introduction

This was a long-term follow-up study, investigating psychosocial functioning in patients who had received surgery for the removal of pituitary adenoma.

It followed a prospective, case controlled study which investigated the effect of therapy for pituitary tumours (Treece, 2005). Two groups of patients were recruited to the study; pituitary disease patients, and sinus surgery patients (the control group). Participants were recruited between 1998 and 2002. Outcome assessments were completed by October 2003. All pituitary disease patients were recruited prior to surgery for the removal of a pituitary tumour. All sinus surgery patients were recruited prior to corrective sinus surgery. Each participant in the study underwent assessments of cognitive function and quality of life. Assessments were conducted pre-surgery (baseline), three months post-surgery and twelve months post-surgery. This methodology allowed for comparisons to be made between pituitary tumour patients as a group and normal controls (who underwent a similar surgical procedure), pre surgery (baseline), 3 months after surgery and 12 months after surgery.

The prospective study (Treece, 2005) demonstrated no significant differences in cognitive functioning in the areas of language, intellectual function, executive function, attention and concentration, between patients who received treatment for pituitary tumours and a matched

control group. Patients with pituitary disease demonstrated poorer cognitive function on a limited number of measures of memory and visuo-spatial functioning. These differences were demonstrated both prior to surgery and after surgery, and it is possible that these differences were a result of the disease process and not any treatment received.

Significant differences were however noted between the pituitary group and the control group in psychosocial functioning at pre-surgery and three months after surgery, with the pituitary patients reporting a poorer overall quality of life. There were no significant differences in health, mood, well-being or quality of life between the pituitary group patients and the control group patients 12 months after surgery.

It would appear that the patients who received surgery to remove a pituitary tumour had experienced an improvement in their quality of life when compared to a control group of patients who had undergone a similar surgical procedure. The reduction in quality of life which had been observed before, and at three months after surgery, had resolved by twelve months after surgery. A long-term follow-up study was proposed to measure if this normalisation in quality of life in the pituitary patients had been maintained.

Method

Each patient who was in the initial prospective study at the 12 month outcome stage was assessed for eligibility for this follow up study. Those patients who had completed measures of psychosocial functioning at 12 months after surgery, and who were alive and contactable were invited to take part in the study. All pituitary group patients had received transsphenoidal surgery

(TSA) for the removal of a pituitary adenoma, and all control group patients had received functional endoscopic sinus surgery (FESS) to correct sinus difficulties. For this long-term follow up study each participant completed an assessment of psychosocial functioning, on a single occasion. This was a postal questionnaire study. The assessments comprised the Hospital Anxiety and Depression Scale (HADS), the Short Form Health Questionnaire (SF-36), the General Health Questionnaire (GHQ28) and the General Well Being Schedule (GWBS). Ethical and R&D permissions were granted. Recruitment to the study began in August 2006 and was complete by December 2006. All questionnaires were returned by 31st January 2007.

Participants

A total of 43 pituitary group patients were eligible and invited to take part in the study. Thirty-six consented to take part in the study, 32 completed and returned the questionnaires. A total of 21 control group patients were invited to take part in the study, 20 consented to take part in the study, 19 completed and returned the questionnaires.

Results

The pituitary group and the control group were matched for age, gender and estimated IQ ($p>0.05$). No significant differences between the pituitary group and the control group on measures of psychosocial functioning were evident at 12 months after surgery, or at long-term follow up.

When comparisons were made within the pituitary group over time it was found that there was a statistically significant change in reported levels of "Change In Health". The pituitary group

experienced a greater positive change in health in the twelve months after their surgery than they experienced in the twelve months before the long-term outcome study. This finding is not unexpected since pituitary adenomas can cause chronic ill health. In the year following surgery for the removal of an adenoma an increase in subjective feelings of improved health may be expected. While this improved health may be maintained, one would not expect to be able to measure a additional subjective feeling of improvement in health at long-term follow up.

When comparisons were made within the control group over time it was found that there was a statistically significant change on the total score for the GHQ28, a measure of psychiatric morbidity. Additional analysis was conducted to examine this difference and it was found that the control group had statistically significant change in the level of somatic symptoms over time and the levels of anxiety and insomnia. Both of these symptoms were at a higher level at long-term follow up.

Conclusion

It would appear that the normalisation in psychosocial functioning which was measured in the pituitary group at 12 months after their surgery for the removal of a pituitary adenoma had been maintained at long-term follow up.

It is most important that treatment for the removal of a pituitary tumour does not cause a decline in psychological functioning. Patients who have received these treatments have a good medical prognosis, the received treatments should prolong their life-span. Most pituitary tumours are regarded as benign adenomas and are removed in order to restore normal pituitary hormonal

function, or to relieve the mass effects the tumour is exerting on other nearby structures. If the surgery to remove a pituitary tumour caused a significant decline in either neuropsychological functioning or psychosocial functioning, then this would be of great concern because the patient would then have to live with the consequences for an extended period of time. The pituitary surgery patients examined by this study showed a resolution of their poor psychosocial functioning at twelve months after their surgery, this study showed that normalisation was maintained at long-term follow up.

Appendix to the Review Paper **Appendix B**

Appendix B.1

Table 4. Neuropsychological assessments used to measure domain specific deficits.

Cognition	Title of Assessment
Intellectual Function	National Adult Reading Test
Intellectual Function	Wechsler Adult Intelligence Scale (Revised)
Intellectual Function	Block Design Sub-test
Intellectual Function	Digit Span Sub-test
Executive Function	Controlled Oral Word Association Test – FAS test
Executive Function	Stroop Neuropsychological Screening Test
Executive Function	Symbol Digit Modalities Test
Executive Function	Modified Card Sorting Test
Executive Function	Cognitive Estimates
Executive Function	Army Individual Battery – Trail Making Test
Memory Function	Wechsler Memory Scale
Non Verbal Memory	Visual Reproduction
Verbal Memory	Logical Memory - Story
Verbal Memory & Recall	Adult Memory & Information Processing Battery - Story
Verbal Memory & Recall	Adult Memory & Information Processing Battery – List
Verbal Memory & Recall	Rey Auditory Learning Test - List
Recognition Memory	Recognition Memory Test
Non Verbal Memory	Faces
Verbal Memory	Words
Visuospatial Function	Rey-Osterreith Complex Figure
Visuospatial Attention	Copy
Visual Memory	Immediate Recall
Visual Memory	Delayed Recall
Language Function	Speed and Capacity of Language Processing
Language	Speed of Comprehension
Language	Spot-the-word-test
Language	Boston Naming Test
Language	Graded Naming Test

Appendix B.2

Treatment types within the groups.

Table 5. Treatments received by the pituitary patients within the studies

Key	Treatment
TF	Transfrontal Surgery (frontotemporal craniotomy)
TSA	Transsphenoidal Adenomectomy
RT	Radiotherapy (type not specified but probably mixed)
RT1	Radiotherapy, arc, single field
RT2	Radiotherapy, bifrontal, two fields
RT3	Radiotherapy, three field fractionated
TF + RT	Transfrontal Surgery plus radiotherapy (type not specified)
TSA + RT	Transsphenoidal Adenomectomy plus RT (type not specified)
TSA + RT3	Transsphenoidal Adenomectomy plus RT three field fractionated
Med	Medication (dopamine receptor agonists)
nonRT	Mixed non RT group (TF, TSA, Pre Surgery, & Not Classified)
S	Surgery to remove pituitary tumour (surgery type not specified)
S + RT	Surgery (type not specified) & radiotherapy (type not specified)

Table 6. Treatments types within each reviewed paper

Abbreviations	Grattan-Smith et al. 1992	McCord et al. 1997	Peace et al. 1997	Peace et al. 1998	Guinan et al. 1998	Noad et al. 2004	Treece et al. 2005
TF		✔	✔	✔			
TSA		✔	✔	✔	✔	✔	✔
RT	✔				✔		
RT1	?	✔	?	?	?		
RT2	?	✔	?	?	?		
RT3	?	✔	?	?	?		
TF + RT	✔	✔	✔	✔	✔		
TSA + RT	✔	✔	✔	✔	✔		
TSA + RT3						✔	✔
Pre Surgery	✔						
Med			✔	✔	✔		
nonRT	✔						
S		✔					
S + RT		✔					

? denotes treatment type not specified within paper but hypothesised

Table 7. Key to the control groups

CG-H	Healthy control group
CG-I	Chronically ill in-patient control group
CG-S	Surgical control group
CG-None	Comparisons made to assessment norms

Table 8. Control group types within each reviewed paper

Abbreviations	Grattan-Smith et al. 1992	McCord et al. 1997	Peace et al. 1997	Peace et al. 1998	Guinan et al. 1998	Noad et al. 2004	Treece et al. 2005
CG-H			✔	✔	✔		
CG-I	✔						
CG-S							✔
CG-None		✔				✔	

Appendix B.3

Table 9. Assessments used by the reviewed studies

Title of Assessment	Test Abbreviation
National Adult Reading Test	NART
Wechsler Memory Scale	WMS
Visual Reproduction	WMS VR
Logical Memory - Story	WMS LM
Wechsler Memory Scale – Revised	WMS(R)
Adult Memory & Information Processing Battery - Story	AMIPB Story
Adult Memory & Information Processing Battery - List	AMIPB List
Rey-Osterreith Complex Figure	Rey OCF
Copy	Rey Copy
Immediate Recall	Rey Recall
Delayed Recall	Rey Delay
Rey Auditory Learning Test - List	RALT
Controlled Oral Word Association Test – FAS test	COWAT
Wechsler Adult Intelligence Scale (Revised)	WAIS(R)
Block Design Sub-test	Block Design
Digit Span Sub-test	Digit Span
Stroop Neuropsychological Screening Test	Stroop
Symbol Digit Modalities Test	SDMT
Recognition Memory Test	RMT
Faces	RMT Faces
Words	RMT Words
Speed and Capacity of Language Processing	SCOLP
Speed of Comprehension	SCOLP SOC
Spot-the-word-test	SCOLP STW
Army Individual Battery – Trail Making Test	TMT
Boston Naming Test	BNT
Graded Naming Test	GNT
Paced Auditory Serial Addition Test	PASAT
Modified Card Sorting Test	MCST
Cognitive Estimates	COG EST
Autobiographical Memory Inventory	AMI
Self Designed Questionnaire	SDQ

Appendix B.4

Table 10. Neuropsychological assessments used by each reviewed study.

Abbreviations	Grattan-Smith et al. 1992	McCord et al. 1997	Peace et al. 1997	Peace et al. 1998	Guinan et al. 1998	Noad et al. 2004	Treece et al. 2005
NART	✔		✔	✔	✔	✔	✔
WMS VM	✔						
WMS LM	✔		✔	✔		✔	
WMS (R)					✔		
AMIPB Story							✔
AMIPB List							✔
Rey Copy	✔					✔	✔
Rey Recall	✔						
Rey Delay						✔	✔
RALT			✔	✔			
COWAT	✔		✔	✔	✔	✔	✔
WAIS(R)					✔		
Block Design			✔	✔	✔		✔
Similarities					✔		✔
Digit Span			✔	✔	✔		✔
Stroop			✔			✔	✔
SDMT							✔
RMT F	✔		✔	✔	✔		✔
RMT W	✔				✔		✔
SCOLP SOC					✔	✔	✔
SCOLP STW					✔	✔	✔
TMT	✔		✔	✔			✔
BNT							✔
GNT					✔		
PASAT					✔		
MCST					✔		
COG EST					✔		
AMI					✔		
SDQ		✔					

Appendix to the Empirical Paper **Appendix C**

Appendix C.1

Full Review of the Previous Studies of psychosocial functioning in patients treated for pituitary tumours with surgery and/or radiotherapy.

There have been a number of studies which have investigated the effects of surgery for the treatment of pituitary tumours on psychosocial functioning. Those which have used standardised measures of psychosocial functioning will be reviewed in full in this appendix.

The majority of the studies were retrospective; only the most recent one by Treece et al. (2005) was prospective. Some of the reviewed studies examined the effects of treatments on psychosocial functioning and neuropsychological functioning (Guinan et al., 1998; Noad et al., 2004; Peace et al., 1997a; Treece et al., 2005). The study by Page et al. (1997) examined psychosocial functioning in patients who had been treated for pituitary disease with the "Gold Standard" treatments. The paper by Peace et al. (1997b) only examined psychosocial functioning, but the sample of patients included in that study seemed to be the same cohort as appeared in their study of cognitive dysfunction following treatments for pituitary disease (Peace et al., 1998).

In a case controlled, retrospective self report study Page et al., (1997) explored psychosocial functioning in patients who had received transsphenoidal surgery (TSA) to remove pituitary adenomas. They compared pituitary surgery patients to control surgery patients (CG-S) on measures of health related quality of life and well-being. They used the Short Form Health Questionnaire (SF-36) (Ware et al., 1993), and the General Well Being Schedule (GWBS) (Dupy, 1977). The two groups were matched for age and gender ($p>0.05$), and were taken from the same

background population. All surgical patients, both pituitary and control, were under long-term follow up care at the Radcliffe Infirmary, Oxford. Page et al. (1997) found no significant differences in psychosocial functioning between the patients who had received surgery for pituitary tumours and a matched surgical control group.

All pituitary patients had received transsphenoidal surgery (TSA), for additional analysis the pituitary patients were divided into two further subsets. The pituitary patients in Subset 1 had received the combined therapy of transsphenoidal surgery followed by conventional three field fractionated radiotherapy (TSA+RT3), this subset was compared to the control group (CG-S) on measures of psychosocial functioning. Page et al. (1997) found that the combined therapy pituitary patients (TSA+RT3) had a significantly worse General Well Being Schedule (GWBS) score than the control group. On the Short Form 36 (SF-36) the TSA+RT3 group had a significantly poorer mental health score than the control group. The pituitary patients in Subset 2 were thought to be Growth Hormone deficient, (TSA+GHD) this subset were compared to the surgical control group (CG-S) on measures of psychosocial functioning. Page et al. (1997) found no significant differences on measures of psychosocial functioning between this subset and the surgical control group. Page et al. (1997) concluded that there may be an effect of radiotherapy on quality of life in patients treated for pituitary disease, and that further research should be conducted in the area.

A possible criticism of this study was that there were no formal comparisons between those pituitary patients who did not receive radiotherapy to either the combined therapy group (TSA+RT3), or the surgical control group (CG-S). The total group of pituitary patients (TSA and

TSA+RT3) was compared to the surgical control group (CG-S). However, in a series of personal communications this researcher was informed that these comparisons had been made but not reported in the paper (R.C.L. Page, April 28, 2003), there were no significant differences between the groups (R.C.L. Page, November 7, 2005).

This was a well designed case controlled study with clear inclusion and exclusion criteria. All pituitary patients in the study received the "Gold Standard" treatments for pituitary disease (see Appendix C.2) as recommended by the Royal College of Physicians (Clayton & Wass, 1997). A well matched surgical control group was recruited for comparison. This group was preferable to a healthy control group because the patients had been subject to similar surgical procedures (mastoid surgery) in the same hospital, were at a similar stage in their treatment and were under long-term follow up. Standardised measures of psychosocial functioning were utilised. This study could be replicated from the information provided in the paper. However replication would be unlikely as a stronger design would be a prospective case controlled study with randomisation to radiotherapy after surgery. This study influenced the design and the research aims of both the Noad et al. study (2000) and the Treece study (2005).

Peace et al. (1997a) conducted a case controlled retrospective study of psychosocial functioning in patients who had been treated for pituitary tumours. They compared a group of pituitary patients to healthy controls on measures of anxiety and depression. They used the Beck Depression Inventory (BDI) (Beck et al., 1979) and the State Trait Anxiety Inventory (STAI) (Spielberger et al., 1983). The two groups were matched for gender, age and years of education. The group of pituitary tumour patients was very diverse, some had received surgery only, others

had received surgery plus radiotherapy and a small number had been treated with medication only (see Appendix C.2). The surgical treatments included both transsphenoidal (TSA) and transfrontal (TF). The type of radiotherapy was not specified, but it is likely that this was mixed as this was a retrospective study which began before 1992 when two-field radiotherapy was frequently administered.

When the pituitary patient group were compared to the healthy control group (CG-H) no significant differences in psychosocial functioning were found. Peace et al. (1997a) concluded that the cognitive deficits that had been observed in the pituitary patients were not related to mood. Peace et al. (1997a) made many comparisons between subsets of pituitary patients. These subsets were formed according to treatment types (for example, transfrontal surgery vs transsphenoidal surgery vs no surgery). They found no significant differences on measures of psychosocial functioning between the different subsets of pituitary patients.

This study utilised standardised measures of psychosocial function. Adequate details of surgical treatments received by each patient were recorded so the pituitary group could be divided into subsets. However, individual subsets of pituitary patients were not compared to the control group on measures of psychosocial functioning. In addition the type of radiotherapy treatments received was not specified, so it is impossible to draw conclusions from this study that would be applicable to modern day practices in the treatment of pituitary tumours. This study added to the research knowledge in this area and provided a basis for further investigations into this patient population.

In another retrospective case controlled study Peace et al. (1997b) investigated the effects of treatments for pituitary tumours on psychosocial functioning. Peace et al. (1997b) compared three groups of pituitary disease patients to healthy controls on measures of anxiety, depression, social adjustment and health. The three pituitary groups had received transfrontal surgery (TF), transsphenoidal surgery (TSA), or medication only (Med). More than half of the pituitary surgery patients (TF or TSA) had also received radiotherapy (type not specified, but likely to be mixed between RT2 and RT3, and possibly RT1). A relative or friend of each pituitary patient also completed questionnaires relating to the patients' social adjustment.

The control group was comparable to the pituitary groups for gender, age and years of education. Standardised measures of psychosocial functioning were used; the BDI (Beck et al., 1979), the STAI (Spielberger et al., 1983), the Social Adjustment Scale (Cooper et al., 1982) and the Nottingham Health Profile (Hunt et al., 1981). Peace et al. (1997b) found the TSA group and the medication group rated themselves as being more depressed, anxious and having poorer social adjustment, than the TF group or the healthy controls. Close informants rated each pituitary group (including the medication group) as having poor social adjustment. Peace et al. (1997b) concluded that the patients who had received TF surgery were unaware of any social difficulties because of lack of insight caused by the invasive frontal surgery, so realistic self-appraisal was unlikely. They noted that the patients with the most serious disease, and greatest mean duration of illness were present in the TF group. Peace et al. (1997b) stated that this highlighted the problems of using self report measures with certain groups of patients. They suggested that this may explain some of the discrepancies in other research projects which employed self report measures. They further suggested that self report measures of mood and health should only be

used in conjunction with standardised objective measures or questionnaires completed by close informants.

This was a retrospective study, which did not specify the type of radiotherapy received by the pituitary patients. The pituitary group included patients with craniopharyngioma (in the transfrontal group). Craniopharyngioma is not a true pituitary adenoma. It emanates from a structure adjacent to the pituitary gland and it is frequently cancerous, resulting in poor prognosis. Peace et al. (1997b) dismissed the self reports of those patients in the TF group, assuming they lacked insight – without performing further assessments to confirm this. The treatments received by each surgery group were diverse, possibly including outdated radiotherapy, there was also a number of confounding factors and therefore the results of this study are of limited value to modern day practices.

In a case controlled retrospective study Guinan et al. (1998) investigated the effects of pituitary tumours and their treatments on psychosocial functioning. They compared five groups of patients who had been treated for pituitary tumours (between 1966 and 1993) to a healthy control group (CG-H). They utilised standardised measures of anxiety, depressions and health related quality of life, (BDI, STAI, NHP). The five treatment groups were; transfrontal surgery with radiotherapy (TF+RT), transsphenoidal surgery with radiotherapy (TSA+RT), transsphenoidal surgery only (TSA), radiotherapy (RT), and bromocriptine (Med). The groups were matched for age and gender ($p>0.05$). Guinan et al. (1998) found no significant differences between the patients who had been treated for pituitary tumours and the matched control group on any

psychosocial measures, although there was a trend for the pituitary patients to show higher scores on the measures of anxiety and depression than the controls.

This was a large well designed retrospective study, which employed standardised measures of psychosocial functioning, and strict exclusion criteria. Comprehensive details of the treatments received by each pituitary patient were collected to allow them to be divided into groups. Guinan et al. (1998) did not specify the types of radiotherapy received by the pituitary patients. Therefore the relevance to present clinical practice was limited because of the advances in treatments over the past forty years.

Noad et al. (2004) conducted a retrospective study which investigated the effects of treatments for pituitary tumours on psychosocial functioning. Two groups of pituitary tumour patients were compared, a surgery only group (TSA) and a surgery plus radiotherapy group (TSA+RT3), on measures of psychosocial functioning. These two treatments are the modern "Gold Standard" treatments for pituitary tumours as recommended by the Royal College of Physicians (Clayton & Wass, 1997). The measures utilised were the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), the SF-36, the General Health Questionnaire (GHQ28) (Goldberg, 1978), and the GWBS. Strict exclusion criteria were applied; participants were excluded if they had undergone brain surgery other than TSA, had Cushing's disease or craniopharyngioma, were under 18 years or over 70 years at the time of recruitment to the study. Noad et al. (2004) established that patients who received combined "Gold Standard" therapies (TSA+RT3) for pituitary tumours reported poorer health related quality of life than patients who had received

surgery alone (TSA), this was noted on the physical health composite (PCS) of the SF-36 ($p<0.01$).

There are a number of criticisms regarding the design of this study. It was a retrospective study, the patients received their treatments up to ten years before recruitment. A prospective randomised study would have been a stronger design. There was no control group and pituitary patients with Cushing's disease were excluded from the study. However, this was a pilot study to see if dysfunction could be measured in pituitary patients who had received radiotherapy to treat pituitary tumours, and a prospective study followed on from it (Treece, 2005). The criticisms were addressed in the design of the prospective study, which recruited a control group for comparisons and included pituitary patients of all aetiologies.

Despite the criticisms cited above this was a well designed study, with strict inclusion and exclusion criteria enforced. There was sufficient detail within the paper to allow for replication, however this would be unlikely as a prospective study would have been a stronger design. The patients compared had received the modern "Gold Standard" treatments and as such the findings of this study were applicable to current medical practices. This study contributed to the evidence base for treatments for pituitary disease.

In a case controlled, multi-centre, prospective study Treece et al. (2005) investigated the effects of treatments for pituitary disease on psychosocial functioning. They compared a group of pituitary patients awaiting surgical removal of pituitary tumours (TSA) to a control group of ENT patients who were awaiting functional endoscopic sinus surgery. Treece et al. (2005) utilised

standardised measures of psychosocial functioning to measure anxiety, depression, psychological well-being and health related quality of life. The measures were the HADS, SF-36, GHQ28 and the GWBS. The participants were assessed at three time points, before surgery, three months after surgery and 12 months after surgery. The groups were comparable for age, gender and IQ ($p>0.05$).

Both the pituitary group and the control group received the "Gold Standard" surgical treatments for their respective illnesses. A surgical control group was used to control for the effects of surgery and recovery from anaesthesia. Strict exclusion criteria were enforced; patients who were younger than 18 or older than 65 at the time of surgery were excluded. Those patients who had received any previous brain surgery or brain radiotherapy were excluded. Pituitary patients with adenomas of all aetiologies were included, those patients with craniopharyngioma were excluded.

Treece et al. (2005) found significant differences on measures of psychosocial functioning between the pituitary group and the control group before surgery and at three months after surgery, with the pituitary patients having a poorer level of psychosocial function than the control group. Significant differences were found before surgery on the General Well-Being Schedule with the control group rating themselves as more "well" than the pituitary group ($p<0.05$). On the GHQ28, the pituitary group also rated themselves as having higher levels of social dysfunction than control group ($p<0.01$) before surgery. At three months after surgery the pituitary group were found to be significantly more depressed than the control group ($p<0.50$) on the depression measure of the Hospital Anxiety and Depression Sale (HADS). They also rated themselves as having lower levels of social functioning, and higher levels of limitations within

their physical and mental roles than the control group at three months after surgery, these were all significant at <0.05. However, at twelve months after surgery there were no significant differences on any measure of psychosocial functioning between the patients who had received surgery for the removal of pituitary tumours and the surgical control group. This indicated that the psychosocial functioning in the pituitary group had returned to normal levels one year after surgery to remove pituitary tumours. There was a significant difference in the "rate of change in health" between the pituitary group and the control group at one year after surgery; the pituitary patients had noticed a greater improvement in health than the control group in the year following surgery.

A recent study by van Beek et al. (2007) examined psychosocial functioning in patients successfully treated for non functioning pituitary adenomas. They investigated patients who had received surgery (TSA or TF) with or without radiotherapy. They reported that combined therapy (TSA+RT or TF+RT) was not associated with reduced quality of life in patients who had been treated for non functioning pituitary adenomas and were on adequate replacement therapies.

Summary of Previous Studies of Psychosocial Functioning after Pituitary Surgery

In 1997 the Royal College of Physicians recommended "Gold Standard" treatments for the removal of pituitary tumours (Clayton & Wass, 1997). These were transsphenoidal surgery (TSA) for the removal of tumours, and, if clinically necessary, conventionally fractionated three-field radiotherapy (RT3) to prevent tumour re-growth following surgery (Clayton & Wass, 1998). Due to the retrospective nature of the majority of the studies, half of the papers reviewed included patients who had received treatments which are no longer recommended for pituitary

tumours, this makes the findings of those papers of little value to the research literature for evidence based medicine. However, the papers have contributed to the overall research debate and have inspired further investigations. See Table 11 to compare the assessments utilised in each study.

Page et al. (1997) compared pituitary patients who had received the "Gold Standard" treatments (TSA and TSA+RT3) to surgical controls. They reported no significant differences in psychosocial functioning between the two groups. They also compared a subset of pituitary patients (TSA+RT3) to the control group and found poorer levels of psychosocial function in the combined therapy pituitary group.

Table 11. Comparison table of assessments used in the reviewed studies.

Assessment	Page et al. 1997	Peace et al. 1997a	Peace et al. 1997b	Guinan et al. 1998	Noad et al. 2004	Treece et al. 2005
HADS					✔	✔
SF-36	✔				✔	✔
GHQ28					✔	✔
GWBS	✔				✔	✔
BDI		✔	✔	✔		
STAI		✔	✔	✔		
SAS			✔			
NHP			✔	✔		

Peace et al. (1997a) compared pituitary patients who had received mixed therapies for pituitary tumours to healthy controls, they found no significant differences in psychosocial functioning. They also found no significant differences in psychosocial functioning when they compared subsets of patients who had received different treatments. Peace et al. (1997b) compared mixed therapy pituitary tumour patients to healthy controls. The groups who had received transsphenoidal surgery or medication rated themselves as having a poorer level of psychosocial functioning than transfrontal surgery patients or healthy controls. Guinan et al. (1998) compared patients who had been treated for pituitary tumours to a control group, they found no significant differences in psychosocial functioning. The comparisons were repeated between the different treatment groups, no significant differences in psychosocial functioning were observed. Noad et al. (2004) reported that those patients who had received the "Gold Standard" surgical treatment (TSA) for the removal of pituitary tumours had a higher level of psychosocial functioning than the patients who received the combine "Gold Standard" treatments of surgery plus radiotherapy (TSA+RT3). Treece et al. (2005) reported that the patients who had received "Gold Standard" treatment for the removal of pituitary tumours (TSA) had a poorer level of psychosocial functioning before surgery and three months after surgery than a comparable surgical control group. Importantly, they also reported that this difference had resolved by twelve months after surgery, with the pituitary group and the control group no longer displaying any significant differences in psychosocial functioning.

In summary, three studies found significant differences in levels of psychosocial functioning between some groups of patients who had been treated for pituitary tumours and comparable control groups (Page et al., 1997; Peace et al., 1997b; Treece et al., 2005). Three studies found no

significant differences in psychosocial functioning between the whole groups of pituitary patients and the control groups (Guinan et al., 1998; Page et al., 1997; Peace et al., 1997a). Two studies found significant differences when they compared psychosocial functioning in pituitary patients who had received different therapies (Noad et al., 2004; Peace et al., 1997b). Two studies found no significant differences in psychosocial functioning when they compared pituitary patients who had received different therapies (Guinan et al., 1998; Peace et al., 1997a). Treece et al. (2005) measured a resolution in psychosocial functioning over a 12 month period following pituitary surgery. Van Beek et al. (2007) found no additional deficits in psychosocial functioning in pituitary patients who had received radiotherapy after surgery.

The research studies which included only those patients who received the "Gold Standard" treatments will be the most useful in informing the debate relating to evidence based medicine (Noad et al., 2004; Page et al., 1997; Treece et al., 2005).

Appendix C.2

Table 12. Treatments received by the pituitary patients.

Key	Treatment
TF	Transfrontal Surgery (frontotemporal craniotomy)
TSA	Transsphenoidal Adenomectomy (Gold Standard Treatment)
RT	Radiotherapy (type not specified)
RT1	Radiotherapy, single field or arc
RT2	Radiotherapy, two field (bifrontal, or opposed lateral)
RT3	Radiotherapy, three field fractionated (Gold Standard Treatment)
TF + RT	Transfrontal Surgery plus radiotherapy (type not specified)
TSA + RT	Transsphenoidal Adenomectomy plus RT (type not specified)
TSA + RT3	Transsphenoidal Adenomectomy plus RT three field fractionated (GST)
Med	Medication (dopamine receptor agonists – to shrink tumour)
UT-PS	Untreated pituitary patients – pre surgery
nonRT	Mixed non RT group (TF, TSA, UT-PS, & Not Classified)
S	Surgery to remove pituitary tumour (mixed or type not specified)
S + RT	Surgery (mixed or type not specified) & radiotherapy (type not specified)
CG-H	Healthy control group.
CG-CI	Chronically ill inpatient control group.
CG-S	Surgical control group.

Table 13. Treatment groups within each study.

Treatment	Page et al. 1997	Peace et al. 1997a	Peace et al. 1997b	Guinan et al. 1998	Noad et al. 2004	Treece et al. 2005
TF		✔	✔			
TSA	✔	✔	✔	✔	✔	✔
RT				✔		
RT1		?	?	?		
RT2		?	?	?		
RT3		?	?	?		
TF+RT		✔	✔	✔		
TSA+RT		✔	✔	✔		
TSA+RT3	✔				✔	✔
Med		✔	✔	✔		
UT-PS						
nonRT						
S						
S + RT						
CG-H		✔	✔	✔		
CG-CI						
CG-S	✔					✔

Appendix C.7

Centre Number:
Study Number:
Patient Identification Number:

CONSENT FORM

Title of Project: **Long-term outcomes of memory and quality of life in patients treated for pituitary tumours**

Name of Researcher: **Karen Treece**

Please initial box

1. I confirm that I have read and understand the information sheet (dated 17th July 2006, Version 3) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to take part in the above study. ☐

5a. Please post the questionnaires to me. ☐

or

5b. Please contact me by telephone to complete the questionnaires. ☐

Telephone number: _____

Preferred day and time: _____

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix C.9 **Assessments used by the reviewed studies**

Table 14. Assessments completed by the pituitary patients.

Title of Assessment	Author	Abbreviation
Hospital Anxiety and Depression Scale	Zigmond & Snaith 1983	HADS
Short Form Health Questionnaire SF-36	Ware et al. 1993	SF36
General Health Questionnaire 28	Goldberg 1978	GHQ28
General Well-Being Schedule	Dupuy 1977	GWBS
Beck Depression Inventory	Beck et al. 1979	BDI
State-Trait Anxiety Inventory	Spielberger 1983	STAI
Social Adjustment Scale	Cooper et al. 1982	SAS
Nottingham Health Profile	Hunt et al. 1981	NHP

Table 15. Assessments used in each reviewed study.

Assessment	Page et al. 1997	Peace et al. 1997a	Peace et al. 1997b	Guinan et al. 1998	Noad et al. 2004	Treece et al. 2005
HADS					✔	✔
SF-36	✔				✔	✔
GHQ28					✔	✔
GWBS	✔				✔	✔
BDI		✔	✔	✔		
STAI		✔	✔	✔		
SAS			✔			
NHP			✔	✔		

Appendix C.10 Normality

Table 16. Measures which did not meet the assumptions for parametric testing.

Measure	Skeweness	Kurtosis	Multi-modal	Floor Effect	Normality
HAD Anxiety	X		X		X
HAD Depression	X			X	X
HAD TOTAL	X		X		X
SF36 CIH	X				X
SF36 PCS		X	X		X
SF36 MCS		X	X		X
GHQ 28 TOTAL	X			X	X
GWBS TOTAL		X	X		X

Appendix C.11

Additional comparisons between the pituitary surgery group and the control surgery group

METHOD

Plan of Analysis

Within Group Comparisons

The pituitary surgery group was compared to itself at 12 month and long-term follow up on measures of psychosocial functioning.

The control group was compared to itself at 12 month and long-term follow up on measures of psychosocial functioning.

Within group comparisons were made using Wilcoxon matched pairs, repeated measures test. This was to see if there were any significant changes in psychosocial functioning in either group over time.

RESULTS

Within Group Comparisons

Comparisons within groups between 12 months after surgery and long term follow up.

Comparisons were made to investigate whether of not there were any significant changes in psychosocial functioning within the groups between the 12 month outcome date and the long-term follow up.

Pituitary Group

Within the pituitary group there were significant changes in the level of Change in Health measured by the SF36 between 12 months after surgery and long term follow up, see Table 17.

Table 17. Comparisons of psychosocial functioning at 12 months after surgery and long-term follow up within the pituitary group.

Measure	Pituitary Group 12 month outcome		Pituitary Group Long term outcome		Wilcoxon Repeated Measures Test	p
	median	inter-quartile range	median	inter-quartile range		
HAD Anxiety	6.0	4.0-9.0	7.0	5.0-8.8	-0.688	0.491
HAD depression	3.5	1.3-6.8	3.0	1.0-6.0	-0.273	0.785
HAD TOTAL	9.5	6.3-14.8	9.5	6.3-15.8	-0.114	0.909
SF36 CIH	75.0	50.0-100.0	50.0	50.0-75.0	-2.509	**0.012***
SF36 PCS	50.7	32.9-56.1	47.3	34.3-53.9	-0.056	0.955
SF36 MCS	53.6	46.1-57.3	52.1	42.2-56.6	-0.617	0.537
GHQ 28 TOTAL	17.0	11.0-23.8	19.0	14.0-29.0	-1.818	0.069
GWBS TOTAL	74.5	64.3-90.5	79.0	65.0-89.8	-0.162	0.871

* = significant at $p<0.05$

The variable "Change in Health" of the SF36 measures the perceived change in health status over the past twelve months. The higher the score the more positive change there has been. Comparison has been made between the 12 month outcome date (which was one year after surgery) and the long-term outcome date (which was 4-8 years after surgery). The pituitary patients had experienced a greater improvement in health in the twelve months after their surgery, than they had in the twelve months before completing the long-term outcome questionnaires. This finding is not unexpected, because you would expect pituitary patients to feel an improvement in health after their surgery, due to the relief of mass effects from the tumour, and/or the normalisation of pituitary hormones.

Control Group

Within the control group there were significant differences in GHQ28 Total between 12 months after surgery and long term follow up ($p<0.05$), see Table 18.

Table 18. Comparisons of psychosocial functioning in the control group at 12 months after surgery and at long-term follow up.

Measure	Control Group 12 month outcome		Control Group Long term outcome		Wilcoxon Repeated Measures Test	p
	median	inter-quartile range	median	inter-quartile range		
HAD Anxiety	6.0	4.0-7.0	7.0	3.0-8.0	-0.625	0.532
HAD depression	3.0	1.0-6.0	2.0	1.0-7.0	-0.029	0.977
HAD TOTAL	9.0	6.0-11.0	8.0	5.0-18.0	-0.256	0.798
SF36 CIH	50.0	50.0-75.0	50.0	50.0-50.0	-1.261	0.207
SF36 PCS	47.9	30.6-53.0	46.7	34.6-51.6	-0.644	0.520
SF36 MCS	55.2	47.4-58.3	54.6	39.8-59.1	-0.161	0.872
GHQ 28 TOTAL	18.0	13.0-21.0	19.0	15.0-32.0	-2.449	**0.014***
GWBS TOTAL	82.0	69.0-87.0	78.0	55.0-89.0	-1.593	0.111

* = significant at $p<0.05$

This indicated that the control group was experiencing a higher level of distress at long-term after surgery than they were at 12 months after surgery.

Post hoc analysis was performed to investigate if it was just the GHQ28 Total Score that was significantly different over time in the control group or if any of the individual variables were independently contributing to this difference. See Table 19. Within the control group there were significant differences over time in the two variables GHQ somatic symptoms and GHQ anxiety and insomnia, both contributed to the significant difference in GHQ28 Total and all three were significant at $p<0.05$. See Table 19.

Table 19. Post hoc analysis of the individual variables within the GHQ28.

Differences observed in the Control Group between 12 month and long term outcomes.

Measure	Control Group 12 month outcome		Control Group Long-term outcome		Wilcoxon Repeated Measures Test	P
	median	inter-quartile range	median	inter-quartile range		
GHQ 28 TOTAL	18.0	13.0-21.0	19.0	15.0-32.0	-2.449	**0.014***
GHQ 28 Somatic	6.0	3.0-9.0	8.0	5.0-12.0	-2.340	**0.019***
GHQ 29 Anxiety	4.0	2.0-6.0	6.0	3.0-9.0	-2.933	**0.003***
GHQ 28 social dysfunction	7.0	7.0-8.0	7.0	6.0-8.0	-0.045	0.964
GHQ 28 Depression	0.0	0.0-1.0	0.0	0.0-2.0	-1.897	0.058

* = significant at $p<0.05$

The control surgery group had changed over time for both somatic symptoms and levels of anxiety as measured by the GHQ28. These had increased between one year following surgery and long-term follow up.

For somatic symptoms the groups overall median score had changed from 4 to 6. A score of 0-7 on a variable indicates functioning to be "better than usual" when comparing oneself to how you have felt over the past month. So the overall clinical level had not changed.

For anxiety the groups overall median score had changed from 6 to 8 over time. A score of 8-14 on a variable indicated functioning to be "the same as usual" when comparing oneself to how you have felt over the past month. So although there is a statistically significant change over time, the change has gone from a feeling of "better than usual", to a feeling of "the same as usual".

Appendix C.12

Additional Minor Analysis

Psychosocial functioning in patients who received radiotherapy after surgery.

In the previous prospective study (Treece 2005) seven patients had received combined therapy (TSA+RT3), they were invited to take part in this long-term outcome study. Five patients consented to take part, only three returned the completed questionnaires.

This small group of patients has not appeared in any of the above analysis.

At 12 months after surgery the pituitary surgery only group (TSA) was compared to the combined therapy group (TSA+RT3) for differences in psychosocial functioning, there were no significant differences (Treece 2005). Because both groups had changed in size at long-term follow up, this 12 month data analysis was repeated. There were no significant differences in psychosocial functioning between the single therapy group (TSA) and the combined therapy group (TSA+RT3) at 12 months after surgery. The two groups were matched for age ($p=0.850$), gender ($p=0.324$) and pre morbid IQ ($p=0.973$).

Comparisons of long-term follow up outcomes, of psychosocial functioning in the groups of pituitary patients were made, using Mann-Whitney U test and exact statistics. One group had received transsphenoidal surgery only ($n=32$), the additional small group of pituitary patients received the combined therapy of transsphenoidal surgery plus conventional three field fractionated radiotherapy ($n=3$).

There were no significant differences in psychosocial functioning between the single therapy group (TSA) and the combined therapy group (TSA+RT3) at long-term follow up, (see Table 20).

Table 20. Long-term outcomes of psychosocial functioning in pituitary patients. Comparisons between the single therapy group and the combined therapy group.

Measure	Combined Therapy Long-term outcome (n=3)		Single Therapy Long-term outcome (n=32)		U	p (exact)
	median	inter-quartile range	median	inter-quartile range		
HAD anxiety	5.0	1.0-6.0	7.0	5.0-8.8	21.5	0.127
HAD depression	2.0	2.0-5.0	3.0	1.0-6.0	47.5	0.990
HAD TOTAL	7.0	6.0-8.0	9.5	6.3-15.8	27.5	0.250
GHQ 28 TOTAL	13.0	11.0-17.0	19.0	14.0-29.0	24.0	0.171
SF36 PCS	50.4	47.4-53.6	47.3	34.3-53.9	42.0	0.843
SF36 MCS	55.2	47.9-56.0	52.1	42.2-56.6	35.0	0.481
SF36 CIH	50.0	50.0-50.0	50.0	50.0-75.0	38.0	0.595
GWBS TOTAL	79.0	74.0-88.0	79.0	65.0-89.8	43.0	0.793

All pituitary patients in this study received the current "Gold Standard" treatments for the removal of pituitary tumours, these are transsphenoidal surgery (TSA), and conventionally

fractionated three field radiotherapy (RT3), as recommended by the Royal College of Physicians in 1997 (Wass 1997). Any studies which investigate the effects of these treatments on long-term outcome, will add to the research evidence base.

Those patients, who received radiotherapy after surgery for the removal of pituitary tumours, were not found to be significantly different to the patients who received surgery only, on measures of psychosocial functioning. This indicated that their overall quality of life and psychosocial functioning had not been affected by radiotherapy at long-term follow up. While this is a positive outcome for patients who had received the combined "Gold Standard" treatments, these results need to be treated with caution, because this was a very small sample (although exact statistics were used).

Appendix C.13 Post Hoc Power Analysis

Post hoc power analysis was conducted using the tutorial by Faul and Erdfelder (1992) to establish the effect size, then using the program GPOWER (Faul & Erdfelder, 1992) to establish the power of the study – post hoc power analysis.

Assuming the study was looking for a large effect size (0.8), 80% power, and 0.05 significance level, a total sample size of 52 would be required. Assuming the study was looking for a medium effect size (0.5), 80% power, and 0.05 significance level, a total sample size of 51 would be required. Assuming the study was looking for a small effect size (0.2), 80% power, and 0.05 significance level, a total sample size of 82 would be required.

A total of 98 participants were recruited to the prospective study between 1998 and 2002, and 51 of those 98 were recruited to this long term follow up study.

For between group analysis the total sample size was N = 51 (pituitary n = 32, control n = 19). For within group analysis the total sample size for the pituitary group was N = 64. (Comparison of the pituitary group at 12 months after surgery and at long term follow up, n1 = 32, n2 = 32). For within group analysis the total sample size for the control group was N = 38. (Comparison of the control group at 12 months after surgery and at long term follow up, n1 = 19, n2 = 19).

Observed effect size, and post hoc power analysis

The largest observed effect size was d = 0.656, this was between the scores for the pituitary group at 12 months and the scores for the pituitary group at long term follow up on the variable SF36 Change in Health.

Total sample size of 64, n1 = 32, n2 = 32, d = 0.656.

Power 0.8290, Critical t (62) = 1.6698, Delta = 2.624.

The observed effect size was 0.656, giving a post hoc power of 82.9%.

Instructions for authors **Appendix D**

CLINICAL ENDOCRINOLOGY

The Clinical Journal of the Society for Endocrinology
Edited by:
J.A. Franklyn and J. Connell
Print ISSN: 0300-0664
Online ISSN: 1365-2265
Frequency: Monthly
Current Volume: 66 / 2007
ISI Journal Citation Reports® Ranking: 2005: 29/89 (Endocrinology & Metabolism)
Impact Factor: 3.412

TopAuthor Guidelines

Instructions for authors (revised January 2005)

Clinical Endocrinology strongly encourages the online submission of your manuscripts. Original articles should be submitted through http://cen.manuscriptcentral.com. Support for online submission is available at http://blackwellsupport.custhelp.com or by e-mail to support@scholarone.com. Telephone support is available in the UK *(+44 (0) 1865 476360).* If online submission is not possible, authors should send papers with a disk to the Oxford office. Papers are accepted on the understanding that no substantial part has been, or will be, published elsewhere. Papers may be subject to editorial revision without notice and remain the copyright of the journal. The Editors reserve the right to make the final decision whether or not a paper is accepted. Authors must indicate in the text the way in which they have complied with the recommendations of the Declaration of Helsinki (*British Medical Journal,* 1964, **ii**, 177). Experimental human studies should first have been approved by a local Ethical Committee, and a statement to this effect should be included.

An Author's Declaration, obtained from the Journal website, http://cen.manuscriptcentral.com, under 'Instructions and Forms' or the Oxford office of *Clinical Endocrinology*, must accompany each paper submitted and should be signed by all authors.

In addition, the Editors request that authors provide them with a statement of any competing interests, using a similar form as is used for this purpose by the British Medical Journal. An electronic version of this form is available under 'Instructions and Forms' on the Journal website. Although the Editors will not reject a paper simply because of a competing interest, they will publish a statement of declared interests.

Copyright information

Papers accepted must be licensed for publication in Clinical Endocrinology and either an Exclusive Licence Form (ELF) or Open Access Exclusive Licence Form (OOF) (please see OnlineOpen below) must accompany every accepted paper. Authors will be required to license copyright in their paper to Blackwell Publishing. Copyright licensing is a condition of publication, and papers will not be passed to the publisher for production unless copyright has been licensed. To assist authors, an appropriate exclusive license form will be supplied by the Editorial Office. Alternatively, authors may like to download a copy of the appropriate form from the journal website at:

http://www.blackwellpublishing.com/pdf/CEN_ELF.pdf or
http://www.blackwellpublishing.com/pdf/CEN_OOF.pdf
OnlineOpen:
OnlineOpen is a pay-to-publish service from Blackwell that offers authors whose papers are accepted for publication the opportunity to pay up-front for their manuscript to become open access (i.e. free for all to view and download) via the Blackwell Synergy website. Each OnlineOpen article will be subject to a one-off fee of £1300 (equivalent to $2600) to be met by or on behalf of the Author in advance of publication. Upon online publication, the article (both full-text and PDF versions) will be available to all for viewing and download free of charge. The print version of the article will also be branded as OnlineOpen and will draw attention to the fact that the paper can be downloaded for free via the Blackwell Synergy service.
Any authors wishing to send their paper OnlineOpen will be required to complete the combined payment and copyright licence form available from our website at:
http://www.blackwellpublishing.com/pdf/CEN_OOF.pdf(Please note this form is for use with OnlineOpen material ONLY.)
Once complete this form should be sent to the Editorial Office along with the rest of the manuscript materials at the time of acceptance or as soon as possible after that (preferably within 24 hours to avoid any delays in processing). Prior to acceptance there is no requirement to inform an Editorial Office that you intend to publish your paper OnlineOpen if you do not wish to.
The copyright statement for OnlineOpen authors will read:
© [2005] The Author(s)
Journal compilation © [2005] [Blackwell Publishing Ltd]
All required forms must be sent by post to Francesca Gibson, *Clinical Endocrinology* Blackwell Publishing Ltd, 9600 Garsington Road, OXFORD OX4 2DQ. Or by fax to +44 (0)1865 471327.
All required forms can be obtained from the Journal website http://cen.manuscriptcentral.com under 'Instructions and Forms' on the log-in screen.
CEN is covered by Blackwell Publishing's OnlineEarly service. OnlineEarly articles are complete full-text articles published online in advance of their publication in a printed issue. Articles are therefore available as soon as they are ready, rather than having to wait for the next scheduled print issue. OnlineEarly articles are complete and final. They have been fully reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are final form, no changes can be made after online publication. The nature of Online Early articles means that they do not yet have volume, issue or page numbers, so OnliveEarly articles cannot be cited in the traditional way. They are therefore given a Digital Object Identifier (DOI), which allows the article to be cited and tracked before it is allocated to an issue. After print publication, the DOI remains valid and can continue to be used to cite and access the article.
When the **final** version of the paper is accepted, please send this as an email attachment or on **disk,** as well as typescript, to francesca.gibson@oxon.blackwellpublishing.com or by post to *Clinical Endocrinology*, Blackwell Publishing Ltd, 9600 Garsington Road, OXFORD OX4 2DQ
The final version of the hard copy and the file on the disk **must** be the same. Note the software used, the type of computer and any special (non-keyboard) characters used.

Online Early

CEN is covered by by Blackwell Publishing's OnlineEarly service. OnlineEarly articles are complete full-text articles published online in advance of their publication in a printed issue. Articles are therefore available as soon as they are ready, rather than having to wait for the next

scheduled print issue. OnlineEarly articles are completed and final. They have been fully reviewed, revised and edited for publication, and the authors' final corrections have been incorporated. Because they are final form, no changes can be made after online publication. The nature of OnLine Early articles means that they do not yet have volume, issue or page numbers, so OnlineEarly articles cannot be cited in the traditional way. They are therfore given a Digital Object Identifier (DOI) which allows the article to be cited and tracked before it is allocated to an issue. After print publication, the DOI remains valid and can continue to be used to cite and access the article.

Online Accepted

Clinical Endocrinology offers Online Accepted for all articles. To learn more about this service, please read the document on the following web page:
www.blackwellpublishing.com/pdf/HA_OnlineAcceptedv4_15_02_2005.doc.
Access to this journal is available free online within institutions in the developing world through the HINARI initiative with the WHO. For information, visit www.healthinternetwork.org

Material storage policy

Please note that unless specifically requested, Blackwell Publishing will dispose of all hardcopy or electronic material submitted two months after publication. If you require the return of any material, please inform the editorial office or production editor as soon as possible.

Original Articles

Manuscripts must be typewritten (double-spaced) on one side of the paper only. The text must be preceded by a structured summary of no more than 250 words, to include the following headings: objective, including a background sentence setting the study in context, design, patients, measurements, results, conclusions.
Only those abbreviations listed below may be used in the summary. A single 'front page' must give: (1) the title; (2) a short title; (3) the name(s) of the author(s); (4) the department(s) in which the work was done; and (5) the name, full postal address, fax number and e-mail address of the author to whom the proofs and requests for offprints should be sent, to be headed 'Correspondence'; (6) a list of no more than five keywords related to subjects discussed in the paper.

Rapid Communications

Rapid communications should consist of new data of sufficient importance to warrant immediate publication. The submitted paper should be self-contained and not a tentative preliminary communication. It will be refereed very quickly and any revision must be dealt with promptly. It is expected that the time interval between the acceptance and subsequent publication of the manuscript will be approximately 3 months. If the Editors consider the article unsuitable for publication as a rapid communication it will be processed as a normal paper unless it is withdrawn by the authors.

Correspondence

Correspondence will be considered for publication if it contains constructive criticism on published articles, the authors of which will be given the right of reply. Items of topical interest, including case reports presenting a significant advance in therapy or highlighting substantial scientific advances in understanding the mechanism(s) of the disease process, will also be considered under this heading. Correspondence should not exceed 1000 words and have no more than 5 references.

Case Reports

We receive a very large number of Case Reports and unfortunately, in line with our current policy, we are no longer able to accept them.

Case Reports should be submitted in a shortened form that could be considered for publication in Clinical Endocrinology in our correspondence section. Such a submission should be a maximum of 1000 words in length, may include one table/illustration and no more than five relevant references.

Review Articles and commentaries

Review articles are normally commissioned, but we welcome suggestions for review titles and authors. Review articles in the 'Clinical Practice Update' category should deal with a defined clinical endocrine topic, and should focus on recent developments in understanding of the clinical presentation, and in clinical endocrine management. Other review articles may take a broader view of the topic and focus more on the basic mechanisms of endocrine dysfunction. Anyone wishing to write a review, clinical practice update or commentary for the journal should first consult the UK Editors (j.a.franklyn@bham.ac.uk; jmcc1m@clinmed.gla.ac.uk).

Papers must be written in clear, concise English. Spelling should follow *The Concise Oxford Dictionary of Current English* (Clarendon Press, Oxford). Avoid jargon and neologisms. The journal is not prepared to undertake major correction of language, which is the responsibility of the author. Where English is not the first language of the authors, the paper must be checked by a native Engligh speaker. Authors may suggest the names of suitable referees if they wish.

Figures and Tables

Digital artwork files for reproduction should preferably be EPS or TIFF and meet our standards, but we may be able to use other formats so please include these (see www.blackwell publishing.com/authors/digill.asp). Figures should be included with online submissions, either as JPEG, GIF, TIFF, BMP, PICT with RTF manuscripts or embedded in the PDF file. Colour reproductions will incur a charge.

Tables should be typed on separate sheets, numbered (with arabic numbers) and have a title.

Colour

If there is colour artwork in your manuscript. Blackwell Publishing require you to complete and return a colour work agreement form before your paper can be published. This form can be downloaded as a PDF from the internet at:

http://www.blackwellpublishing.com/pdf/Sub3000_X_CoW.pdf once completed, please return the form to Francesca Gibson at Clinical Endocrinology, 9600 Garsington Road, Oxford OX4 2DQ, UK; Fax: +44 (0) 1865 471 327.

Statistics

Special attention must be paid to the appropriate use of statistical methods in both the design and analysis of the study. Authors are advised to consider the recommendations published in the *British Medical Journal* (1983) **286**, 1489-1493. Manuscripts may be reviewed by the journal's medical statisticians.

Units

SI units should be used throughout, with molar, in preference to mass units wherever possible. Mass units may, however, be used for peptide hormones (e.g. leptin, ghrelin). Pituitary and other hormones expressed in units per litre should quote the appropriate standard reference preparation used in the assay. Concentrations should be expressed per litre, rather than per mL or dL and laboratory reference ranges quoted as appropriate.

Abbreviations

In general the Journal follows the recommendations in *Units, Symbols and Abbreviations* (1988). Royal Society of Medicine, London.

The following abbreviations may be used without definition:

ACTH corticotrophin; ADH antidiuretic hormone, vasopressin; AVP arginine vasopressin; FSH follicle stimulating hormone; GH growth hormone; GnRH gonadotrophin releasing hormone; HCG human chorionic gonadotrophin; hMG human menopausal gonadotrophin: hPL human placental lactogen; IGF insulin-like growth factor: IGFBP insulin like growth factor binding protein; LH luteinizing hormone; OT oxytocin; PRL prolactin; PTH parathyroid hormone; SHBG sex hormone binding globulin; T4 thyroxine; T3 triiodothyronine; rT3 reverse T3: TRH thyrotrophin releasing hormone; TSH thyrotrophin: VIP vasoactive intestinal peptide.

The *Biochemical Journal* (1975) **145**, 1011, enumerates abbreviations for certain compounds and also describes the correct use of chemical names and formulae.

All other abbreviations must be defined where they are introduced.

Chemical symbols and formulae should not be used in the text.

Steroids

Authors should follow the recommendations for steroid nomenclature published in the *Journal of Endocrinology* (1980) **84**, 3-4.

Amino Acids

Abbreviations may only be used in tables and for representing polymers or sequences in the text [see *Biochemical Journal* (1975) **145**, 11].

Isotopically Labelled Compounds

See *Biochemical Journal* (1975) **145**,13-14 and the *Radiochemical Catalogue* (Radiochemical Centre, Amersham, Bucks).

Solutions

Solutions should be described in terms of molarity (M), not normality (N). For values less than 0.1 M use mM (50 mM not 0.05 M). Buffers: composition, pH and method of adjustment should be given, e.g. 0.1 M potassium dihydrogen phosphate adjusted to pH 7.4 with 2 M sodium hydroxide. Volume ratios - e.g. methanol: water, 8 2 v/v (use 'by vol.' instead of v/v if more than two substances are involved).

References

These should conform to Vancouver style. The references in the text should be numbered consecutively in the order in which they appear and indicated by superscript numerals. Examples are given below:

Edge. J.A., Matthews, D.R. & Dunger, D.B. (1990) The dawn phenomenon is related to overnight growth hormone release in adolescent diabetics. *Clinical Endocrinology* **33**, 729-737.

Russell, W.E. & Van Wyk, J.J. (1989) Peptide growth factor. In *Endocrinology* (ed. L. J. De Groot), pp. 2504-2524. W. B. Saunders, Philadelphia, pp.2504-2524.

Disclaimer

The Publisher, The Society for the Endocrinology and Editors cannot be held responsible for errors or any consequences arising from the use of information contained in this journal; the views and opinions expressed do not necessarily reflect those of the publisher, The Society for Endocrinology and Editors, neither does the publication of advertisments constitute any endorsement by the advertised.