CUSHING'S SYNDROME - A CLINICAL, BIOCHEMICAL AND PSYCHIATRIC STUDY OF 209 PATIENTS

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A thesis submitted to the University of London
for the degree of Doctor of Medicine.

I dedicate this thesis to my wife Miranda
and our children Adam and Juliet.

QUOTATIONS

"We have, to be sure, more hormones than Galen had humours, but they serve much the same speculative purpose".

Harvey Cushing, 1930

"The co-existence of disordered endocrine mechanisms with psycho-neurotic or psychotic states suggests some relationship between pituitary-adrenal activity and mental processes. The precise nature is not yet established".

Hans Selye, 1950

PATIENT WITH CUSHING'S SYNDROME



BEFORE AFTER TREATMENT

4 months 28 months

DECLARATION OF CANDIDATE

I, William Francis Kelly declare that:

1. I am the author of the thesis entitled "Cushing's syndrome - a clinical, biochemical and psychiatric study of 209 patients".
2. This thesis, which is now submitted for the degree of Doctor of Medicine, has not been submitted for any other degree.
3. Some of the work has been performed in collaboration with others. The extent to which assistance has been obtained from others is stated in the page of acknowledgments.
4. In my thesis I have referred to seven published papers of which I am the first author. The major part of the research and writing for these papers was undertaken by me.
5. Unless otherwise stated, all books and papers referred to have been consulted by me personally.

Signed William Kelly

Date June 20th 1983.

ABSTRACT

1. 209 patients with Cushing's syndrome have been studied. 147 (70%) were seen by me. Details were obtained from the case records of the other 62 patients.

2. The causes were: pituitary Cushing's disease (79%), adrenal adenomas (9%), adrenal carcinomas (5%), ectopic ACTH (4%) and miscellaneous (3%). Details are given of symptoms and signs at diagnosis, and the success or failure of therapies..

3. 37% of 83 patients at risk developed Nelson's syndrome at a mean interval of 6.3 years (range 1-14) after total adrenalectomy.

4. Significant psychiatric abnormalities were identified in 65% of 209 patients with untreated Cushing's syndrome. Depressive illness was common (63% of patients). Other diagnoses were anxiety (12%), and mania or hypomania (3% of patients). Psychiatric abnormalities were more frequent in patients with Cushing's disease compared to a control series of patients with other pituitary tumours.

5. A prospective study was commenced of patients with active Cushing's syndrome. Present State Examinations with Catego analysis were done on 43 patients of whom 20 (46%) had neurotic depression, 6 (14%) retarded depression, 8 (19%) non-specific neurotic symptoms and only 8 patients (19%) were normal.

Hamilton depression scale ratings were obtained on 53 patients, Crown-Crisp Experiential Index on 39 patients and Eysenck Personality Inventory on 39 patients.

6. After treatment which lowered cortisol levels to normal there were statistically significant improvements in: Catego ratings (25 patients), depression measured on the Hamilton Scale (36 patients), depression, anxiety and somatic symptoms on the Crown-Crisp Experiential Index (25 patients), and neuroticism on the Eysenck Personality Inventory (26 patients).

7. Associated with the psychiatric and psychological improvements there were statistically significant improvements in urinary and plasma cortisol (decrease); serum oestradiol and sex hormone binding globulin in females (increase); and in serum testosterone in males (increase). There were no significant changes in concentrations of serum thyroxine, gonadotrophins or prolactin. There were no significant changes in plasma total or free tryptophan, which is therefore unlikely to be the cause of depression in patients with Cushing's syndrome.

8. The most important factor in relieving the depression associated with Cushing's syndrome is to reduce the cortisol levels to normal.

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ABBREVIATIONS

CUSHING'S SYNDROME - DIAGNOSTIC CATEGORIES

CD ____ Pituitary-dependent Cushing's Disease

AA ____ Adrenal Adenoma

AC ____ Adrenal Carcinoma

EA ____ Ectopic ACTH

OC ____ Other Cushing's syndrome: Cyclical, Alcoholic, Nodular Adrenal Hyperplasia

CUSHING'S SYNDROME - TREATMENTS

BA ____ Bilateral Adrenalectomy

UA ____ Unilateral Adrenalectomy

PI ____ Pituitary Implant

NS ____ Neurosurgery

RT ____ Radiotherapy

MET ____ Metyrapone

MED ____ Medical

MISC____ Miscellaneous

ABBREVIATIONS

PSYCHIATRIC RATING SCALES

PSE ____ Present State Examination

CATEGO ____ Diagnostic Category

- R ____ Retarded Depression
- N ____ Neurotic Depression
- X ____ Non-specific Neurotic
- O ____ Other Psychosis

CCEI ____ Crown - Crisp Experiential Index

- ANX __ Anxiety
- PHO __ Phobia
- OBS __ Obsession
- SOM __ Somatic
- DEP __ Depression
- HYS __ Hysteria

EPI ____ Eysenck Personality Inventory

- E ___ Extraversion
- N ___ Neuroticism
- L ___ Lie

ABBREVIATIONS

BIOCHEMISTRY

ACTH	____	Adrenocorticotrophic Hormone
UFC	____	Urinary Free Cortisol
17 OGS	____	17 Oxogenic Steroids
17 OS	____	17 Oxo Steroids
E_2	____	Oestradiol
T	____	Testosterone
SHBG	____	Sex Hormone Binding Globulin
LH	____	Luteinising Hormone
FSH	____	Follicle Stimulating Hormone
PRL	____	Prolactin
T_4	____	Thyroxine
T_3	____	Tri-iodo-thyronine
Na	____	Sodium
K	____	Potassium
TRY	____	Tryptophan

SCOPE OF THESIS

The original observations that led to this study were that many previous assessments of psychiatric abnormalities in patients with Cushing's syndrome had been retrospective, qualitative (rather than quantitative), and lacking in control data. I was able to interview and examine large numbers of patients who had Cushing's syndrome so I took the opportunity to assess many of these prospectively. I used modern, well-validated rating scales for psychiatric and psychological assessments. A series of other patients with other endocrine disorders matched for age and sex were included for control purposes. During the period of observation after endocrine treatment, usually adrenal or pituitary surgery, hormone assessments were made including thyroxine, sex steroids, gonadotrophins and prolactin to see if these correlated with the mental changes. The hypothesis was tested that depression in patients with Cushing's syndrome may be due to the lowering of plasma total and free tryptophan (and hence brain serotonin) by an effect of cortisol on the enzyme tryptophan oxygenase. My objective has been to make a comprehensive clinical, psychiatric and biochemical assessment of patients with Cushing's syndrome in order to delineate and explain the mental changes that were noted.

CHAPTER 1

HISTORICAL REVIEW OF DIAGNOSIS AND TREATMENT OF CUSHING'S SYNDROME

The existence of the pituitary gland was known to the ancient Greeks. However, detailed knowledge of its function and the inter-relationship with the hypothalamus and adrenal cortex has only become available during the last 60 years. Claudius Galen (AD I30-200) taught that the pituitary gland acted as a filter or trap by which the fluid in the cerebral ventricles was transformed from vital to animal spirits, which were discharged into the nose and pharynx(Siegel, I968). As with the other teachings of Galen, this was accepted as infallible for many centuries. Bartholomew Eustachius described the adrenal glands in man in I563, but the first understanding of their functions did not occur until Thomas Addison's clinical observations of adrenal insufficiency in I855(Addison, I868). Diseases due to overactivity of the adrenal gland were recognised later. In I9I2 Harvey Cushing, an American neurosurgeon, observed a patient with a syndrome which included obesity, increased hair growth and amenorrhoea. In his classical monograph, Cushing (I932) published details of twelve patients who had the symptoms and physical signs of the syndrome that was later named

"Cushing's syndrome". In six of the eight patients for whom there was full pathological evidence, there was a pituitary adenoma, usually basophilic, and often small. The first pituitary adenoma was the size of a millet seed and Cushing's prescient observation was that a small anatomical lesion could cause a very severe clinical syndrome. It was not possible to measure either cortisol or ACTH when Cushing made his observations. Cushing believed that the pituitary gland was primarily at fault, causing secondary pathological changes in the adrenal gland. This is true for most patients with Cushing's syndrome, and the term "pituitary Cushing's disease" is used for the condition of bilateral adrenal gland hyperplasia, secondary to excessive pituitary secretion of ACTH. The first pituitary adenoma causing Cushing's disease was reported in 1915 by Dr Anderson, who then believed it to be a case of hypopituitarism with secondary adrenal hyperfunction. Two other cases with similar clinical signs with small pituitary adenomas were reported by Dr Zondek in 1923 and by Dr Parkes-Weber in 1926. In 1931 one of Professor Cushing's co-workers, Dr Teel, predicted correctly, before death, the presence of a small basophil adenoma in a patient with the signs of Cushing's syndrome.

In I927 Hartman had showed that an extract of the adrenal cortex had a role in maintaining life. In I936 Kendall in the United States and Reichstein in Switzerland obtained cortisone from the adrenal cortex. In I949 the clinical application of cortisone by Hench in treating rheumatoid arthritis, and then a variety of other diseases, led to the widespread availability of corticosteroids for therapeutic purposes, commencing in the I950's.

Knowledge was advanced with the development and availability of biochemical assays for urinary corticosteroids and their metabolites in the I950's, and by a cheap and simple method of estimating "cortisol" in plasma (Mattingly, I962). Before I950 it was known that the varied features of Cushing's syndrome could be alleviated by adrenalectomy but that patients often died within a few days of operation from symptoms of adrenal insufficiency. When corticosteroid replacement therapy became available partial and total adrenalectomy became acceptable as a safe and effective method of treating all forms of Cushing's syndrome(Welbourn et al, I97I). In I958, Nelson and his colleagues from Boston noted increased skin pigmentation and expansion of the pituitary gland in a patient who had been treated three years previously by total adrenalectomy for pituitary Cushing's disease. Enlargement of a pituitary adenoma may cause bitemporal visual field

defects, blindness, and cranial nerve palsies, compression of the hypothalamus and spontaneous infarction of the adenoma. The incidence of Nelson's syndrome, is between 10 to 48% of patients with pituitary Cushing's disease who have been previously treated by total adrenalectomy (review, Kelly et al, 1983b). The incidence depends on the duration of follow up and the skill with which the pituitary has been radiographed. This refocused attention on the pituitary gland as the primary seat of pathology in pituitary Cushing's disease, but it remains possible that in some patients the basic abnormality is in the hypothalamus (Krieger, 1982). Treatment of pituitary Cushing's disease was therefore directed at the pituitary gland by neurosurgeons who attempted to remove a discrete microadenoma, while leaving other pituitary functions intact (Hardy, 1978) or by the implantation of radioactive seeds (Burke et al, 1973b). Medical treatments for pituitary Cushing's disease included metyrapone, an inhibitor of cortisol biosynthesis (Jeffcoate et al, 1977 and 1979), and cyproheptadine, which may act on the hypothalamus (Krieger, 1975). Cushing's syndrome due to adrenal adenomas or carcinomas is best treated by surgical removal of the primary tumour (Welbourn et al, 1971; Kelly et al, 1979). In 1962 Meador et al described the ectopic ACTH syndrome where ACTH is

made by a tumour. The most common primary tumour is in the lung, although other tumours secreting ACTH have been discovered in the thymus, gonad, pancreas, and small bowel (Freidman et al, 1966; Landon et al, 1967). The case of Cushing's syndrome described by Brown in 1928 is probably the first recorded patient with the ectopic ACTH syndrome.

The clinical diagnosis of Cushing's syndrome is made from the well-known symptoms and physical signs. These include obesity, plethoric face, hypertension, menstrual disturbances and hirsutism in females, muscle weakness and wasting, easy bruising, and mental disorders (Cushing 1932; Soffer et al, 1961a; Ross et al, 1966; Welbourn et al, 1971; Liddle GW, 1981). A useful biochemical screening test for Cushing's syndrome is a 24 hour urine collection for estimation of free cortisol (Beardwell et al, 1968). In addition, patients with Cushing's syndrome have elevated serum cortisol at midnight, with a lack of the usual diurnal rhythm (Doe et al, 1960). The aetiology of Cushing's syndrome is then investigated by dexamethasone suppression (Liddle, 1960), metyrapone stimulation (Liddle et al, 1959), assay of plasma ACTH (Rees et al, 1971) and radiographs of the pituitary and adrenal gland. Recently, computerised tomography scanning has improved the detection rate of pituitary and adrenal lesions.

It has been well recognised that many kinds of physical and psychological stress can result in increased secretion of cortisol, with increased serum concentrations, and increased excretion of free cortisol in the urine (Albright, 1943; Bliss et al, 1956; Mason, 1959 and 1968). Papez (1937) linked the limbic system and emotions. Hans Selye developed the idea of a general adaptation syndrome to stressful stimuli (Selye, 1950 and 1952). More recent work has demonstrated that neuronal influences cause the release of corticotrophin releasing factor from the hypothalamus, with consequent release of ACTH from the pituitary, and cortisol from the adrenal cortex (review, Krieger, 1982). It has been demonstrated that patients with depressive illness have elevated plasma and urinary corticosteroid levels, with disturbance of the diurnal rhythm, and resistance to dexamethasone suppression (Board et al, 1957; Gibbons and Mc Hugh, 1962; Gibbons 1965; Butler and Besser, 1968; Carroll et al, 1968, 1972, 1976 a-c; Cope, 1972). It has been suggested that diagnostic difficulties may occur in the interpretation of cortisol results in a depressed patient in whom Cushing's syndrome is suspected (Butler and Besser, 1968). These abnormalities of cortisol return to normal with the successful treatment of depression. (Butler and Besser 1968, Carroll 1972).

Pituitary-adrenal function has been very thoroughly studied in patients with depressive illness, (Sachar, 1967a,b; Becker, 1974; Mendels, 1975), but studies of depression in patients with Cushing's syndrome are less common. This probably reflects the availability of patients since depressive illness is common, but Cushing's syndrome is rare.

CHAPTER 2

HISTORICAL REVIEW OF PSYCHIATRIC ABNORMALITIES IN PATIENTS WITH CUSHING'S SYNDROME

The interaction of mind and body and the physiological basis of the emotions has fascinated philosophers and scientists of all ages. The idea that changes in the pituitary and adrenal glands could cause physical and mental illness is surprisingly old.Hippocrates of Cos (circa BC 460-375) taught that our temperaments are based on four humours- phlegm, blood, yellow bile and black bile (Lloyd, I978). Over two thousand years later, people are still described as phlegmatic, sanguine, choleric or melancholic. Galen of Pergamon (AD I20-200) thought that certain combinations of humours were associated with changes in body and mind. Nasal mucus, or phlegm, was the humour that was believed to be a waste product of the brain. Indeed, the Latin word " pituita " means phlegm, and the pituitary gland was given that name since it was thought to be a filter or trap for phlegm as it passed to the nose. Galen also described the position of the adrenal glands, but he did not name them or associate them with a particular bodily humour. Renaissance physicians extended Galen's views with the hypothesis that black bile, or melancholia, was concentrated in the adrenal glands. Bartholinus (AD I6I6- I680) proposed that black bile is eliminated from the adrenal glands, or glandulae atrabiliares as Eustachius had named them. Siegel (I968) has summarised the views of Galen in a historical context. The renaissance philosopher and bachelor of Divinity Robert Burton,

(AD I577- I640), wrote the classic treatise " The Anatomy of Melancholy ". An eloquent statement of the difficulty in classifying and measuring psychiatric symptoms was made by Burton:

" the tower of Babel never yielded such confusion of tongues as this chaos of melancholy doth variety of symptoms ".

Substituting "hormone" for "humour" in the classical texts gives them a surprisingly modern appearance. Harvey Cushing wrote in I930:

" We have to be sure more hormones than Galen had humours, but they serve much the same speculative purpose. It was the pituitary body of old that secreted the phlegm which was cold and humid and when predominant caused constitutional indolence or apathy. In Galenic terms, we could well enough explain the placid temperament of a patient with a chromophobe adenoma as one who is dry and sluggish from retention of pituita in the phlegmatic glandula ". (Cushing, I930).

Harvey Cushing recognised depression and anxiety in several of his patients with "pituitary basophilism" (Cushing, I932). In the first isolated descriptions of other patients with Cushing's syndrome, there were several reports of mental disorders.Schlezinger and Horwitz (I940) described a depressed patient with Cushing's syndrome in whom autopsy showed changes in the right frontal lobe. They wondered whether the patient had

suffered from an encephalitic-neuroendocrine disorder. Spillane (1951) described 7 patients with Cushing's syndrome, of whom 4 had nervous or mental symptoms; a review of 50 patients in the literature up to 1950 showed that 18 had psychotic disturbances, and that depression was the commonest psychiatric symptom (Spillane, 1951).

When cortisone and ACTH became available in the 1950's and were given to patients with a variety of different diseases there were reports of psychiatric illness (Rome and Braceland, 1950; Glaser, 1953; Quarton et al, 1955; Hall et al, 1979). Many patients suffered from depression but there was a significant incidence of mania, and hypomania (Woodbury, 1958; Michael and Gibbons, 1963). It was difficult to ascertain whether these disturbances were primarily caused by the drugs, or a reflection of the underlying diseases for which the drugs were given.

In 1952 Trethowan and Cobb reported on 25 patients with Cushing's syndrome with full details of the neuropsychiatric abnormalities. The question arose as to whether the psychiatric abnormalities, usually depressive illness, were produced as a result of the abnormal hormone levels or whether psychiatric abnormality was a reactive product of physical changes, which include disfigurement, weakness and pain. The other question is whether life-events, such as bereavement, or personal misfortunes, can predispose a person to develop Cushing's syndrome, or cause psychological abnormality when Cushing's syndrome develops.

It was proposed by Gifford and Gunderson (1970a,b) that some cases of Cushing's syndrome represent a psychosomatic disorder, defined as a pathophysiological reaction to bereavement. Furger (1961) stated that Cushing's syndrome developed when prolonged and severe mental stress occurred in 7 of 13 patients, and that the severity of the psychological abnormalities was related to the previous personalities of the patients. A similar view was expressed by Regestein et al (1972) in a study of 7 patients, in whom it was believed that elevated steroid levels had elicited latent psychopathological tendencies found premorbidly in the patients.

The difficulty in measuring psychiatric abnormalities was commented on by Cushing in 1913:

" it is even more common for the physician or surgeon to eradicate or otherwise treat the obvious focus of disease, with more or less success, and to leave the mushroom of psychic deviations to vex and confuse the patient for long afterwards, if not actually to unbalance him. Unhappily for those of us who lean on instruments of precision there is no acceptable psychometer from which we may take readings - nor will there be".

I believe that Dr Cushing was too pessimistic. Recently rating scales have been developed, so that psychiatric morbidity can be assessed objectively, and it is therefore appropriate to make a new study of patients with Cushing's syndrome. The rating scales are

described in detail in the next chapter.

No previous study of patients with Cushing's syndrome has used control groups of patients with other illnesses, although depression is a common symptom of patients in hospital (Maguire et al, 1974; Moffic and Paykel, 1975). Therefore I included a control group of patients in my study

Hans Selye said:

" the coexistence of disordered endocrine mechanisms with psychoneurotic or psychotic states suggests some relationship between the pituitary-adrenal activity and mental processes. The precise nature is not yet established" (Selye, 1950). The obvious hormones to measure are cortisol and ACTH, and interesting quantitative studies were later reported (Carroll,1968 to 1976). In this study I decided to make comprehensive measurements of other hormones for three reasons. Firstly, many patients with Cushing's disease are treated by pituitary surgery or radio-therapy which can cause secondary changes in thyroid and gonadal hormones. Hypothyroidism and hyperthyroidism are well known to cause psychiatric symptoms (Granville Grossman, 1971; Whybrow and Hurwitz, 1976; Lishman, 1978). Secondly, adrenalectomy eliminates the adrenal contribution to sex steroid metabolism with potential psychological consequences. Thirdly, there is evidence

from experiments in animals that raised cortisol levels could affect the metabolism of monoamines, and therefore alter the availability of these at receptor sites in the brain. In 1965 Schildkraut developed the hypothesis that depressive illness may be caused by a deficit of noradrenaline at receptor sites in the brain. A deficit of brain serotonin is also a possible factor in some depressive illnesses (Lapin and Oxenkrug, 1969; Asberg et al, 1976; Träskman et al, 1980; Van Praag and de Haan, 1980). Coppen showed in 1973 that when depressed females were observed until they were clinically recovered, then plasma free tryptophan increased, but total tryptophan was unchanged. In my study a biochemical mechanism has been tested whereby depression might occur in patients with Cushing's syndrome. Cortisol at pathological levels can increase the activity of the enzyme tryptophan oxygenase (l-tryptophan: oxygen oxidoreductase, EC 1.13.1.12)(Knox and Auerbach, 1955; Altman and Greengard, 1966a,b). As a result there will be more oxidative metabolism of tryptophan, so that less may be available for uptake into the brain and for the subsequent conversion to 5-hydroxytryptamine (5-HT, serotonin). Under these conditions brain serotonin concentrations fall (Curzon and Green, 1971). There is evidence that the concentration of free tryptophan regulates brain uptake of tryptophan,

and hence serotonin synthesis (Knott and Curzon, 1972; Tagliamonte et al, 1973; Curzon and Knott, 1974). Fernstrom and co-workers, (1971 and 1976) have shown positive correlations between total tryptophan concentrations in plasma and brain. It was not possible to measure serotonin concentrations in the brains of the patients with Cushing's syndrome, so plasma total and freely diffusible tryptophan was measured. The hypotheses to be tested were that (1) patients with active Cushing's syndrome would have lower levels of plasma tryptophan than control patients; (2) that there would be a correlation between the biochemical severity of Cushing's syndrome (as assessed by urinary free cortisol excretion) and plasma tryptophan, and (3) that the severity of depressive illness would be correlated with the level of freely diffusible tryptophan. Therefore I decided to include measurements of plasma concentrations of total and free tryptophan, in addition to comprehensive hormone measurements in a prospective study of patients with Cushing's syndrome.

CHAPTER 3

METHODS

METHODS

Patients

All of the 209 patients in this study had some of the classical physical signs described by Harvey Cushing in 1932. One hundred and forty seven patients (70%) of the patients were investigated by me during the routine evaluation of their disease; after an explanation all patients gave consent to an interview and blood tests. A note was made on a standardised questionnaire form of the past medical and past psychiatric history. Enquiry was made about life events which might be connected with physical or psychiatric illness. Blood was taken for analysis of hormones and urine was collected for analysis of steroids excreted. Blood samples for ACTH and tryptophan estimations were taken into cooled tubes, centrifuged immediately, and the plasma was deep frozen at -20^{0}C. Physical examinations and psychiatric assessments were made on the same days that biochemical tests were done.

Clinical assessment was made of the presence or absence of plethora, 'moon' face, 'buffalo' hump, hirsutism, weakness, conjunctival oedema, ankle oedema, bruising, striae, and acne. Obesity was diagnosed on examination, provided the patient was also in excess of average body weight for the patient's height, age

and sex according to tables (Diem and Lentner, 1970, page 711 for adults and Tanner et al, 1966 for children). Hypertension was diagnosed when either the systolic or diastolic pressure (or both) was greater than two standard deviations above the mean for age and sex (Diem and Lentner, 1970, page 553). Exophthalmos was assessed by me using a Hertel exophthalmometer; the mean value for 50 normal adults (36 female) was 11.8mm, SD 2.1, Kelly et al, 1983c, so values exceeding 16mm were taken as denoting exophthalmos. Diabetes mellitus was diagnosed when the random blood glucose exceeded 9mmol/l, or the value 2 hours after 50g glucose orally exceeded 6.7 mmol/l (impaired glucose tolerance) or 10 mmol/l (diabetes mellitus, Oakley, Pyke and Taylor, 1978.)

Patients were treated at these hospitals: Hammersmith Hospital, London - 109 (52%); Manchester Royal Infirmary - 87 (42%); Christie and Withington Hospitals, Manchester - 12 (6%) and Middlesex Hospital - 1 patient.

Psychiatric assessments

Clinical interviews with patients followed conventional English psychiatric practice (Slater and Roth, 1977). In addition I used the Present State Examination (PSE) of Wing et al, 1974. The PSE was developed to provide

reliable, precise and objective data concerning the present mental state of patients suffering from neuroses and functional psychoses. The reliability of the PSE has been validated in a population study (Wing et al, 1977). The data from the PSE was analysed on the Catego programme to measure and classify the psychiatric symptoms. There are several scales for measuring the severity of depressive illness. I chose the Hamilton Rating Scale (HRS, Hamilton 1960 and 1967) since this has been used in many studies of psychiatric patients,(discussed by Hamilton, 1979). The correlation coefficient for HRS ratings between independent observers in the present study was high ($r= 0.87$, $p<0.01$, $n=20$). The Crown-Crisp Experiential Index (CCEI, Crown and Crisp, 1979) was designed to quantify the common symptoms and traits relevant to the conventional categories of psychoneurotic illness and personality disorder; the six subscales are designated: anxiety, phobia, obsession, somatic, depression and hysteria. The CCEI was published originally as the Middlesex Hospital Questionnaire (Crown, 1974) and has been used in many studies (references given in Crown and Crisp, 1979).

In addition, I used the Eysenck Personality Inventory (EPI, Eysenck and Eysenck, 1964). The EPI was selected to quantify the two major dimensions of personality, namely extraversion and neuroticism; the

views of Eysenck have been published in detail (Eysenck, 1967), and the EPI has been used in many clinical studies, but it has not been used previously for patients with Cushing's syndrome. Additional objective quantitative evidence of symptoms was obtained from analogue scales where depression and anxiety were self-rated by patients on a linear scale measuring 100mm. For the data in Chapter 6 psychiatric illness was also rated by clinical judgement as absent, mild, moderate or severe after considering all the known facts about an individual patient.

Biochemical assays

The following methods were used: urinary free Cortisol - Beardwell et al, 1968; 17-oxogenic and 17- oxosteroids - Medical Research Council Committee, 1963; plasma cortisol by fluorimetry, - Mattingly, 1962 and by competitive protein binding; plasma ACTH - Rees et al, 1971; serum testosterone and oestradiol - Large and Anderson, 1979; serum sex hormone binding globulin (SHBG) - Anderson et al, 1976; serum luteinising hormone (LH), follicle stimulating hormone (FSH), and prolactin (PRL) were measured using specific double antibody radioimmunoassays. Assay results were expressed in terms of the appropriate standard

preparations from the National Institute of Biological Standards and Control, Holly Hill, Hampstead. The standards employed were LH 68/40, FSH 69/104, and PRL 75/504. Thyroxine and T_3 were measured by radioimmunoassays; plasma total tryptophan - Denkla and Dewey, 1967, and binding to albumin - Bender et al, 1975, allowing the calculation to be made of diffusible or free tryptophan. Details of biochemical assays done by me or by others are detailed under Acknowledgements (please see index).

Statistics

Data with a theoretical Normal distribution were analysed using the appropriate parametric tests (e.g. Student t-test, analysis of variance). The summary statistics used were means and standard deviations. Data with a non-Normal (usually skewed) distribution were analysed using either contingency tables (categorical data) or an appropriate non-parametric test (Wilcoxon test, Mann- Whitney U-test). The summary statistics used were either frequency counts or medians and ranges. Survival curves were calculated using actuarial life table methods. Correlations between variables were measured using the Spearman correlation coefficient, which is a rank sum test and makes no assumption about the distribution of the 2 parameters.

Statistical data was stored and analysed on the computer facilities of Manchester University Regional Computer Centre, using the Statistical Package for the Social Sciences, version 8 dated June 1979.

Control patients

These were selected from patients with pituitary adenomas secreting growth hormone or prolactin who were admitted to the same ward as the patients with Cushing's syndrome. The control patients were submitted to the same kind of investigative procedures including blood tests and radiographs of the pituitary gland, and these patients knew that surgical or medical therapy might be necessary. There were 24 control patients of whom 20 (83%) were female; the mean age was 40 years (range 19 to 65 years). Therefore the control series was closely matched for age and sex distribution with the patients with Cushing's syndrome (79% female; mean age 39 years, see Tables 2 and 3).

CHAPTER 4

CLINICAL DETAILS OF PATIENTS

Details are given in Appendix 1 of the 209 patients with Cushing's syndrome. The details include sex, age at diagnosis of Cushing's and Nelson's syndromes, type and effect of primary and subsequent treatments, together with relevant and significant life events and an assessment of psychiatric morbidity. Most patients (70%) were known to me personally. Where necessary I have contacted patients, their relatives, and hospital and general medical practitioners.

Details of the causes of Cushing's syndrome are shown in Table 1, the sex distribution in Table 2, and age at diagnosis in Table 3. Pituitary Cushing's disease was diagnosed in 166 patients (79%). The majority of patients (162 of 209; 78%) were female. The mean age at diagnosis of the patients with pituitary Cushing's disease (36.7 years) was less than that due to other causes ($p < 0.001$, analysis of variance). Figures 1 and 2 show the age at diagnosis according to the sex of the patients and the causes of Cushing's syndrome.

The duration from onset of symptoms to diagnosis of Cushing's syndrome is shown in Table 4. The time interval was less for patients with adrenal carcinomas and with ectopic ACTH secretion compared to other causes of Cushing's syndrome ($p < 0.01$, Wilcoxon test).

TABLE 1

DETAILS OF PATIENTS - CAUSE OF CUSHING'S SYNDROME

DIAGNOSIS	NUMBER OF PATIENTS	PER CENT	CASE HISTORIES (INCLUSIVE) See Appendix 1
CD	166	79.4%	1 - 166
AA	18	8.6%	167 - 184
AC	10	4.8%	185 - 194
EA	9	4.3%	195 - 203
OC	6	2.9%	204 - 209
	209	100%	

CD ____ Pituitary Cushing's Disease

AA ____ Adrenal Adenoma

AC ____ Adrenal Carcinoma

EA ____ Ectopic ACTH

OC ____ Other Cushing's:

Nodular adrenal hyperplasia	1
Alcoholic	3
Iatrogenic	1
Cyclical	1
	6

TABLE 2

DETAILS OF PATIENTS - SEX AND CAUSE OF CUSHING'S SYNDROME

DIAGNOSIS	FEMALES	PER CENT	MALES	PER CENT	TOTAL
CD	129	78%	37	22%	166
AA	17	94%	1	6%	18
AC	8	80%	2	20%	10
EA	7	78%	2	22%	9
OC	1	17%	5	83%	6
	162		47		209
PER CENT	78%		22%		100%

TABLE 3

AGE AT DIAGNOSIS OF CUSHING'S SYNDROME

DIAGNOSIS	NUMBER OF PATIENTS	AGE - YEARS MEAN	RANGE	
CD	166	36.7	8 - 67	*
AA	18	41.9	25 - 63	
AC	10	48.1	30 - 73	
EA	9	55.3	29 - 74	
OC	6	47.6	17 - 70	
Total	209	38.7	8 - 74	

* 95% confidence limits 34.4 - 38.9 years.
Age at diagnosis of CD less than for other groups ($p < 0.001$, analysis of variance).

FIGURE 1

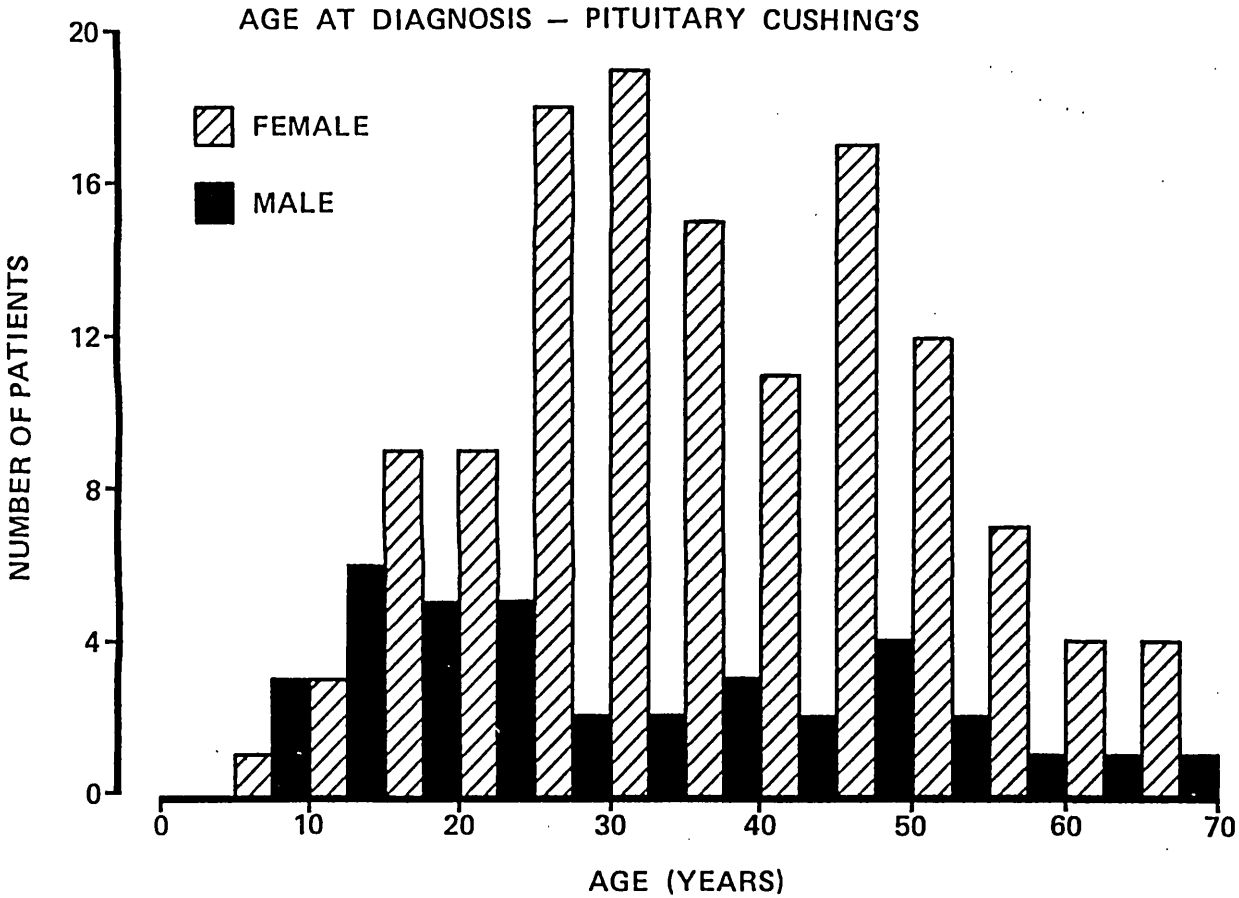

AGE AT DIAGNOSIS – PITUITARY CUSHING'S
FEMALE
MALE
NUMBER OF PATIENTS
0
4
8
12
16
20
0
10
20
30
40
50
60
70
AGE (YEARS)

FIGURE 2

AGE AT DIAGNOSIS – ADRENAL TUMOURS

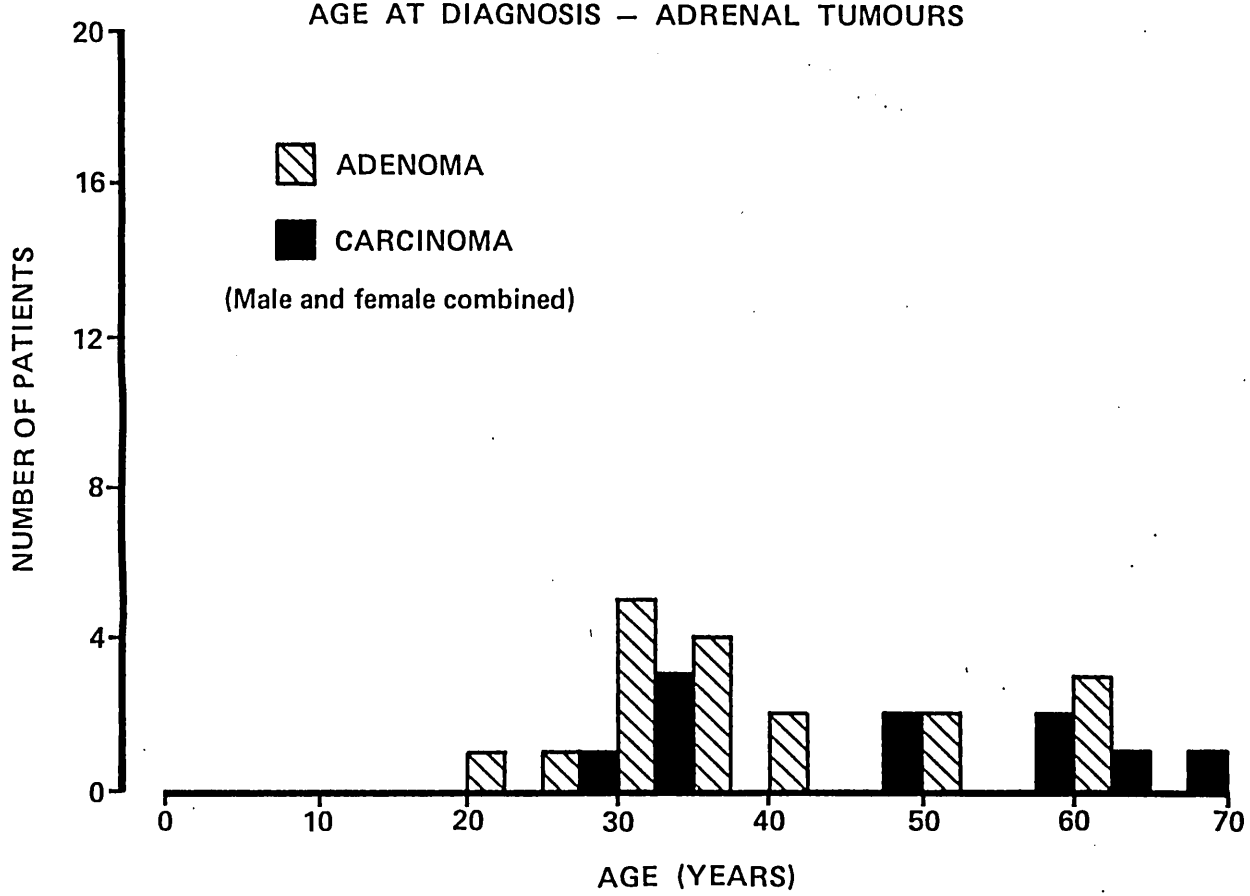


TABLE 4

CUSHING'S SYNDROME

DURATION OF SYMPTOMS - YEARS

	MEDIAN	RANGE	n=
CD	2.0	0.3 - 9	110
AA	2.0	0.3 - 7	15
AC	0.5*	0.3 - 1	8
EA	0.5*	0.2 - 1	8
OC	2.0	1 - 3	2
TOTAL	2.0	0.2 - 9	143

*p <0.01 compared to other types, Wilcoxon's test

SYMPTOMS AND SIGNS OF CUSHING'S SYNDROME

Twenty-four symptoms and signs of Cushing's syndrome have been analysed in Tables 5 and 6. These symptoms and signs are ranked in order of frequency in the present series, and details from two other published series (Soffer et al, 1961a; Ross et al, 1966) are included for comparison. Conjunctival oedema (79%) ranks high in the present series and this was one of the features specially sought in the patients from Hammersmith Hospital. Hypertension was taken as BP >140/90mmHg by Ross and BP >150/90 by Soffer. Details of blood pressure in the present series are on Table 6. Since the patients studied by me ranged from 8 to 74 years, I decided to define hypertension based on age and sex-matched persons (see Methods). The incidence of psychiatric illness of 65% in the present series is substantially higher than those from the other two series. This may be due to the special care with which psychiatric illness was searched for my study. It is possible that exophthalmos is underdiagnosed in patients with Cushing's syndrome. The present series includes the only objective measurements that have been reported. In 12 consecutive, unselected patients with active Cushing's syndrome (all with Cushing's disease) the

mean exophthalmos reading was 16.3mm (SD 2.9, range 12.5 to 22mm). This is significantly more ($p < 0.05$, Student's unpaired t-test) than that of a control population of 50 patients without endocrine disease where the mean exophthalmos reading was 11.8mm (SD 2.1, range 8 - 17mm). However there was no clinical disability related to the exophthalmos in patients with Cushing's syndrome, in marked contrast to the severe symptoms and signs noted by me in 18 patients with Graves' ophthalmopathy where the mean exophthalmos reading was 21.6mm (SD 4.1, range 12 - 29mm, Kelly et al, 1983c). It is interesting that Cushing's first patient, Minnie G, had "slight exophthalmos", and this was noted in 4 of the 12 patients (33%) reported by Cushing in 1932. Since then exophthalmos has received little attention in the literature on Cushing's syndrome, being noted in only 1 of 50 patients studied by Ross (1966) and 14 of 50 patients studied by Soffer (1961a).

URINARY FREE CORTISOL AT DIAGNOSIS

Details of urinary free cortisol are available at diagnosis for 92 patients (Table 7). There was a wide range of values for each type of Cushing's syndrome, and the distribution of results is log-Normal. The median value was lowest in patients with adrenal adenomas, and highest in patients with ectopic secretion of ACTH.

TABLE 5

SYMPTOMS AND SIGNS OF CUSHING'S SYNDROME

	PRESENT SERIES		REPORTED SERIES (%)	
	Per Cent	Number of Patients	Ross (n=50)	Soffer (n=50)
1. PLETHORA	97	133	84	78
2. MOON FACE	96	90	80	92
3. OBESITY	92	172	94	86
4. BUFFALO HUMP	91	64	?	34
5. FATIGUE	88	122	58	58
6. HIRSUTISM (Females)	86	111	82	84
7. AMENORRHOEA (Females)	85	67	76	72
8. WEAKNESS	80	127	58	58
9. CONJUNCTIVAL OEDEMA	79	43	?	?
10. ANKLE OEDEMA	75	61	?	66
11. EASY BRUISING	72	108	36	68
12. HYPERTENSION	68	164	72	88
13. PSYCHIATRIC ILLNESS	65	209	40	40
14. STRIAE	62	111	52	50
15. BACK PAIN	60	63	50	32
16. DECREASED LIBIDO	59	27	?	43
17. EXOPHTHALMOS	58	12	2	28
18. OSTEOPOROSIS	53	62	46	56
19. ACNE	50	58	40	36
20. HEADACHES	40	62	14	46
21. DIABETES MELLITUS	39	93	22	84
22. PATHOLOGICAL FRACTURES	24	67	?	40
23. IMPAIRED WOUND HEALING	20	49	?	14
24. RENAL CALCULI	12	65	16	?

See Chapter 3 for definitions of obesity, hypertension, exophthalmos and diabetes mellitus.
See Chapter 4 for discussion of Table 5.

TABLE 6

SIGNS OF CUSHING'S SYNDROME

BLOOD PRESSURE mm Hg

	MEAN	(SD)
SYSTOLIC	160	(32)
DIASTOLIC	102	(20)

n=153

OBESITY - % OF AVERAGE BODY WEIGHT

MEAN (SD)	126%	(27)
MEDIAN (RANGE)	121%	(63-187)

Weight exceeded average in 81%

n= 74

TABLE 7

URINARY FREE CORTISOL (nmol/24h) AT DIAGNOSIS

DIAGNOSIS	NUMBER OF PATIENTS	MEDIAN	RANGE
CD	67	712	302 - 11,150
AA	9	581	333 - 1,436
AC	7	1,540	866 - 18,280
EA	4	1,648	723 - 6,493
OC	5	787	280 - 4,390
TOTAL	92	765	280 - 18,280
NORMAL			< 270

INTERESTING PATIENTS

The following patients have been selected to draw attention to the problems of management of Cushing's syndrome. Details are in Appendix 1.

Cushing's disease (CD)

CD 19 Cyclical Cushing's syndrome. Very high urinary free cortisol. Euphoria and depression.

CD 21 Reactive depression.

CD 32 Paranoia. Depression. Good clinical and psychiatric response to a pituitary implant.

CD 63 Depression associated with Cushing's syndrome and also with post-operative adrenal insufficiency.

CD 89 Difficult treatment of Cushing's and Nelson's syndrome. Severe depression.

CD 92 Adverse social circumstances and stressful life events.

CD 125, 128 Hypomania and depression.

CD 129 Depression. Possible suicide.

CD 163 Psychopath.

Adrenal adenoma(AA)

AA 167 Anxiety and depression.

Adrenal carcinoma (AC)

AC 185, 186 Psychosis.

DISCUSSION

The present study comprises 209 patients with Cushing's syndrome. This may be compared with the personal series of: Harvey Cushing in 1932 (12 patients), Hurxthal and O'Sullivan in 1959 (34 patients), Soffer in 1961 (50 patients), Orth in 1971 (108 patients), Welbourn in 1971 (60 patients), Burke and Beardwell in 1973a (40 patients) and Nabarro in 1977 (68 patients). 79% of the present series were pituitary-dependent, compared to 69% (Soffer et al, 1961), 59% (Orth and Liddle, 1971), 58% (Welbourn et al, 1971) and 69% (Nabarro, 1977). In a collected series pituitary Cushing's disease was reported in 70% of adults (Soffer et al, 1961b). Adrenal adenomas accounted for 9% of the present series compared to 16% (Soffer et al, 1961a), 10% (Welbourn et al, 1971) and 16% (Orth et al, 1971). Therefore pituitary-dependence is found in the majority of patients with Cushing's syndrome, the incidence varying between 58-79%. The majority (78%) of patients in the present series were female, in agreement with the incidence of 79% of cases collected from the literature by Soffer (1961b). The mean age at diagnosis of pituitary Cushing's disease in the present series was significantly less than that from other causes of Cushing's syndrome. The peak incidence of age at diagnosis of pituitary Cushing's disease was between 31-35 years in females and between 11-15 years in males. However, the disease can occur at any age.

CHAPTER 5

RESULTS OF TREATMENT FOR CUSHING'S SYNDROME

TREATMENT OF CUSHING'S SYNDROME

Details are shown in Table 8. The treatments given reflect the type of Cushing's syndrome and the facilities that were available at different hospitals. The most frequently used primary treatment was bilateral adrenalectomy (68 patients). Second, third and fourth treatments were needed in 70, 22 and 4 patients respectively.

CLINICAL RESPONSE TO TREATMENT OF CUSHING'S SYNDROME

With successful treatment of Cushing's syndrome a remission of the physical signs noted in Table 5 occurs. Objective improvements were found in:

1. Increase in height of children (<17 years at treatment)in 100% of 16 patients.
2. Improvement (reduction) in blood pressure in 89% of 106 patients.
3. Improvement in glucose tolerance 85% of 13 diabetic patients.
4. Decrease in weight of adults (≥17 years at treatment in 78% of 115 patients.

TABLE 8

TREATMENT OF CUSHING'S SYNDROME

TREATMENT	NUMBER OF PATIENTS							
	FIRST	%	SECOND	%	THIRD	%	FOURTH	%
BA	68	33	10	5	5	2	0	0
UA	36	17	14	7	3	1	1	.5
1+2/3A	9	4	1	1	1	1	0	0
PI	54	26	21	10	8	4	1	.5
NS	9	4	4	2	0	0	1	.5
RT & MET	8	4	7	3	2	1	0	0
MED	7	3	12	6	2	1	0	0
MISC	18	9	1	1	1	1	1	.5
	209	100%	70	35%	22	11%	4	2%

URINARY FREE CORTISOL AFTER TREATMENT

After treatment urinary free cortisol values were available at latest assessment for 77 patients; the median value was 129 nmol per 24 hours (range 30-1,530, normal <270). After treatment 86% of the 77 patients had normal excretion of urinary free cortisol; there were 7 patients with urinary free cortisol values between 271 and 400 nmol/24 hours, 3 patients with values between 401 and 1,000 nmol/24 hours, and one patient with an adrenal carcinoma who had a value of 1,530 nmol/24 hours. The decrease in urinary free cortisol after treatment is highly significant (n= 52, $p<0.0001$, Wilcoxon's test).

ASSESSMENT OF EFFECTIVENESS OF TREATMENTS

a) PITUITARY CUSHING'S DISEASE - TABLE 9

Of the 166 patients with pituitary Cushing's disease, 62 patients (37%) were treated firstly by bilateral adrenalectomy. There were 3 deaths which occurred within three months of this treatment, and 5 patients died during follow-up having had no further treatment. Further treatment was only required in 4 patients and this was adrenalectomy followed by a pituitary implant, and pituitary surgery in one patient;

TABLE 9

TREATMENT ANALYSED BY TYPE OF CUSHING'S SYNDROME

CUSHING'S DISEASE	FIRST TREATMENT NUMBER	PER CENT	DIED <3 months	DIED >3 months	OTHER TREATMENT NEEDED NUMBER
BA	62	37	3	5	4
UA	14	8	0	0	14
1+2/3A	9	5	0	1*	7
PI	54	33	1	8X	21 "
NS	8	5	1	0	5
RT & MET	8	5	0	2+	5
MED ⊡	6	4	0	0	4
MISC ◎	5	3	1	1	0
	166	100%	6	17	60 (36%)
MORTALITY			23(14%)		

* 1 Died after second treatment (adrenalectomy)

X 7 Died after second, third or fourth treatments

\+ 2 Died after adrenalectomy

"14 Treated by Pituitary Implants

⊡ 2 Metyrapone, 2 Trilostane, 2 Metyrapone and Aminoglutethimide

◎ 1 Refused treatment, 2 Terminal - pain and anxiety relieved, 2 Mild Cushing's - observation, retesting pending

pituitary implants in one patient; external pituitary irradiation and metyrapone, followed by an implant in one patient; pituitary irradiation and metyrapone in the fourth patient. Unilateral adrenalectomy was done in 14 patients (8%) and failed as a primary treatment in all of these. There were no deaths during follow-up but all 14 patients required further treatment which was eventually successful in all patients although one patient required 3 attempts at adrenalectomy, followed by a successful pituitary implant. Sub-total (one and two thirds) adrenalectomy was done in 9 patients. One patient died following surgery. Two patients have not required any further treatment but the remaining 7 have required other treatments. Pituitary implants were the first treatment in 54 patients (33%). There was one death in less than three months and a further 8 deaths during follow-up. Pituitary surgery was performed on 8 patients (5%). There was one death in less than three months and further treatment was not needed in 2 but was required in the other 5 patients. Medical treatment was given to 6 patients (4%) and miscellaneous treatments to 5 patients (3%). Of the 166 patients with pituitary Cushing's disease, there were 6 deaths within three months of primary treatment, and a further 17 deaths during follow-up. Of the 143

survivors, treatment was successful in 140; one patient refused treatment, and 2 patients with mild Cushing's syndrome are being observed and retested. Of the 140 patients successfully treated the methods that were eventually successful are analysed on Table 10.

b) ADRENAL ADENOMAS - TABLE 11

Of the 18 patients with adrenal adenomas, unilateral adrenalectomy was the primary treatment in 12, and relieved signs of Cushing's syndrome in all of them. One patient died during follow-up, more than three months after surgery. Bilateral adrenalectomy was done on 5 patients, one of whom died within three months. No patient required further treatment for an adrenal adenoma following adrenalectomy. One patient (AA 174) with an adrenal adenoma also had a pituitary tumour, shown both radiologically, and confirmed by histology after an initial pituitary operation. However, Cushing's syndrome persisted and was due to the co-existence of an adrenal adenoma which was removed, but the patient died six months afterwards.

c) ADRENAL CARCINOMAS - TABLE 11

Of the 10 patients with adrenal carcinomas, 9 were treated initially by adrenalectomy. One patient who was

TABLE 10

CUSHING'S DISEASE

SUCCESS OR FAILURE ANALYSED ACCORDING TO LATEST (OR ONLY) TREATMENT

	NUMBER OF PATIENTS			
TREATMENT	SUCCESS	FAILURE	TOTAL	PER CENT
BA	74	9	83	89%
UA	0	14	14	0%
1+2/3A	2	7	9	22%
PI	47	11	58	81%
NS	5	2	7	71%
RT & MET	9	3	12	75%
MED	3	3	6	50%
	140	49	189	74%

ADD UNTREATED:

Patient refused(CD 153)	1
Pending (CD 85 & 127)	2
	143
ADD PATIENTS —— WHO DIED	23
TOTAL WITH CUSHING'S DISEASE	166

TABLE 11

TREATMENT ANALYSED BY TYPE OF CUSHING'S SYNDROME

AA n=18	FIRST TREATMENT NUMBER	DIED <3 months	DIED >3 months	OTHER TREATMENT NEEDED NUMBER
UA	12	0	1	0
BA	5	1	0	0
NS	1	0	1*	1*
	18	1	2	1
AC n=10				
UA	9			
MED	1			
	10	All died		< 2 years

* Patient AA 174, had a pituitary adenoma and an adrenal adenoma; she died after adrenalectomy

AA - ADRENAL ADENOMA

AC - ADRENAL CARCINOMA

judged inoperable was treated medically.

d) ECTOPIC ACTH

The 9 patients had several treatments, including surgical removal of the primary tumour and chemotherapy, but all measures failed to relieve Cushing's syndrome.

e) OTHER AETIOLOGIES

Successful treatments in this group were: bilateral adrenalectomies for 1 patient with nodular adrenal hyperplasia (OC 204) and 1 patient with cyclical Cushing's syndrome, (OC 209), and withdrawal of steroids from 1 patient with iatrogenic disease (OC 208). Alcohol withdrawal succeeded temporarily in 3 patients with alcoholic pseudo- Cushing's syndrome (OC 205 - 207 inclusive).

NELSON'S SYNDROME

The patients at risk of developing Nelson's syndrome were those 83 who had been treated initially or eventually by total adrenalectomy. Of these 83 patients, 31 (37%)so far have developed Nelson's syndrome during a mean period of 6.3 years after adrenalectomy. Of the 31 patients with Nelson's syndrome, this was detected in 25 of the 64 (39%) who had never had previous pituitary

surgery or radiotherapy, during a mean period of observation after adrenalectomy of 6.7 (SD 3.8)years, range 2-14 years. However, Nelson's syndrome also occurred in 6 of the 19 patients (32%) who had previously had some form of pituitary surgery or radiotherapy, and who had been observed from the time of initial or eventual total adrenalectomy for a mean period of 5.0 (SD 3.9) years,range 1-12 years. There is no significant difference (chi^2 =0.4, p=0.50) in the incidence of Nelson's syndrome in patients with (32%) or without (39%) previous treatment to the pituitary gland, which might have been expected to have a prophylactic effect. The mean period of follow up was similar in the two groups of patients. It should be pointed out, however, that adrenalectomy was usually done where previous therapy had failed.

The treatments given to the 31 patients with Nelson's syndrome are shown in Table 12. Pituitary surgery was the most frequent first treatment (12 patients- 7 transethmoidal, 4 transsphenoidal, and 1 transfrontal). Seven patients with Nelson's syndrome required further treatment after a mean interval of 1.4 years from the primary treatment for Nelson's syndrome. The most common secondary treatment was external pituitary irradiation.

TABLE 12

TREATMENT OF NELSON'S SYNDROME

	NUMBER OF PATIENTS			
	FIRST	%	SECOND	%
NS	12	39	2	6
PI	9	29	1	3
RT	4	13	4	13
MISC	5	16		
PENDING	1	3		
	31	100%	7	22%

SURVIVAL OF PATIENTS WITH CUSHING'S SYNDROME

The mean duration of follow-up of 209 patients was 6.3 years (median 4.0 years, range 0.1-33), and 45 patients have died. Survival is analysed according to the cause of Cushing's syndrome in Table 13. Actuarial survival curves for patients with Cushing's syndrome are shown in Figure 3. Nineteen patients with neoplastic disease,due to carcinomas or tumours secreting ectopic ACTH all died in less than two years. Of the remaining 190 patients with non-malignant disease 26 (14%) have died during a median period of observation of 5 years.

DETAILS OF CAUSES OF DEATH

Of the 23 fatalities in patients with pituitary Cushing's disease, death was due to cerebro-vascular accidents in 7, myocardial infarction or congestive cardiac failure in 5, pneumonia in 2, renal failure in 2, suicide in 1, pancreatitis (also with pneumonia) in 1, adrenal insufficiency in 1, pulmonary embolus in 1, and septicaemia in a diabetic patient; details are lacking in two patients. Thus, cardiovascular and circulatory causes accounted for 13 of the 23 deaths. Ten of the deaths occurred less than three months after surgical procedures. One death occurred immediately after a carotid angiogram and 1 death

from renal failure resulted from therapy with vitamin D. One patient who died of adrenal insufficiency and 1 patient who died of septicaemia might have survived if they had presented sooner for medical treatment. Thus 14 of 23 deaths (61%) occurred soon after surgery or were preventable, iatrogenic, or potentially treatable. Of the 3 patients with adrenal adenomas who died, 1 had a cerebro-vascular accident 7 years after adrenalectomy, and she had been treated for hypertension. One patient died less than three months after adrenal surgery, which was complicated by a gastric fistula, an arterial thrombosis, and pneumonia. The third patient died of a pulmonary embolus, within three months of operation. All the patients with adrenal carcinomas had extensive metastatic disease and deaths were attributed to carcinomatosis. In 1 patient there was an abscess cavity around a hip prosthesis, and the physical signs of infection were probably suppressed by the endogenous production of cortisol. Metastatic cancer was present in all of the 9 patients with ectopic ACTH syndrome. In two of these 9 patients the immediate cause of death was peritonitis, the symptoms and signs of which were probably obscured by the high cortisol levels.

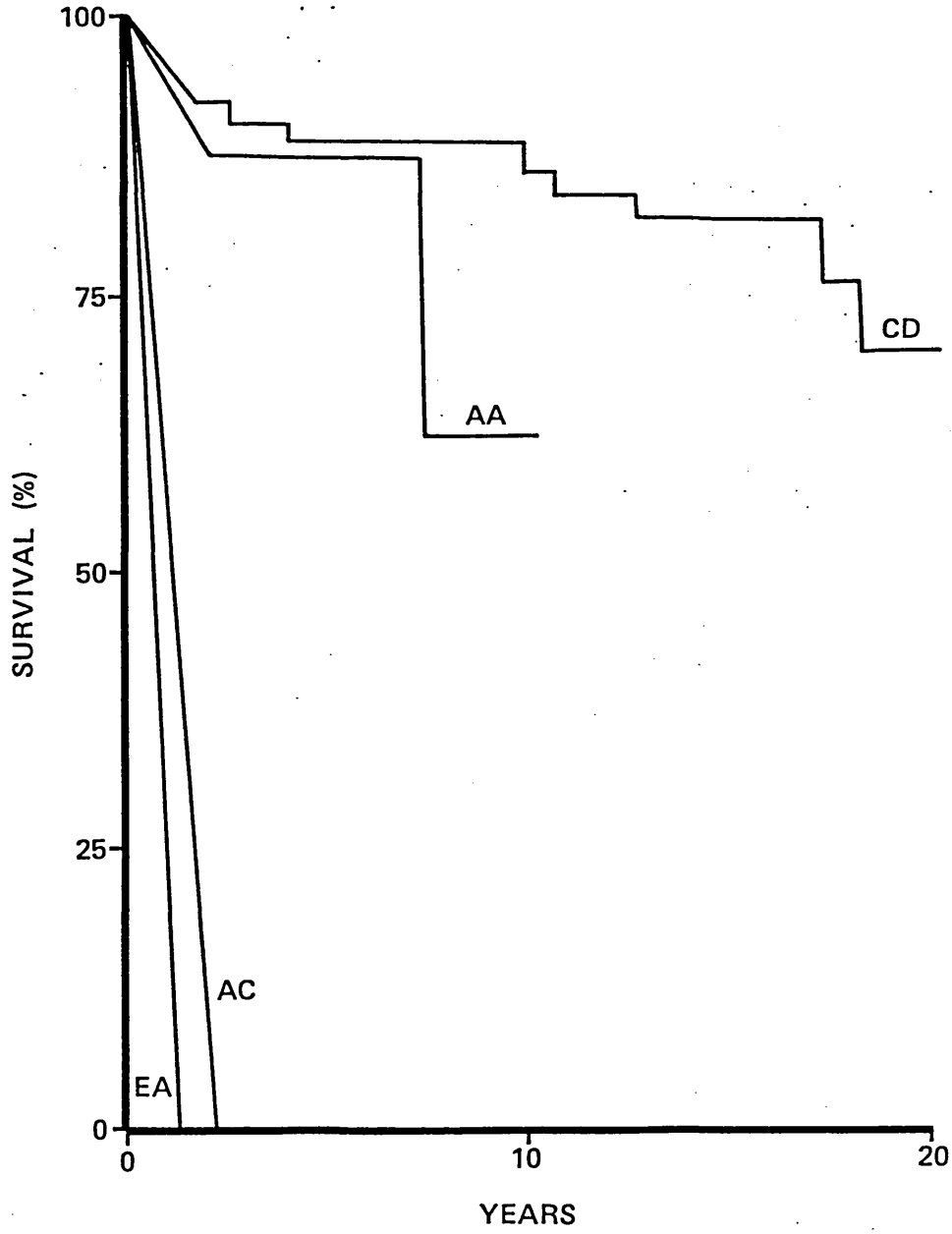
TABLE 13

SURVIVAL OF PATIENTS WITH CUSHING'S SYNDROME

TYPE	ALIVE		DEAD		TOTAL	FOLLOW-UP YEARS	
	Number	%	Number	%		Median	Range
CD	143	86	23	14	166	5.0	0.1 - 33
AA	15	83	3	17	18	3.0	0.2 - 11
AC	0	0	10	100	10	0.6	0.1 - 2
EA	0	0	9	100	9	0.5	0.1 - 0.8
OC	6	100	0	0	6	1.3	0.5 - 3
	164	79%	45	21%	209	4.0	0.1 - 33

FIGURE 3

SURVIVAL OF PATIENTS WITH CUSHING'S SYNDROME



CD ___ CUSHING'S DISEASE

AA ___ ADRENAL ADENOMA

AC ___ ADRENAL CARCINOMA

EA ___ ECTOPIC ACTH

DISCUSSION

TREATMENT FOR CUSHING'S SYNDROME

The most frequent primary treatment for any form of Cushing's syndrome was bilateral adrenalectomy in the present series. The difficulties in achieving definitive treatment of Cushing's syndrome are emphasised by the need for second, third, and fourth treatments in 70, 20 and 4 patients respectively. The effectiveness of treatments is best analysed according to the type of Cushing's syndrome.The success rate in a centre clearly depends on the expertise and facilities that are available. For adrenal adenomas, unilateral adrenalectomy is the treatment of choice, in agreement with Welbourn et al, 1971. It is important not to remove both adrenal glands (done in 5 patients in this series) since this exposes the patient to the risk of adrenal insufficiency,and the need to take life-long steroid therapy.Recent reports confirm the successful treatment of Cushing's disease using implants of yttrium (White et al, 1982) or using trans-sphenoidal surgery (Hardy, 1978). Only a small number of patients in the present study were treated primarily with metyrapone, amino-glutethimide and/or trilostane. Cushing's syndrome relapsed rapidly when metyrapone and aminoglutethimide were stopped, and surgical treatment or radiotherapy were necessary in the long-term management of patients.

The author's experience in using trilostane was disappointing (Dewis, Anderson, Bu'lock, Earnshaw and Kelly, 1983). The prognosis for patients with Cushing's syndrome caused by adrenal carcinomas, or ectopic ACTH was very bad as emphasised by other reports (Hutter and Kayhoe, 1966a,b; Friedman et al, 1966; Welbourn et al, 1971; Kelly et al, 1979).

NELSON'S SYNDROME

Provided the patient survives more than three months after adrenal surgery, the prognosis for successful cure of pituitary-dependent Cushing's syndrome is very good, but the prospect of developing Nelson's syndrome then becomes a serious disadvantage of bilateral adrenalectomy. The detection rate of Nelson's syndrome has varied from 10 to 48% in 5 recent series (review, Kelly et al, 1983b). In the patient first reported by Nelson in 1958, pituitary expansion and increased ACTH levels were found three years after total adrenalectomy. In the present series the interval between total adrenalectomy and detection of Nelson's syndrome ranged between 1 and 14 years. It was initially surprising that Nelson's syndrome was detected in 39% of patients who had never had previous pituitary surgery or radiotherapy, but in 32% of patients who had previously had some form of pituitary surgery or radiotherapy. It should be remembered however that adrenalectomy was

usually done where previously therapy had failed for technical reasons, and a controlled study comparing bilateral adrenalectomy with and without pituitary irradiation or pituitary microsurgery would be very interesting. The treatment of Nelson's syndrome is usually unsatisfactory (Nabarro, 1977; Gold, 1979; Kelly et al, 1983b,d). Pituitary implantation has been successful in some patients (Cassar et al, 1976). Advances in heavy ion therapy may eventually prove to be a useful treatment for Nelson's syndrome (Linfoot, 1979). The author has recently investigated the treatment of 11 patients with Nelson's syndrome using sodium valproate. After 6 weeks, sodium valproate 600mg daily, slightly decreased ACTH levels but the clinical benefits were insignificant. The main disadvantage was weight increase (Kelly et al, 1983d).

In favour of total adrenalectomy as treatment for Cushing's disease is the near-certainty of rapid cure, but against this must be weighed the immediate surgical morbidity, and mortality, and the need for replacement therapy, and the risk of later pituitary expansion. In favour of pituitary surgery, is the lower early morbidity and mortality, but this must be balanced against a slightly lower cure rate and the risk of partial or total pituitary failure.

SURVIVAL OF PATIENTS

It has been estimated that before replacement corticosteroids were available, in the times when surgical treatment had a very high mortality, that 50% of patients with untreated Cushing's syndrome would die within five years (Plotz et al, 1952). The data from the present series indicate that preventable deaths still occurred in some patients with Cushing's disease but provided the patient is well three months after total adrenalectomy, then the long term prognosis is excellent. Most deaths arose from cardiovascular and circulatory causes. The prognosis after adrenalectomy for an adrenal adenoma is good. Advances in treatment of Cushing's syndrome due to adrenal carcinomas or ectopic ACTH secretion will depend on preventing the disease, or detecting it at an early stage, or effective chemotherapy.

CHAPTER 6

PERSONAL DETAILS AND PSYCHIATRIC ILLNESS IN PATIENTS WITH CUSHING'S SYNDROME

SCHOOL AGE AT DIAGNOSIS OF CUSHING'S SYNDROME

There were 16 patients (8%) who were school children with ages from 8 to 16.5 years at the time of diagnosis. Fifteen had pituitary Cushing's disease and one had nodular adrenal hyperplasia.

MARITAL STATUS

When Cushing's syndrome was diagnosed 109 patients (52%) were married, and 42 patients (20%) were single. (Table 14).

CUSHING'S SYNDROME ASSOCIATED WITH PREGNANCY

There were 8 patients (5% of the 162 females) in whom Cushing's syndrome was diagnosed during or at the end of a pregnancy when weight remained elevated and the physical signs of Cushing's syndrome appeared within six months of a previous childbirth. Seven patients had pituitary Cushing's disease and 1 had an adrenal adenoma.

LIFE EVENTS PRECEDING DIAGNOSIS OF CUSHING'S SYNDROME

In 72 patients (34%) there was a history of a significant adverse life event in the two years preceding the onset of symptoms and signs of Cushing's syndrome. This incidence of life events was no more common than

TABLE 14

CIVIL STATUS AT DIAGNOSIS

DIAGNOSIS	MARRIED	SINGLE	WIDOWED	SEPARATED	TOTAL
CD	85	38	1	4	128
AA	11	1	0	0	12
AC	6	0	1	0	7
EA	3	1	1	0	5
OC	4	2	0	0	6
	109	42	3	4	158 *
	(52%)	(20%)	(1%)	(2%)	(75%)

* No details for 51 patients (25%)

for the control patients (present in 6 of 24 =25%, chi^2 =2.8 with 1 degree of freedom p= 0.10).The presence or absence of life events was not correlated with the subsequent development of any particular type of Cushing's syndrome (Table 15). Depressive illness was significantly associated with the presence of adverse life events ($p < 0.001$, Table 16).

There has been considerable interest regarding the relationship of life events to physical and mental illness (Paykel et al, 1969). It has not always been easy to establish causal links between the three variables (life event, physical illness, eg Cushing's syndrome and mental illness, eg depression), since in theory any variable could influence the remaining two. In the present series antecedent adverse life events were no more common in patients with Cushing's disease than in control patients. Mazet et al, (1981) found significant "physical or psychological trauma" in 68% of their 50 patients with Cushing's syndrome but no control data was obtained. In the present series, depressive illness was significantly associated with the presence of life events. The life events were of an adverse nature being "exits" rather than "entrances" in social terms. One of the problems in a retrospective study is the long duration of time from the onset of the first symptoms to treatment

TABLE 15

LIFE EVENTS AND TYPE OF CUSHING'S SYNDROME

DIAGNOSIS	LIFE EVENTS PRESENT	LIFE EVENTS ABSENT	TOTAL
CD	61 (37%)	105 (63%)	166 (100%)
AA	3	15	18
AC	2	8	10
EA	4 (26%)	5 (74%)	9 (100%)
OC	2	4	6
	72 (34%)	137 (66%)	209 (100%)

$(\text{CHI})^2 = 4.2$ WITH 4 DEGREES OF FREEDOM

$p = 0.38$

TABLE 16

LIFE EVENTS AND DEPRESSIVE ILLNESS

SEVERITY OF DEPRESSION	LIFE EVENTS		TOTAL
	ABSENT	PRESENT	
NONE	73	4	77*
MILD	28	29	57
MODERATE	21	26	47
SEVERE	15	13	28
	137	72	209

$(CHI)^2$ = 46 WITH 3 DEGREES OF FREEDOM

* $p < 0.001$

of Cushing's syndrome. In this study it was shown that for this interval the median value was 2 years with a range from 0.2 to 9 years. Therefore at the time of diagnosis and treatment of Cushing's syndrome the nature and significance of a life event in the distant past may not be appreciated. It is of interest that Cushing's syndrome was detected in 16 school-children, in all social classes and marital states, and in association with pregnancy. However none of these factors can be regarded as causes of Cushing's syndrome, which remains very rare in the general population in which these life situations are common.

PSYCHIATRIC ILLNESSES

On reviewing the case histories of all 209 patients with Cushing's syndrome, there were 73 (35%) in whom there was no psychiatric abnormality. Psychiatric illnesses were rated as mild in 53 patients (25%), moderate in 44 patients (21%) and severe in 39 patients (19%). There were no significant differences in the psychiatric changes in the various types of Cushing's syndrome (Table 17). Cushing's syndrome was diagnosed in thirteen patients (6%) who were already attending psychiatric clinics. Eleven of these patients had pituitary Cushing's disease and 2 had adrenal adenomas. In 77 patients (37%) there was no evidence of depressive illness. Symptoms of depression were mild in 57 patients

TABLE 17

PSYCHIATRIC ILLNESS BEFORE CUSHING'S SYNDROME DIAGNOSED

TYPE	SEVERITY OF MENTAL ILLNESS				TOTAL
	ABSENT	MILD	MODERATE	SEVERE	
CD	51	46	38	31	166
AA	10	3	3	2	18
AC	4	1	0	5	10
EA	4	2	2	1	9
OC	4	1	1	0	6
	73	53	44	39	209
	(35%)	(25%)	(21%)	(19%)	(100%)

$(CHI)^2$ = 17 WITH 12 DEGREES OF FREEDOM

p = 0.15

(27%), moderate in 47 patients (23%) and severe in 28 patients (13%). There were no significant differences in the severity of depression in the different types of Cushing's syndrome (Table 18). Depressive illness was more common in females ($p < 0.01$, Table 19). Pathological anxiety had been diagnosed in 26 patients (12%), comprising 21 with pituitary Cushing's disease, 3 with adrenal adenomas and 2 with adrenal carcinomas. Mania or hypomania had been diagnosed in six patients (3%), comprising 5 with pituitary Cushing's disease and 1 with an adrenal carcinoma. Confusion had been diagnosed in three patients (1%), mean age 62 years, comprising two with pituitary Cushing's disease and one with ectopic ACTH secretion. Alcoholism had been diagnosed in three patients (1%) who were male. Psychosexual problems had been diagnosed in 3 patients (1%) who all had pituitary Cushing's disease . Psychotic illness had been diagnosed in 16 patients (8%), comprising 10 patients with pituitary Cushing's disease, 4 with adrenal carcinomas, and 1 with ectopic ACTH secretion. Thus psychotic behaviour was present in 4 of the 10 patients (40%) with adrenal carcinomas but in only 16 of the 209 patients overall (8%)($p < 0.01$, Table 20). The one patient who was a violent psychopath had pituitary Cushing's disease. Apart from the high

TABLE 18

DEPRESSIVE ILLNESS BEFORE CUSHING'S SYNDROME DIAGNOSED

	SEVERITY OF DEPRESSIVE ILLNESS				TOTAL
TYPE	ABSENT	MILD	MODERATE	SEVERE	
CD	54	49	40	23	166
AA	10	3	4	1	18
AC	5	1	0	4	10
EA	4	3	2	0	9
OC	4	1	1	0	6
	77	57	47	28	209
	(37%)	(27%)	(23%)	(13%)	(100%)

$(CHI)^2 = 18$ WITH 12 DEGREES OF FREEDOM

$p = 0.12$

TABLE 19

DEPRESSIVE ILLNESS BEFORE CUSHING'S SYNDROME DIAGNOSED

SEVERITY OF DEPRESSION	NUMBER MALE	FEMALE	TOTAL
NONE	29	48	77*
MILD	8	49	57
MODERATE	6	41	47
SEVERE	4	24	28
	47	162	209
	(22%)	(78%)	(100%)

$(\text{CHI})^2$ = 16 WITH 3 DEGREES OF FREEDOM

* $p < 0.01$

TABLE 20

PSYCHOTIC ILLNESS AND TYPE OF CUSHING'S SYNDROME

DIAGNOSIS	PSYCHOTIC ILLNESS PRESENT	ABSENT	TOTAL	
CD	10	156	166	
AA	1	17	18	
AC	4	6	10	*
EA	1	8	9	
OC	0	6	6	
	16	193	209	
	(8%)	(92%)	(100%)	

$(\text{CHI})^2 = 16$ WITH 4 DEGREES OF FREEDOM

* $p < 0.01$

incidence of affective illness(namely depression and hypomania) the presentation of other psychiatric illness was not different to that found in the general population (S Checkley, 1983, personal communication).

DEPRESSION AND NUMBER OF TREATMENTS FOR CUSHING'S AND NELSON'S SYNDROMES

The case histories in Chapter 5 show that there was considerable technical difficulty and morbidity associated with therapy, and many patients required more than one treatment. Previously ineffective therapy might be a cause of depressive illness, so Table 21 was constructed. Depression was more common in patients who had several treatments.

TEMPORAL RELATIONSHIP OF PSYCHIATRIC ILLNESSES AND CUSHING'S SYNDROME

There was a history of significant psychiatric illness, usually depressive illness, which preceded the onset of the symptoms and signs of Cushing's syndrome in 25 patients (12%). Twenty three patients developed pituitary Cushing's disease and 2 patients developed adrenal adenomas. When Cushing's syndrome was diagnosed significant psychiatric illness, usually depression, was present or had been a feature of the Cushing's syndrome

TABLE 21

DEPRESSIVE ILLNESS AND NUMBER OF TREATMENTS

	DEPRESSIVE ILLNESS		TOTAL
	ABSENT	PRESENT	
NUMBER OF TREATMENTS			
ONE ONLY	52	67	119
MORE THAN ONE	25	65	90
	77	132	209

$(\text{CHI})^2$ = 4.9 WITH 1 DEGREE OF FREEDOM

$p < 0.03$

in 120 patients (57%). One hundred of these patients had pituitary Cushing's disease, 8 adrenal adenomas, 5 adrenal carcinomas, 5 ectopic ACTH secretion and 2 patients had other causes. When Cushing's syndrome had been treated significant psychiatric illness, always depressive, remained in 56 patients (27%), excluding 9 (4%) who were not assessed since treatment of Cushing's syndrome was pending. Of these 56 depressed patients (Table 22) 15 died in less than three months, and are therefore excluded, leaving 41 patients who were depressed for the following reasons - temporarily hypoadrenal, which responded to replacement corticosteroid therapy in 9 patients; other medical or surgical problems, including arthritis, myocardial infarctions, and vascular accidents in 10 patients; other life events occurring in 9 patients; and no remission of Cushing's syndrome in 2 patients. There remained 11 patients who were depressed for no apparent reason.

To determine the relationship between the severity of Cushing's syndrome, as measured by the excretion of urinary free cortisol, this was correlated with the psychiatric diagnosis using Spearman's coefficient. This data is shown on Table 23. There were no significant correlations between the biochemical severity of the illness and the severity of the psychiatric illness,

TABLE 22

REASONS FOR DEPRESSIVE ILLNESS AFTER TREATMENT OF CUSHING'S SYNDROME

	REASONS FOR DEPRESSIVE ILLNESS						TOTAL
	Temporarily Hypoadrenal	Other Health	No Remission	Other Life Events	Died <3 Months	Not Known	
CD	8	10	1	8	9	11	47
AA	1	0	0	1	0	0	2
AC	0	0	0	0	3	0	3
EA	0	0	1	0	3	0	4
	9	10	2	9	15	11	56

TABLE 23

CORRELATIONS[1] BETWEEN CORTISOL EXCRETION[2] AND PSYCHIATRIC ILLNESS[3]

ACTIVE CUSHING'S SYNDROME	PAIRS	SPEARMAN CORRELATION COEFFICIENT	p
Cortisol v Psychiatric Illness	92	0.17	0.10
Cortisol v Depressive Illness	92	0.12	0.24
Cortisol v Anxiety	92	0.08	0.45
Cortisol v Psychotic Illness	92	-0.13	0.20
Cortisol v Hypomania	92	-0.28	0.01
TREATED CUSHING'S SYNDROME			
Cortisol v Psychiatric Illness	77	0.07	0.55
Cortisol v Depressive Illness	77	0.02	0.87
Cortisol v Anxiety	77	-0.05	0.69
Cortisol v Psychotic Illness	77	-0.20	0.08
Cortisol v Hypomania	77	-0.07	0.55

1 SPEARMAN'S TESTS

2 URINARY FREE CORTISOL

3 BASED ON INTERVIEW

with the possible exception of the patients with hypomania. This lack of correlation, notably for patients with depressive illness may be explained by the natural history of Cushing's syndrome. The urinary excretion of free cortisol can vary greatly from time to time in an individual patient (eg patient CD 19 and review by Kammer and Barter, 1979), whereas the severity of psychiatric illness is an overall rating based on a longer period of time, so the two parameters may not be significantly correlated. The lack of correlations in the patients with treated Cushing's syndrome is not surprising since most patients were psychiatrically normal, and had normal cortisol levels.

DISCUSSION

In the present series of 209 patients the incidence of serious psychiatric abnormalities was 65%. Estimates of the frequency and severity of psychiatric illness have varied in reported series. Cushing noted depression and anxiety in some of his patients (Cushing, 1932). Starr (1952) noted "personality changes" in 53 patients with Cushing's syndrome as follows - 21 were normal or had minimal changes, 19 had severe or moderately severe changes, and 13 patients had very severe changes. Trethowan and Cobb (1952) in an unselected series of 25 patients noted that their patients presented a "galaxy of mental symptoms", but that " no single clear-cut psychiatric picture emerged". Soffer et al (1961a) noted " mental disturbances" in 40% of 50 patients with Cushing's syndrome; these authors reviewed the literature (Soffer et al, 1961b) and found "mental changes" in 46% of patients with Cushing's syndrome. Ross et al (1966) noted "psychological difficulty" in 40% of 50 patients, compared to 42% of patients in their survey of published cases. Gifford and Gunderson (1970a,b) selected 10 patients from 60 with Cushing's syndrome in support of their claim that Cushing's disease (which 9 of the 10 patients had) was a psychosomatic disorder.

Jeffcoate et al (1979) reported psychiatric abnormalities in 65% of 38 patients with Cushing's syndrome.

Cohen (1980) reported "distinct affective disorders" in 86% of 29 patients with Cushing's syndrome. Starkman et al (1981a,b) found a wide range of symptoms in 35 patients with Cushing's syndrome, rating the "psychiatric disability" as mild in 34%, moderate in 26%, severe in 29% and very severe in 11%.

Anxiety was diagnosed in 26 of the 209 patients in the present series (12%) and the incidence of anxiety has varied among published series, being highest in that of Starkman et al (1981a,b), where it was 66% of 35 patients. Hypomania had been present in 6 of the 209 patients in the present series (3%). Two of the 38 patients reported by Jeffcoate et al (1979) were "frankly manic". Starkman et al (1981a,b) noted that a minority of patients with Cushing's syndrome had experienced episodes of elation-hyperactivity early in the course of their disease and noted that as the Cushing's syndrome progressed, before treatment had been given, this type of episode became rare or disappeared entirely; one of their patients had a manic syndrome. Confusion was rare in the present series (3 patients, 1%)

and in most patients psychiatric assessments could readily be made.

Depression was the commonest psychiatric abnormality in the present series of 209 patients, affecting two-thirds of the patients. Depression has been the commonest psychiatric abnormality noted in other series (Spillane, 1951; Soffer et al, 1961a; Jeffcoate et al, 1979; Cohen, 1980; Starkman et al, 1981a,b; Mazet et al, 1981). In the present series 25 patients (12%) had had a significant psychiatric illness many years before the onset of the symptoms and signs of Cushing's syndrome. This would appear no higher than one would expect in the normal population. When Cushing's syndrome was diagnosed, significant psychiatric illness was present in 120 patients (57%). There was improvement in this psychiatric illness (usually depressive illness), as Cushing's syndrome was successfully treated, although significant psychiatric illness remained in 41 patients for a variety of reasons. Other workers have reported that successful treatment of the physical signs of Cushing's syndrome, with lowering of plasma cortisol, results in amelioration of the psychological abnormalities (Gifford and Gunderson, 1970a,b; Jeffcoate et al, 1979; Cohen, 1980; Mazet et al, 1981; Starkman et al, 1981a,b).

There are rare examples of Cushing's syndrome

associated with schizophrenia - Ross et al in 1966 noted that one of their 50 patients had paranoid schizophrenia, which was regarded as being independent of the endocrine disorder. One of the 34 patients reported by Hurxthal and O'Sullivan (1959) had acute schizophrenia. In Jeffcoate's series (1979) of 38 patients, one was noted to have paranoid delusions. Michael and Gibbons in 1963 stated that "typical schizophrenia is not seen in patients with Cushing's syndrome". This conclusion was supported by Johnson (1975) who surveyed the literature and wrote a case report of a patient with Cushing's syndrome, who also had schizophrenia.

When psychiatric abnormalities in the present series were analysed according to the type of Cushing's syndrome, psychotic illness was more frequent in patients with adrenal carcinomas. Friedland and Whetsell (1978) have described an organic psychosis in a lady with Cushing's syndrome due to an adrenal carcinoma. However, their patient also had a brain tumour which may have been partly responsible for the abnormal psychiatric behaviour. Carroll (1976c) noted that depressive symptoms were more likely to be present in pituitary Cushing's disease, compared to other causes of Cushing's syndrome, but noted that sampling errors could have occurred in the reported series. Therefore a consideration of the above

discussion emphasises the need for a careful,prospective, clinical study using modern, well-validated measures of psychiatric and psychological morbidity, together with accurate measurements of hormone concentrations. This was attempted as described in Chapters 7 to 10.

CHAPTER 7

PRESENT STATE EXAMINATION WITH CATEGO ANALYSIS

The discussion in the previous chapter demonstrates the need for reliable, objective assessments of the psychiatric abnormalities in patients with Cushing's syndrome. Therefore Present State Examinations were done on 43 patients when Cushing's syndrome was active. Most of the patients (28 of 43= 65%) had Cushing's disease, and the other diagnoses were obtained in relatively small numbers of patients, as follows: adrenal adenomas (4 patients, 9%), adrenal carcinomas (3 patients, 7%), ectopic ACTH (3 patients, 7%), and other Cushing's (5 patients, 12%). Using Catego analysis only 8 patients (19%) were rated as normal; psychiatric ratings were obtained as follows: Neurotic depression (N+) in 20 (46%), N? in 1 (2%), Retarded depression (R+) in 6 (14%), and non-specific neurotic symptoms (X) in 8 (19%). Additional Catego ratings of suspected Other psychosis (O?) were made for three patients who all had severe psychiatric illnesses; thus patient CD 21 with pituitary Cushing's disease was rated as R+ and O? before treatment and X after treatment for Cushing's syndrome; patient AC 191 with an adrenal carcinoma was R+ and O? before treatment and N+ during treatment for Cushing's syndrome; patient AC 194, also with an adrenal carcinoma was N+ and O? when Cushing's syndrome was diagnosed, but she rapidly deteriorated and

died. None of the 43 patients with active Cushing's syndrome had Catego ratings of schizophrenia or mania, obsessional neurosis or pathological anxiety.

In the control series of patients with pituitary adenomas secreting excessive growth hormone or prolactin, 13 patients (87%) were normal; 1 patient with acromegaly had an anxiety state (A+) and 1 patient with a prolactinoma had neurotic depression (N+). Eighteen other patients who had previously had treatment for Cushing's syndrome had Present State Examinations when cortisol levels were normal. Six of these 18 patients (33%) had Nelson's syndrome. Of these 18 patients, 9 (50%) were normal, 4 patients were rated N+, 4 patients were rated X, and 1 patient was rated R+.

During follow-up, 7 patients have died before they could be reassessed by the Present State Examination. Twenty-five patients have been observed until Cushing's syndrome has been successfully treated (urinary cortisol normal in 22; improved, but still slightly elevated range 310 - 367 nmol/24 hours, (normal < 270) in 3 patients). They were then reassessed by the Present State Examination (Table 24). The mean period of observation after treatment was 14 months (range 1-39 months). Improvements were noted, since at the latest assessment 17 patients (68%) were normal, 4 patients were rated as N+, 2 patients were rated R+, 1 patient was rated R? and

TABLE 24

PRESENT STATE EXAMINATION - CATEGO DIAGNOSIS

BEFORE AND AFTER TREATMENT OF CUSHING'S SYNDROME

		AFTER					
		R+	R?	N+	X	NORMAL	TOTAL
BEFORE	R+	0	0	2"	1	1	4
	N+	2	0	1	0	8	11
	N?	0	0	1	0	0	1
	X	0	1*	0	0	3	4
	NORMAL	0	0	0	0	5	5
TOTAL		2	1	4	1	17	25

* PATIENT CD 21 ALSO RATED (O?) BEFORE TREATMENT

" PATIENT AC 191 ALSO RATED (O?) BEFORE TREATMENT

NORMAL RATINGS IN 20% BEFORE TREATMENT AND IN 68% AFTER TREATMENT.

CHI^2 = 11.7 WITH 1 DEGREE OF FREEDOM, $p < 0.01$

1 patient was rated X. Therefore when cortisol levels had been substantially reduced (to normal in 88%), the percentage of normal Present State Examinations increased from 20% to 68% (Table 24). This improvement in patients rated as normal is significant (chi^2 = 11.7 with 1 degree of freedom, $p < 0.01$). Eighteen patients were assessed by PSE only after treatment, which had been prolonged and complicated in several patients; 6 of these 18 patients had developed Nelson's syndrome. Of the 18 patients, only 9 patients (50%) were normal, and 9 had psychiatric abnormalities, usually of depressive illness. Therefore the present study suggests that when followed up for a mean period of 14 months after successful treatment of Cushing's syndrome, then depression improved significantly, but in the long-term follow-up period depression may become more common especially if complications such as Nelson's syndrome develop. No previous study has answered the question as to whether patients with Cushing's syndrome have a greater incidence of psychiatric abnormalities than a control population. The present study shows that patients with active Cushing's syndrome had a higher incidence of abnormalities using the PSE than a carefully selected control series of patients.

CHAPTER 8

HAMILTON RATING SCALE FOR DEPRESSION

The severity of depressive illness in patients with Cushing's syndrome was assessed by the Hamilton Rating Scale (Table 25). When Cushing's syndrome was active, Hamilton Rating Scale scores were obtained on 53 patients of whom 41 (77%) were female; the scores ranged from 0 to 28, mean 8.5, SD 6.6. Hamilton Rating Scale scores were obtained for 24 control patients, of whom 20 (83%) were female; the scores ranged from 0 to 10, mean 2.0 SD 2.3, (compared to patients with active Cushing's syndrome $p < 0.001$, Student's paired t-test). There were 36 patients who had Hamilton Rating Scale scores both when Cushing's syndrome was active, and an average of 14 months after treatment, when cortisol levels were normal (Figure 4). The mean HRS values improved from 9.2 to 2.4 ($p < 0.001$ Student's paired t-test). This data confirms and adds to that previously reported by the author (Kelly et al, 1980 and 1983a). Although the Hamilton Rating Scale has been widely used in psychiatric research, no previous workers have used it prospectively for the study of patients with Cushing's syndrome. The results are therefore original and statistically significant.

TABLE 25

HAMILTON RATING SCALE SCORES

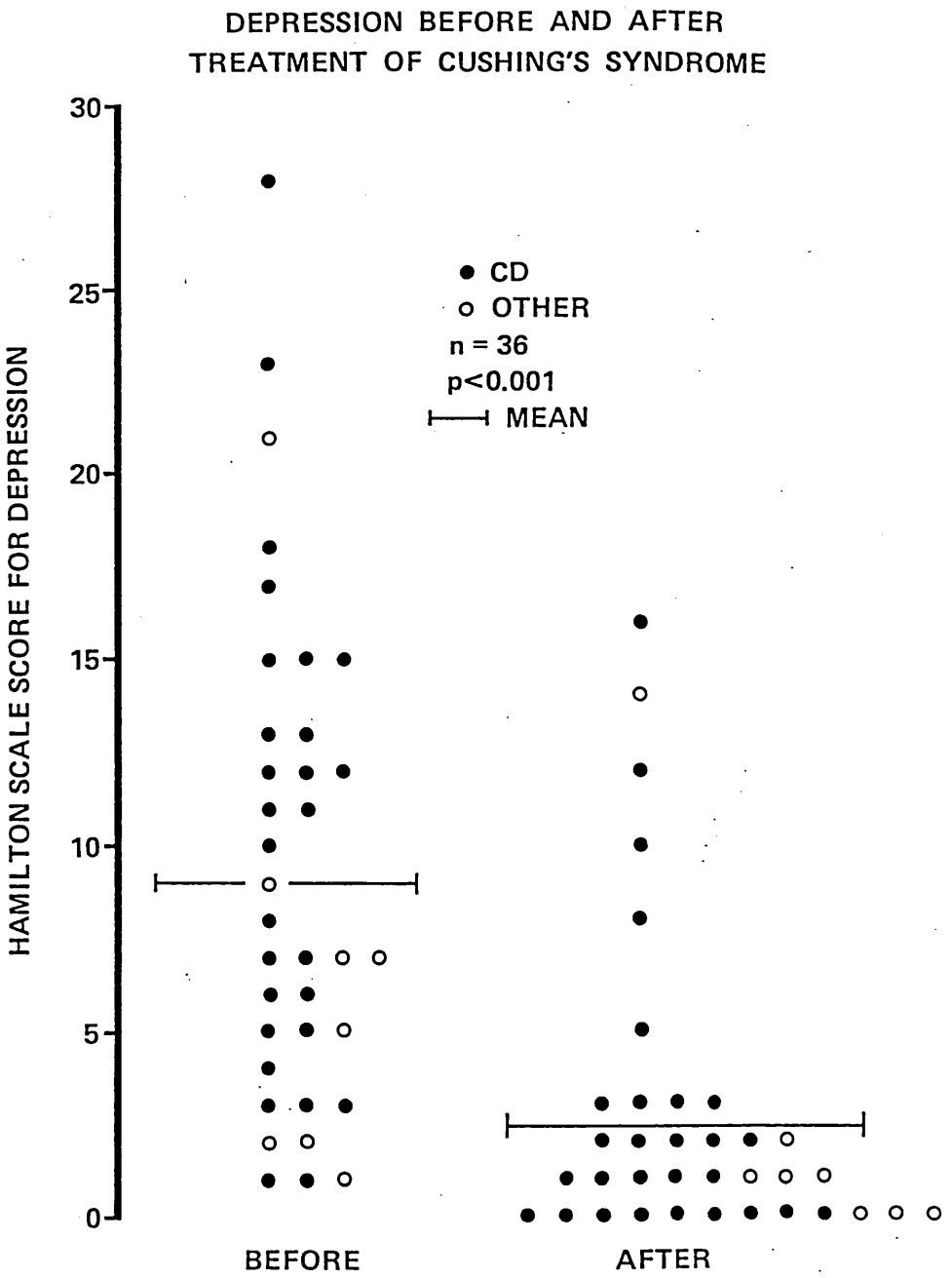
CUSHING'S SYNDROME	NUMBER	MEAN	SD
ACTIVE (Note 1)	53	8.5	6.6
PROSPECTIVE DATA			
ACTIVE (Note 2)	36	9.2	6.5
TREATED	36	2.4	4.0
CONTROL PATIENTS	24	2.0	2.3

Note 1 ANALYSIS BY TYPE OF CUSHING'S SYNDROME

Type of Cushing's Syndrome	Number	Per Cent	Hamilton Score Mean	SD
CD	38	71%	9.6	6.6
AA	4	8%	2.5	-
AC	3	6%	15.2	-
EA	3	6%	3.1	-
OC	5	9%	4.1	-
	53	100%	8.5	6.6

Note 2 $p < 0.001$ Student's t-test compared to treated patients and controls

FIGURE 4



CD ___ CUSHING'S DISEASE

CHAPTER 9

CROWN - CRISP EXPERIENTIAL INDEX

EYSENCK PERSONALITY INVENTORY

ANALOGUE SCALE

CROWN - CRISP EXPERIENTIAL INDEX

Experiential index ratings were obtained on 39 patients when Cushing's syndrome was active (Table 26). The data was normally distributed. Compared with the control patients, those with Cushing's syndrome had higher scores for all scales except hysteria; there were no significant differences (taking $p < 0.05$ on Student's unpaired t-test), but for depression $p = 0.06$ and for somatic symptoms $p = 0.05$. Twenty-five patients have been observed both before and after treatment for Cushing's syndrome. There were improvements in all the Experiential Index Scales and this was statistically significant ($p<0.05$, Student's paired t-test) for the anxiety, somatic and depression scales. (Table 26). When compared to the normal adult population studied by Crisp et al in 1978 the 39 patients with Cushing's syndrome had higher ratings for anxiety, obsession, somatic symptoms, depression, hysteria and phobia. However the psycho-neurotic patients studied by Crown in 1974 had higher scores for anxiety, depression, obsession, somatic symptoms and hysteria than the patients with Cushing's syndrome. When 25 patients in the present series were re-assessed after effective treatment of Cushing's syndrome these original observations were made: there had been significant

TABLE 26

CROWN - CRISP EXPERIENTIAL INDEX RATINGS - MEAN (SD)

PATIENTS	NUMBER	ANX	PHO	OBS	SOM	DEP	HYS
CUSHING'S-Active	39	7.2(4.0)	5.8(3.2)	8.4(3.2)	7.2(3.1)	5.6(3.2)	3.7(3.4)
CONTROLS	15	7.0(3.6)	3.1(2.5)	7.9(3.3)	5.1(3.0)	3.9(2.3)	5.0(3.0)
p value *		0.93	0.11	0.68	0.05	0.06	0.16
PROSPECTIVE DATA							
CUSHING'S:							
ACTIVE	25	7.9(4.4)	5.8(3.8)	9.1(3.1)	7.0(3.4)	5.8(3.5)	3.7(2.9)
TREATED	25	5.1(3.8)	4.3(4.1)	8.2(3.5)	5.3(3.3)	3.8(3.4)	3.5(2.9)
p value **		0.01	0.18	0.09	0.05	0.01	0.69

* ACTIVE v CONTROLS - Student's unpaired t-test

** ACTIVE v TREATED - Student's paired t-test

decreases in depression, anxiety and somatic symptoms but no significant changes in obsession, phobia or hysteria scales.

EYSENCK PERSONALITY INVENTORY

Eysenck Personality Inventory assessments were made of 39 patients when Cushing's syndrome was active (Table 27). The data was normally distributed. Compared with control patients there were no significant differences. Twenty-six patients were assessed before and after treatment for Cushing's syndrome. There was a significant improvement in the neuroticism scale ($p < 0.05$, Student's paired t-test). Eysenck Personality Inventory has not previously been used in patients with Cushing's syndrome assessed before and after treatment. It is of interest therefore that there was a significant decrease in the neuroticism score and a small increase (not statistically significant) in the extraversion rating. The changes other than depression noted in ratings of the Crown-Crisp Experiential Index and in the Eysenck Personality Inventory may be explained as a consequence of a reduction in the severity of depression.

ANALOGUE SCALE

Twenty-four patients were assessed using the self-rating analogue scales both before and after treatment

TABLE 27

EYSENCK PERSONALITY INVENTORY - MEAN (SD)

TYPE	NUMBER	EXTRAVERSION Mean	EXTRAVERSION SD	NEUROTICISM Mean	NEUROTICISM SD	LIE Mean	LIE SD
CUSHING'S - ACTIVE	39	8.2	4.5	12.3	5.1	4.4	1.5
CONTROL PATIENTS	16	8.9	3.4	13.0	3.5	3.6	1.7
p value *		0.474		0.448		0.075	
PROSPECTIVE DATA							
CUSHING'S - ACTIVE	26	7.7	4.9	12.7	5.7	4.5	1.5
TREATED	26	8.1	4.4	10.2	5.3	4.4	1.8
p value **		0.505		0.016		0.640	

* Student's unpaired t-test

** Student's paired t-test

EYSENCK SCALE A

for Cushing's syndrome. There were improvements in depression ($p < 0.01$) and anxiety ($p = 0.05$) using Student's paired t-test.

CORRELATIONS BETWEEN PSYCHIATRIC RATING METHODS

The correlations between the scores on the psychiatric rating scales were ascertained using Spearman's test, both when Cushing's syndrome was active (Table 28) and treated (Table 29). There were significant positive correlations ($p < 0.05$) between Hamilton rating scale scores and depression measured on the Crown-Crisp Experiential Index and on the analogue scale, for patients with active and treated Cushing's syndrome.

The Hamilton rating scale score for depression was also significantly correlated with the Eysenck neuroticism score for patients with active and treated Cushing's syndrome ($p < 0.005$). These significant correlations therefore strengthen the conclusions that can be deduced from the data in this study.

TABLE 28

CORRELATIONS BETWEEN PSYCHIATRIC RATINGS

ACTIVE CUSHING'S SYNDROME		SPEARMAN CORRELATION COEFFICIENT	p
HRS v CCEI	ANX	0.53	0.001
	OBS	0.39	0.015
	DEP	0.41	0.009
	PHO	0.41	0.010
	SOM	0.37	0.022
	HYS	0.20	0.225
HRS v EPI	E	-0.29	0.069
	N	0.48	0.002
	L	-0.04	0.816
HRS v ANALOGUE	DEP	0.47	0.004
	ANX	0.23	0.166

TABLE 29

CORRELATION BETWEEN PSYCHIATRIC RATINGS

TREATED CUSHING'S SYNDROME		SPEARMAN CORRELATION COEFFICIENT	p
HRS v CCEI	ANX	0.68	0.001
	OBS	0.33	0.038
	DEP	0.46	0.003
	PHO	0.38	0.013
	SOM	0.57	0.001
	HYS	0.24	0.140
HRS v EPI	E	-0.29	0.064
	N	0.51	0.001
	L	0.04	0.807
HRS v ANALOGUE	DEP	0.48	0.003
	ANX	0.40	0.012

CHAPTER 10

HORMONES

Biochemical data were collected for those patients who had psychiatric assessments before and after treatment for Cushing's syndrome. Normal ranges are shown on Table 30. Data for urinary free cortisol, 17 oxogenic steroids and 17 oxosteroids, and plasma cortisol and ACTH are shown in Table 31; this data is not Normally distributed, so median values have been shown. There were significant decreases ($p < 0.01$, Wilcoxon's test) in all parameters except plasma ACTH. There were no significant changes in serum luteinising hormone, follicle-stimulating hormone or prolactin (Table 32). There were significant increases in serum oestradiol and sex hormone binding globulin in females and also in serum testosterone in males ($p < 0.05$, Student's paired t-test, Table 33). There were no significant changes in serum thyroxine or tri-iodo-thyronine (Table 34). There was a small but significant increase in serum potassium ($p < 0.05$) but no change in serum sodium (Table 35).

DISCUSSION

HORMONE CONCENTRATIONS BEFORE AND AFTER TREATMENT OF CUSHING'S SYNDROME

The prospective study showed the expected highly significant decreases in urinary free cortisol, 17 OGS and 17 OS, and plasma cortisol at both 09.00 and 24.00 hours. For most patients the values became normal. All

TABLE 30

NORMAL RANGES - BIOCHEMISTRY

URINE - 24 hours		MALE AND FEMALE	UNITS
UFC		< 270	nmol
17 OGS		20 - 60	µmol
17 OS		15 - 55	µmol
SERUM OR PLASMA			
CORTISOL	09.00h	150 - 650	nmol/l
	24.00h	< 200	nmol/l
T_4		50 - 150	nmol/l
T_3		1.1 - 2.8	nmol/l
Na		132 - 144	mmol/l
K		3.5 - 5.0	mmol/l
TRYPTOPHAN	total	69 - 101	µmol/l
	free	6 - 15	µmol/l

	FEMALE	MALE	
T	0.3 - 2.0	10 -30	nmol/l
SHBG	30 - 110	< 40	nmol/l
PRL	< 350	< 300	mu/l
LH	see below	2 - 8	u/l
FSH	see below	1 - 6	u/l
E_2	see below	<130	pmol/l

FEMALES

	E_2 pmol/l	LH u/l	FSH u/l
Premenopausal:			
Follicular	110 - 440	5 - 9	4 - 6
Ovulatory	550 - 1290	45 - 60	8 - 14
Luteal	370 - 770	1 - 6	1 - 3
Postmenopausal	< 130	25 -117	34 -123

TABLE 31

CORTISOL AND ACTH MEDIAN AND (RANGE)

	URINE - 24h			PLASMA		
	FREE CORTISOL nmol	17OGS µmol	17OS µmol	CORTISOL 09.00h nmol/l	ACTH 24.00h nmol/l	ACTH 09.00h ng/l
CUSHING'S SYNDROME - ACTIVE (Median)	651	80	43	639	427	47
(Range)	(302-4390)	(24-355)	(15-123)	(360-1472)	(281-1041)	(20-302)
CUSHING'S SYNDROME - TREATED (Median)	187	55	21	450	261	42
(Range)	(15-1959)	(10-196)	(6- 74)	(30-1080)	(30- 726)	(7-428)
NUMBER OF PAIRS	28	21	21	25	18	12
p value (Wilcoxon test)	0.001	0.001	0.001	0.001	0.003	0.638

Normal ranges on TABLE 30

TABLE 32

SERUM PITUITARY HORMONES MEDIAN AND (RANGE)

	LH u/l	FSH u/l	PRL mu/l
FEMALES			
ACTIVE	5.2 (2-40)	5.3 (2-40)	364 (105-520)
TREATED	6.5 (1-33)	3.8 (1-20)	285 (123-640)
n=	16	16	15
p value (Wilcoxon)	0.776	0.136	0.363
MALES			
ACTIVE	3.0	3.0	251
TREATED	3.0	3.0	218
n=	3	3	3
p value (Wilcoxon)	0.655	0.317	0.109

Normal ranges on TABLE 30

TABLE 33

SERUM SEX HORMONES

	OESTRADIOL pmol/l		TESTOSTERONE nmol/l		SEX HORMONE BINDING GLOBULIN nmol/l	
	Mean	SD	Mean	SD	Mean	SD
FEMALES						
ACTIVE	144	129	2.45	1.41	21	11
TREATED	353	325	1.86	1.81	35	14
n=	15		16		13	
p value (Student's paired t-test)	0.037		0.283		0.004	
MALES						
ACTIVE	72		10.0	3.1	14	
TREATED	182		22.1	5.5	31	
n=	3		5		2	
p value (Student's paired t-test)	0.332		0.010		0.118	

Normal ranges on TABLE 30

TABLE 34

SERUM THYROID HORMONES

	THYROXINE nmol/l		T_3 nmol/l	
	Mean	SD	Mean	SD
CUSHING'S SYNDROME				
ACTIVE	92	22	1.7	0.2
TREATED	85	23	2.0	0.6
n=	19		7	
p value (Student's paired t-test)	0.160		0.240	

Normal ranges on TABLE 30

TABLE 35

SERUM ELECTROLYTES

	SODIUM mmol/l		POTASSIUM mmol/l	
	Mean	SD	Mean	SD
CUSHING'S SYNDROME				
ACTIVE	141	3	3.45	0.52
TREATED	140	4	3.87	0.35
n=	15		15	
p value (Student's paired t-test)	0.220		0.004	

Normal ranges on TABLE 30

these changes occurred over the same time interval during which significant improvements in psychiatric symptoms occurred. Prospective biochemical data also showed significant increases in the following hormones, which thereby became closer to normal: serum testosterone in males, serum oestradiol in females, and sex hormone binding globulin in females. There were no significant changes in serum oestradiol in males, sex hormone binding globulin in males and in LH, FSH, and prolactin in males and females. The changes in sex hormone concentrations would be expected to be associated with an increased feeling of well-being in the patients, and this fits with the objective evidence of improvement in psychological symptoms. There were no significant changes in serum concentrations of thyroxine, T_3 or sodium. Although the increase in serum potassium was significant statistically, it is difficult to believe that the small increase would have any significant effect on psychiatric and psychological ratings. This lack of effect of serum potassium on psychiatric status is supported by studies on a patient with an adrenal tumour secreting excessive quantities of the mineralocorticoid deoxycorticosterone (but not excessive cortisol or aldosterone) who had a serum potassium of 2.3 mmol/l, and a normal Present State Examination (patient EM, Kelly et al, 1982); in addition

there is no known reference in the literature to psychiatric abnormalities in patients with primary aldosteronism.

TOTAL AND FREE TRYPTOPHAN

The mean value for plasma total tryptophan was low in patients with active Cushing's syndrome (Table 36). There was no significant change after treatment for Cushing's syndrome. The mean value for plasma free tryptophan was normal for patients with active Cushing's syndrome. The small increase after treatment was not statistically significant. There were no significant differences when males and females were analysed separately. There was no significant correlation between depression ratings (Hamilton scale) and total tryptophan, free tryptophan and severity of Cushing's syndrome as assessed by the urinary free cortisol (Table 37). This lack of significance was noted both when Cushing's syndrome was active and when patients had been treated.

DISCUSSION

The hypothesis was tested that in Cushing's syndrome depression occurs by the induction of tryptophan oxygenase, and the consequent depletion of brain 5-hydroxytryptamine (5-HT). In experimental animals injection of cortisol leads to an increase in tryptophan oxygenase activity and a decrease in brain concentrations of tryptophan and 5-HT (Green and Curzon, 1968; Curzon and Green, 1971; Green et al, 1975). The hypothesis was tested that a similar effect occurs in patients with Cushing's

TABLE 36

PLASMA TRYPTOPHAN μmol/l

	TOTAL		FREE	
	MEAN	SD	MEAN	SD
CUSHING'S SYNDROME				
ACTIVE	56	15	12	4
TREATED	53	11	15	5
n=	19		19	
p value (Student's paired t-test)	0.326		0.112	

Normal ranges on TABLE 30

TABLE 37

CORRELATIONS[1] BETWEEN DEPRESSION RATINGS[2], TRYPTOPHAN[3] AND CORTISOL[4]

ACTIVE[5] CUSHING'S SYNDROME	PAIRS	SPEARMAN CORRELATION COEFFICIENT	p
Depression v Total Tryptophan	29	0.35	0.07
Depression v Free Tryptophan	28	-0.13	0.52
Depression v Cortisol	33	0.06	0.73
Total Tryptophan v Free Tryptophan	28	0.39	0.04
Total Tryptophan v Cortisol	23	-0.04	0.86
Free Tryptophan v Cortisol	22	-0.02	0.96

1 SPEARMAN'S TEST

2 HAMILTON RATING SCALE SCORE

3 PLASMA TOTAL AND FREE TRYPTOPHAN

4 URINARY FREE CORTISOL

5 NO SIGNIFICANT CORRELATIONS FOR TREATED CUSHING'S SYNDROME

syndrome. It was predicted that compared with control patients, those with active Cushing's syndrome would have lower plasma concentrations of total tryptophan, and this has been demonstrated. However, the free tryptophan concentrations were normal. In the prospective study, there were no significant changes in plasma concentrations of total or free tryptophan. It is therefore unlikely that in Cushing's syndrome depression results from a deficiency of tryptophan, and hence of serotonin.

CHAPTER 11

CONCLUSIONS

CONCLUSIONS

DIAGNOSIS OF CUSHING'S SYNDROME

From a consideration of the evidence in Chapter 4 several conclusions can be drawn. The present study is large when compared to those previously reported. Pituitary-dependent Cushing's disease accounted for 79% of patients, compared to 58 to 70% in reported series. This may reflect the referral pattern at the hospitals where I worked. The rank order of presence of symptoms or signs differs from other series. This is partly due to the criteria used, and partly due to the diligence with which evidence has been sought. Exophthalmos is possibly underdiagnosed in patients with Cushing's disease. The present series gives objective measurements of exophthalmos, which was significantly more than that in control patients, but less than that found in severe Graves' ophthalmopathy.The present study emphasises the wide range of ages in which Cushing's disease can occur.

TREATMENT FOR CUSHING'S SYNDROME

The most frequent primary treatment of Cushing's syndrome was bilateral adrenalectomy in the present series. The difficulties in achieving definitive treatment are emphasised by the need for second, third, and fourth treatments in 70, 20 and 4 patients respectively.

Bilateral adrenalectomy was initially or eventually successful in 89% of 83 patients with pituitary Cushing's disease and this may be compared to 81% of 58 patients treated by pituitary implants, 75% of 12 patients treated by external pituitary irradiation plus metyrapone, and 71% of 7 patients treated by pituitary surgery. The success rate in a centre clearly depends on the expertise and facilities that are available. For adrenal adenomas, unilateral adrenalectomy is the treatment of choice. It is important not to remove both adrenal glands, which was done in 5 patients in this study, since this exposes the patient to the risk of adrenal insufficiency, and the need to take life-long steroid therapy. The prognosis for patients with Cushing's syndrome caused by adrenal carcinomas or ectopic ACTH secretion was very bad, with a median period of survival after diagnosis of only six months.

The objective, quantitative improvements in physical signs denoting clinical remission of Cushing's syndrome after treatment were: increase in height in patients <17 years; reduction in blood pressure, and decrease in weight in patients ≥ 17 years old. The decrease in urinary excretion of free cortisol which accompanied these changes was highly significant.

NELSON'S SYNDROME

Provided the patient survives more than three months after adrenal surgery, the prognosis for successful cure of pituitary-dependent Cushing's syndrome is very good, but the prospect of developing Nelson's syndrome later becomes a serious disadvantage of bilateral adrenalectomy. The detection rate of Nelson's syndrome has varied from 10 to 48% in 5 recent series (see Kelly et al, 1983b). In the present series the interval between total adrenalectomy and detection of Nelson's syndrome ranged between 1 and 14 years during which time 37% of 83 patients at risk have developed Nelson's syndrome. It is important to note that more cases may be detected in future.

In favour of total adrenalectomy as treatment for Cushing's disease is that rapid cure is almost certain, but against this must be weighed the immediate surgical morbidity, and mortality, and the need for replacement therapy, and the risk of later pituitary expansion. In favour of pituitary surgery, is the lower early morbidity and mortality, but this must be balanced against a slightly lower cure rate and the risk of partial or total pituitary failure.

SURVIVAL OF PATIENTS

Before replacement corticosteroids were available, when surgical treatment had a very high mortality, 50% of patients with untreated Cushing's syndrome died within five years. (Plotz et al, 1952). The data from

the present series indicate that preventable deaths still occurred in some patients with Cushing's disease, but provided the patient is well three months after total adrenalectomy, then long term survival is likely. Most deaths arose from cardiovascular and circulatory causes. The prognosis after adrenalectomy for an adrenal adenoma is good. Advances in treatment of Cushing's syndrome due to adrenal carcinomas or ectopic ACTH secretion will depend on preventing the disease, or detecting it at an early stage, or effective chemotherapy.

PSYCHIATRIC ILLNESS RESULTING FROM TREATMENT OF CUSHING'S SYNDROME

It is apparent from the evidence that medical and surgical treatments presently available for Cushing's syndrome have substantial disadvantages. The hypothesis was tested that the need for additional treatments may initiate, or exacerbate psychiatric illness in patients with Cushing's syndrome. The incidence of depressive illness was found to be higher in those patients who required more than one treatment.

LIFE EVENTS

In the present series adverse antecedent life-events were no more common in patients with Cushing's syndrome than in control patients. Depressive illness was however

significantly associated with the presence of adverse life-events.

PSYCHIATRIC ILLNESS

In the total of 209 patients, the incidence of serious psychiatric abnormalities was 65%. The most frequent psychiatric diagnoses were depression and anxiety. There was a significant decrease in the incidence of depressive illness when the cortisol levels were restored towards normal.

The present study is the first to use prospectively the Present State Examination with Catego diagnosis, together with the Hamilton Rating Scale. It has now been clearly demonstrated by quantitative, objective measurements that:

1. Depressive illness was the commonest psychiatric abnormality, being present in two-thirds of patients with Cushing's syndrome.
2. Patients with Cushing's syndrome have a higher incidence and severity of depressive illness than a carefully selected group of control patients.
3. Treatment which was successful in lowering cortisol levels towards normal was associated with alleviation of depression.

In the present study two personality inventories were also used. The significant changes noted on the Crown - Crisp Experiential Index and in the Eysenck Personality Inventory are probably a result of the improvement in depression.

The establishment of a causal connection between Cushing's syndrome and depression provided a new way of investigating the biochemistry of depressive illness, in particular to investigate the relationship between tryptophan and depression.

TOTAL AND FREE TRYPTOPHAN

The hypothesis was tested that in Cushing's syndrome depression occurs by the induction of tryptophan oxygenase, and the consequent depletion of brain 5-hydroxytryptamine (5-HT). In experimental animals injection of cortisol leads to an increase in tryptophan oxygenase activity and a decrease in brain concentrations of tryptophan and 5-HT. The hypothesis was tested that a similar effect occurs in patients with Cushing's syndrome. It was predicted that compared with control patients, those with active Cushing's syndrome would have lower plasma concentrations of total tryptophan, and this has been demonstrated. However, the free tryptophan concentrations were normal. In the prospective study, there were no significant changes in serum concentrations

of total or free tryptophan. It is therefore unlikely that in Cushing's syndrome depression results from a deficiency of tryptophan, and hence of serotonin.

HORMONE CONCENTRATIONS BEFORE AND AFTER TREATMENT OF CUSHING'S SYNDROME

The prospective study showed highly significant decreases in urinary free cortisol, 17 OGS and 17 OS, and plasma cortisol at both 09.00 and 24.00 hours, and for most patients the values became normal. All these changes occurred over the same time interval during which significant improvements in psychiatric symptoms occurred. Prospective biochemical data also showed significant increases in the following hormones, which thereby became closer to normal: serum testosterone in males, serum oestradiol in females, and sex hormone binding globulin in females. The changes in sex hormone concentrations would be expected to be associated with an increased feeling of well-being in the patients, and this fits with the objective evidence of improvement in psychological symptoms.

ENDORPHINS AND ENKEPHALINS

Finally, the present study suggests a new way of examining the roles of endorphins in mental illness. The endogenous opiate met-enkephalin was first identified

by Hughes et al (1975). Endorphins and enkephalins act on endogenous opiate receptors but their role in psychiatric disease is as yet unclear (Goldstein, 1978; Verebey et al, 1978). Beta-endorphin and ACTH are both derived from a common pro-hormone (Smyth, 1978). Patients with pituitary Cushing's disease have inappropriately high ACTH concentrations (Krieger et al, 1979). When treated by total adrenalectomy the ACTH concentrations may become very high, and be accompanied by large quantities of beta-endorphin (Nakai et al,1978; Nakao et al, 1978). During insulin-induced hypoglycaemia, ACTH, beta-lipotropin and beta-endorphin immuno-reactivity rose in parallel, but plasma metenkephalin did not change significantly (Smith et al, 1981). Now that assays for these opiate agonists are becoming available, this suggests that they should be measured in patients with Cushing's disease before and after treatment to see if there is any correlation between the opiate peptides and the behavioural changes noted.

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APPENDIX 1

PATIENTS CASE HISTORIES

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CD I

He was married, with three children and worked as an accountant. At the age of 33, he suffered from insomnia and depression which was relieved by amitriptyline. At 37, Cushing's syndrome was diagnosed and treated by left adrenalectomy. He felt psychologically better for two months and then became depressed again and took amitriptyline. He suffered from insomnia, decreased libido and social withdrawal. The right adrenal gland was removed. One year later he had regained his former cheerfulness, and sexual function was normal. At 42, headaches and brown skin pigmentation were noted. Plasma ACTH was 4,600 ng/l (normal less than 80). A pituitary implant was done successfully at the age of 45 when he was seen by me and he was not depressed.

CD 2

He was single, and worked as a lawyer. At the age of 20, Cushing's syndrome was diagnosed. The right adrenal gland was removed but there was no remission, so the left adrenal gland was removed at the age of 22. Before this second operation he had been psychologically normal. Two months afterwards he

complained of weakness, lack of appetite and a continuous state of anxiety. One year after the operation he was physically active and sexual function was normal. At age 30, he was reviewed when his main complaint was feeling nervous and agitated, occasionally getting up at 03.00h and being unable to sleep after that. He was taking hydrocortisone 20mg in the morning and I0mg at night. He was then married with one son and his mild anxiety was treated with a low dose of diazepam.

CD 3

Pituitary Cushing's disease was diagnosed at the age of I0. She had become obese, with cessation of growth in height for I8 months previously. She was unable to play games, but she remained cheerful and intelligent with no psychiatric problems. A pituitary implant was done at the age of II. Two months after this she had symptoms of adrenal insufficiency with vomiting, and was lethargic and unhappy. She was clinically and biochemically steroid deficient. There was a dramatic improvement when oral steroids were commenced and these were withdrawn gradually over six months. At the age

of I2 she was noted to be intelligent and alert and passed her II+ examination and was euthyroid. She left school, having failed her GCE Examination at the age of I5,and worked as a shop assistant. When reviewed at the age of 28 she was physically well. She has had no periods yet and there is poor development of secondary sexual characteristics. She now has no features of depression. She thought that the depression associated with Cushing's syndrome was because her appearance had changed, and she felt weak and unwell.

CD 4

She was married to a painter and she worked in a laundry. She became depressed over weight gain. She was living at home with her mother and step-father in a maisonette, and was unhappy about this home situation. At the age of 33 a pituitary implant was done and the cure from Cushing's syndrome was rated as "spectacular". Her periods became regular and she became pregnant one year later and a child was born in April I973. In July I973 there was an acute neurological illness, possibly due to cavernous sinus thrombosis or meningitis and she had a temperature of 40°C, a fixed dilated left pupil with proptosis of her left eye and an extensor right plantar response. Lumbar puncture

was turbid but grew no bacteria. She was treated with antibiotics, and made a gradual and full recovery. In 1975 she became pregnant again and in 1976 had a normal son, weighing 3.2 Kg. She was unable to breast feed.At this time she was separated from her husband and living on social security. Seven years after the pituitary operation she was extremely well with normal adrenal and thyroid function, both clinically and biochemically and with no features of depression.

CD 5

She developed diabetes mellitus requiring insulin at the age of 11. She married, and had a son at the age of 24 years, when she was unable to cope and an anxiety state was diagnosed. The obstetric notes at this time stated that she was plump and with a high colour. She had severe depressive illness and was admitted to a psychiatric hospital, where she had electroconvulsive therapy, chlorpromazine and diazepam. On one occasion she was noted to be manic. At the age of 32, Cushing's syndrome was diagnosed at the psychiatric hospital. She was noted to worry over trivialities, and was easily distracted. Cushing's syndrome remitted after a pituitary implant, but she remained anxious

and depressed and was unable to return home. The last four years of her life were spent in hospital, and she suffered several complications from diabetes mellitus, including gangrene of the leg requiring amputation. She died at 43 and in the last year of her life she was treated with amitriptyline for depression. She died suddenly, probably from a cardiovascular cause.

CD 6

She worked as a civil servant. Total adrenalectomy was done at age 28. At age 48, she had depression and anxiety and was seen by a psychiatrist. Other medical conditions include diverticular disease and a benign breast tumour. She remains in clinical remission from Cushing's syndrome, having been followed for 24 years. The replacement dose of hydrocortisone is 70mg per day.

CD 7

Cushing's syndrome was suspected at age 2I but not confirmed until 28 when she was treated then by total adrenalectomy. Before the operation she was depressed and this improved afterwards. She has now been observed for I3 years without major psychological problems. Her pigment and ACTH levels

have increased slightly but her pituitary fossa x-ray is normal.

CD 8

Cushing's syndrome was diagnosed at the age of II. He had gradually become more tired and unable to participate in games but he was coping well with school. A pituitary implant was done and one month later his mother noted a marked improvement and he was much happier, more settled and less restless, more energetic and less self-conscious. He required a second pituitary operation to obtain a full remission. After this he did well at school, became top of his class in all subjects. At I2 he was noted to be cooperative and intelligent and was in a form with boys mainly above his age. At I4 there was a clinical relapse of Cushing's syndrome and he was treated with another pituitary implant, which was successful. At I6 he was in the middle of his class in the top form of a Grammar school and hoped to study chemistry. He did not do well in his GCE examinations and became apprenticed as an engineer and later worked as a machine tool fitter. He married and fathered two children. When reviewed at age 29 he was physically, mentally and sexually well with no features of Cushing's

syndrome. His adult height is I55 cms and his weight is 56 Kg. He takes no replacement hormones. When reviewed, he felt the depression at the time of his Cushing's syndrome preceded any bodily signs of the illness and that before this he had been happy. He was depressed during his illness because he was a long way from home and was not sure what was going to happen to him and after the operation he remembers waking and feeling unwell and scared. He has made a good psychological adjustment to life but his intellectual achievements fell short of his early promise.

CD 9

Cushing's syndrome was diagnosed and treated by total adrenalectomy at age 20. At 33 he developed Nelson's syndrome and was treated by neurosurgery, and at 35 by external irradiation to the pituitary gland. There were no significant psychological problems.

CD I0

Cushing's syndrome was diagnosed at 57. Before treatment she was noted to be emotionally disturbed and depressed and this was attributed to concern for her mother, who was said to suffer from

Huntingdon's chorea. Surgical hypophysectomy was attempted but this failed and she had a left retro-orbital haematoma with paralysis of left eye movements. She died two months later from haemorrhage from the left internal carotid artery.

CD II

Cushing's syndrome was diagnosed at the age of 20, and treated by total adrenalectomy. After operation she had a left subphrenic abscess, a deep venous thrombosis, and a respiratory tract infection, but she gradually recovered. In the next six years, she had one successful pregnancy, and one stillbirth. At 23, she had a depressive illness and was referred to a psychiatrist. At the last review she was well physically and psychologically.

CD I2

Cushing's disease was diagnosed at the age of I3, when he had become obese, and stopped growing in height for I½ years. Bilateral adrenalectomy was done at I4. Cushing's syndrome did not remit, so he was given external radiotherapy to the pituitary gland at I6, again without clinical cure, so pituitary implantation was done at I7. He then developed diabetes insipidus and hypothyroidism. At 22, he had a third cranial nerve palsy. He was obese and went to a faith healer,

and managed to lose 20 Kg in weight. At the age of 23, adrenal insufficiency was diagnosed and treated with cortisone. At 24 diabetes mellitus was diagnosed and treated first with tolbutamide and later with insulin. At 27 he developed diarrhoea and vomiting and was admitted to hospital where he rapidly deteriorated and died.

CD I3

He worked as a labourer. External irradiation to the pituitary was given at 58, and a pituitary implant at 59. There was no previous history of depression. When Cushing's disease was active he developed paranoid delusions, including a conviction that a doctor had caused the illness. He became anxious and depressed. There was an acute psychosis when he screamed and sang continuously until tranquilised with chlorpromazine. Pituitary radiographs showed a tumour. Three days after operation he became hypotensive with ventricular tachycardia, and a pulmonary infection, and he died.

CD I4

External irradiation was given at 4I but she did not remit and a bilateral adrenalectomy was done at 46,

followed by successful remission. One year after adrenalectomy she was noted to be depressed. Her depression can be attributed to life events, since her ex-husband used to visit, and later married, the next door neighbour and the marriage of the patient's daughter broke up, and her granddaughter was taken to live abroad. Nelson's syndrome was diagnosed at 58 and treated by transethmoidal hypophysectomy.

CD I5

She was married to a school teacher and had three children. A pituitary implant at age 46 resulted in clinical remission.There was no significant depression before, during or after treatment for Cushing's disease.

CD I6

Cushing's disease was diagnosed at age II, when she stopped growing in height for two years. Bilateral adrenalectomy was done. At 26 she developed headaches and these were attributed to expansion of the pituitary fossa and bromocriptine was given, which gave relief. Serum Prolactin was 983 and I00 mu/l (normal < 425) before and during bromocriptine therapy. There were no significant features of depression before, during or after treatment for her endocrine disturbance.

She remains concerned about her short stature (at age 29 she is I40 cm tall and weighs 44 Kg). Nelson's syndrome is currently being treated with sodium valproate.

CD I7

She was treated by a pituitary implant at 36, and total adrenalectomy at 37. At 4I she developed Nelson's syndrome with a right third nerve palsy and right-sided optic atrophy. She was treated by external pituitary irradiation. There was no significant psychiatric abnormality.

CD I8

At age 28 she suffered from depression and had electroconvulsive therapy. At 33 Cushing's disease was diagnosed and treated by one and two-thirds adrenalectomy. There was a clinical remission, during which she had a normal pregnancy at 35. There was a mild clinical relapse at 42 and she was observed for several years. At 43 she was re-investigated and had bilateral carotid angiograms and an air encephalogram. Four days after these procedures she had a focal fit and a right hemiparesis. An intracranial clot was aspirated through a burr hole but she deteriorated and died. She was depressed during the period when

Cushing's disease was active, she improved after the adrenalectomy, but depression recurred when Cushing's disease relapsed.

CD I9

He was a single man who lived with his sister and worked as a school teacher until he retired at 60. He was well until he was 63, when he developed weakness, polyuria and polydipsia. He had a raised blood glucose and signs of Cushing's syndrome. Plasma and urine cortisol values were elevated. Two months later depression was diagnosed and this was attributed to weakness. He had intermittent episodes when he felt " not being part of things" each lasting for about I5 minutes. He became confused, and had intermittent euphoria, which was severe at times. He was treated with metyrapone and there were clinical, biochemical and psychological remissions. He has a rare form of Cushing's syndrome of a cyclical nature and his urinary free cortisol has been as high as II,000 nmol/24 hrs. When seen by me during remission at 65 and 66 and in relapse at the age of 67, there was no psychological abnormality. In contrast to his previous illness he was a charming man with no abnormal thought processes, not depressed, and not hypomanic.

CD 20

Pituitary Cushing's disease was diagnosed at age 45 and treated by one and two-thirds adrenalectomy. She was married with three children. At 57 she developed thyrotoxicosis which was successfully treated with radioactive iodine. At 67 she had low back pain, osteoporosis and cervical spondylosis. She was well for many tears after her subtotal adrenalectomy but at the age of 68 she had clinical and biochemical evidence of a relapse of Cushing's syndrome. She was treated with metyrapone but the side effects exceeded the benefits. She has mild depression but no more than one would expect from her various medical conditions.

CD 2I

Cushing's disease was diagnosed at age I9. She was treated initially with metyrapone and external radiotherapy. She has three elder sisters and one younger brother. At I5 she became pregnant but there was a spontaneous abortion and she still feels resentful about this. She left school at I6 and worked as a packer. She had a three year illness, during which she gained weight and was depressed. At I9, she was seen by a Consultant Psychiatrist, who noted that she was very depressed, paranoid

and suffering from auditory hallucinations. There was noted to be a strong reactive element, since she had changed from a vivacious young lady to an obese introspective one, who avoided contact with strangers lest they see her face, which had become red, rounded and hirsute. She tried to avoid looking in a mirror. She had planned to train as a designer and felt frustrated at working in a more mundane job. In addition to the treatment for her Cushing's syndrome she was given mianserin, thioridazine, chlorpromazine and haloperidol. She remained withdrawn and depressed, especially about the appearance of her face. At 20 she had auditory hallucinations, in particular that doctors and nurses said that she did not wash and was lazy. She admitted that two months previously she had taken an overdose of 20 aspirin tablets on an impulse and later vomited. She did not tell anybody about this at the time. She threatened to commit suicide and was transferred to a psychiatric unit for observation. One month later the paranoid symptoms had disappeared. She was offered a holiday abroad with old friends but she declined this, and remained socially withdrawn. At 22 , since she had had depression with psychotic features and persistent Cushing's syndrome for two years , a bilateral adrenalectomy was done. Her depression became less after this.

CD 22

At 69 she had a bilateral adrenalectomy. In recent years she has had anaemia, diverticular disease, folate deficiency, congestive heart failure and hypertension. At 77 she had an infarction of the right occipital cortex. There was no particular link of Cushing's syndrome with depression.

CD 23

She was married with six children. A one and two-third adrenalectomy was done at the age of 34, and she has remained in remission for II years of follow up, apart from depression at 4I when her husband left. There has been no other psychiatric abnormality and she now remains well and happy.

CD 24

Cushing's disease was diagnosed at 34 and treated by total adrenalectomy. Nelson's syndrome was diagnosed at 44 and treated with bromocriptine and sodium valproate. She was depressed when Cushing's disease was active and this persisted for three years, even though there was clinical remission. She stopped her tablets for three days at age 38, and this was regarded as a "suicide equivalent" and steroids were recommenced and she was given

amitriptyline. She was reviewed at 44, when she was not depressed. . .

CD 25

At 52 a total adrenalectomy was done. She has had peptic ulcers. At another hospital osteoporosis was treated with calciferol for four years and she became hypercalcaemic and uraemic. Nelson's syndrome was diagnosed at 56 but she was judged too unwell for treatment.She died at 62.

CD 26

At 23 she developed hypertension during pregnancy and she was sedated with phenobarbitone and became depressed. Cushing's syndrome was diagnosed during this pregnancy. Three months after delivery a pituitary implant was done. She has remained well with no evidence of depression for 8 years.

CD 27

She was divorced and worked in a factory. Bilateral adrenalectomy was done at age 50 and she was observed for five years. There were no features of depressive illness before, during or after treatment for Cushing's disease.

CD 28

Bilateral adrenalectomy at age 42 relieved Cushing's syndrome. At 47 she developed Nelson's syndrome and had a pituitary implant. She worked as a teacher, her husband was a headmaster and her son attended University. She had a happy childhood. Two years before Cushing's syndrome was diagnosed she was unwell and depressed and attributed this to working for an unpleasant superior. At age 50 she felt too depressed to continue with her work and saw a psychiatrist, who prescribed flupenthixol. She cheered up with the prospect of her son's marriage, which took her mind off her own problems. After the adrenalectomy she felt very well "bursting with confidence, too good to be true". At latest assessment she was neither depressed nor hypomanic. Depression was linked both to Cushing's syndrome and to life events.

CD 29

Cushing's syndrome remitted after right adrenalectomy at age 21, recurring at age 42, and remitted again after left adrenalectomy. At 54 Nelson's syndrome was diagnosed and treated with a pituitary implant. She has been observed for 33 years. At 43 she was depressed and saw a psychiatrist, who treated her with diazepam. When reviewed at 54 she had had mild depression for three months attributed to headaches, recurrent cystitis and the need for treatment for Nelson's syndrome.

CD 30

Total adrenalectomy was done at age 35. Nelson's syndrome was diagnosed at 39 and treated with a pituitary implant. She was married with one adopted child. There was no significant depressive illness before or during the period when Cushing's syndrome was diagnosed. The only significant depressive illness occurred during the steroid withdrawal after adrenalectomy, when she became extremely tired, dizzy, nauseated, weak and depressed, and these symptoms all resolved when she was started on a replacement dose of steroids.

CD 3I

At age 39 a total adrenalectomy was done. She was married with two children.Symptoms of headache, backache and depression with suicidal thoughts, had been present for four years during which she had had I2 courses of electroconvulsive therapy. Cushing's disease remitted and the depression became less after adrenalectomy. She remained depressed for two years afterwards, but her husband left her during this time and this may have been a contributing factor. She has now been observed for I3 years since diagnosis and is not clinically depressed.

CD 32

She was a housewife who worked part-time as a typist and

her husband was a clerk. Her father died of pulmonary tuberculosis when the patient was one year old. Her marriage was not consummated for nine years due to vaginismus, and a child was adopted.She became pregnant at 34, and had a daughter. After the birth she became depressed and this increased in severity. Between the ages of 38 and 40 she became tired and short of breath and her face became red. At 40 she was admitted for investigation of Cushing's syndrome, which was suggested by her physical appearance, but not confirmed biochemically. She had delusions of gangrene of her limbs, brain tumour and diabetes, and thought she was being injected with live tuberculosis bacteria and that she was going to die. She was then referred to a psychiatric hospital. Physical examination was normal. Mental assessment-" solitary and brooding, always requesting to go home and only partly co-operative. She spoke in a monologue and was pre-occupied with disease processes. Paranoid statements with ideas of reference. Depressed, bewildered, frightened and anxious. Believed that she was being spied upon and going to die. No hallucinations. No compulsive phenomena. Orientation correct. Memory poor. Attention and concentration poor". During this time she walked out of hospital and took an overdose of 70 aspirin tablets and was admitted to another hospital.

She was then deluded and suspicious and probably aurally and visually hallucinated. Electroconvulsive therapy was commenced. Once more she discharged herself against medical advice. The diagnosis from the psychiatric hospital was schizo-affective psychosis. At 40 her intelligence quotient on progressive matrices was 85. The GP commented "I have known her for some years as her GP and on several occasions she has had mild symptoms of psychosis". Three months after electroconvulsive therapy she was rated as being very well " never so well in all my life", and off all tablets. She was sleeping well and her energy was good and she did not feel that further electroconvulsive therapy would help. At 43, she was referred back to the Consultant Psychiatrist with increasing depression, early morning wakening and feeling miserable at the thought of getting through another day. She had obsessional features and was treated with imipramine. At 44 her weight had increased, she had signs of Cushing's syndrome, and tests showed this to be pituitary-dependent. She had a pituitary implant with remission of Cushing's syndrome. Steroid replacement was gradually decreased to Prednisolone 6 mg per day and she was discharged home. Prednisolone was eventually withdrawn 7 years later. There were no signs of Cushing's syndrome or depression and she had plenty of energy.

She remembered feeling depressed when she had Cushing's syndrome and attributed this to change in her appearance and said that the depression antedated the appearance of Cushing's syndrome. The patient remained obsessive, especially about housework. Therefore she had a severe psychiatric disease when Cushing's syndrome was active.

CD 33

She was treated by total adrenalectomy at age 59. She was married with three grown-up children and her husband was a railway engineer.She cried when she became unable to walk upstairs, but apart from this there were no features of depressive illness and she was cheerful and pleasant when interviewed before the operation. The adrenalectomy was complicated by a left subphrenic abscess and a gastrointestinal bleed. She coped well with this, and her Cushing's syndrome remitted. At 64 she was remarkably active and able to fly to America and go for long walks with her relatives. She gave up work as a result of her illness.

CD 34

At age 52 she had a pituitary implant. She was married with three children. She was mildly depressed when her Cushing's syndrome was active and when she developed

adrenal insufficiency after her operation, when steroids had been withdrawn. Relevant factors include the unstable marriage of her daughter, and the patient's own diverticular disease.

CD 35

Cushing's disease was diagnosed at age 13 years and treated by total adrenalectomy. There was a good clinical remission and he commenced growing again. He was reviewed before, during and after treatment. Apart from a slight shyness about his appearance he was normal, in particular there was no depressive illness.

CD 36

Cushing's disease was diagnosed at age 8 and treated by total adrenalectomy. He has been followed for 10 years and recently his pigment has increased but the pituitary fossa is normal. No features of depression were noted.

CD 37

Cushing's disease was diagnosed at 12 and treated by a pituitary implant. Before her illness she was doing well at school and interested in gymnastics. She recalled feeling sad when her Cushing's syndrome

occurred because of obesity and weakness, which made her less popular with the other children. From the ages of I2 to I6 the school performance deteriorated academically and there were behavioural problems and she was noted to associate with younger girls who would respect her, and to avoid her own peers and to be isolated and lacking a close friend.She had hoped to study medicine but she only achieved five 'O' levels. She then wished to do physiotherapy but was too small, being I48 cm tall. She left school and worked as a data processing clerk and at the age of I7 wrote a long letter, saying that she had made lots of new friends, had come to terms with her short stature and her previous illness and summed it up by saying "I have had a fair share of joy and sadness and that I really can't complain. At the moment it is hard to think how I feel when I am unhappy because I feel quite content".

CD 38

Pituitary Cushing's disease was treated at age 5I by external irradiation, and metyrapone. After three years on metyrapone he still had some signs of Cushing's syndrome and was being re-assessed for a possible pituitary operation. There were no features of depressive illness.

CD 39

Pituitary Cushing's disease was treated at age 40 by total adrenalectomy. Nelson's syndrome was diagnosed at 44 and a pituitary operation was planned. She was depressed before her adrenal operation and this improved afterwards when her Cushing's syndrome remitted, and she recalled feeling depressed when her steroids were stopped for a trial period.

CD 40

She had a pituitary implant with good clinical remission at age 25. She had two children and her husband worked as a builder. Cushing's disease was diagnosed at the end of her second pregnancy. Depression commenced before Cushing's syndrome was diagnosed but after facial plethora and weight-gain developed. She remembers rejecting the baby, blaming it for the illness, and she cried daily. She was treated with antidepressants. Her libido diminished and her husband rejected her and her marriage was threatened. She lost interest in going out and meeting people. There was no hypomania. After operation her depression improved. She had a miscarriage two years later. When reviewed at 30 she was physically and mentally normal. Cushing's syndrome therefore developed during her pregnancy and was associated with severe depression.

CD 41

Pituitary Cushing's disease was treated at 65 years by total adrenalectomy. She has been observed for seven years and remains well with no evidence of depressive illness.

CD 42

Cushing's disease was diagnosed at 46 and treated by total adrenalectomy. Invasive Nelson's syndrome was diagnosed at 52 with a visual field defect and a third nerve palsy. Two pituitary operations were done. After operation she was noted to have agitated depression and was referred to a psychiatrist. During follow-up she was noted to be depressed which could easily be attributed to the symptoms from her illness plus low back pain and headaches.

CD 43

She was married to a business man. Pituitary Cushing's disease was diagnosed at age 37 years and treated by pituitary implants at the ages of 37 and 38, then by total adrenalectomy at 40. Before treatment she was bed-ridden due to back pain associated with osteoporosis. After the second implant there was meningitis, from which she made a full recovery on antibiotic treatment. One year after the adrenalectomy she was well and fully mobile.

CD 44

Hypertension had been present for 20 years, and she had already sustained a stroke when Cushing's disease was diagnosed at age 45. She was obese, hypertensive and aphasic, and was judged too unwell for surgery. She survived four years. At the time of diagnosis her pituitary fossa was enlarged.

CD 45

Bilateral adrenalectomy was done with good clinical remission at age 49. Before the operation he had been physically over-active, especially in the mornings. After the operation he became more passive, denied anxiety, stated that his concentration was less good but that his sexual function had improved. He returned to work as a dockyard rigger. It is probable that hypomania was associated with Cushing's syndrome.

CD 46

Treatment was a pituitary implant at age 27, followed after one year by a total adrenalectomy. She was a typist, married with three children. Before her first operation she was described as "comfortable, happy, relaxed and a good historian". Although her Cushing's disease did not remit clinically after the first treatment, she had no psychiatric symptoms. Six years later she suffered from loss of libido.

CD 47

Pituitary Cushing's disease was diagnosed at age 3I. She was treated by bilateral adrenalectomy at 32. Cushing's syndrome remitted clinically. At 39 she became agitated and depressed and diazepam was prescribed. At 34 skin pigment increased but ACTH levels were only slightly above normal and her pituitary fossa has remained normal during follow up.

CD 48

Pituitary Cushing's disease was diagnosed at the age of 43. She was married with two children. She had commenced training as a nurse and later left this to become a secretary. Her previous personality was outgoing. During the onset of symptoms of Cushing's syndrome she became depressed thinking " will I ever be right again and have enough energy". Transethmoidal pituitary surgery was done at 44 and there was remission lasting for eight months. During this time there were life events concerning her husband's elderly parents and she became anxious about them. At 46 her Cushing's syndrome had relapsed and she was treated successfully by total adrenalectomy. She had only mild features of depression when interviewed before treatment of Cushing's syndrome and no depression when her Cushing's syndrome had been successfully treated.

CD 49

Cushing's disease was diagnosed at age 52 years. She was successfully treated by pituitary implant. She was married with four children. One brother had a nervous breakdown. One year before Cushing's disease was diagnosed, she was anxious with inability to concentrate. A psychiatrist commented that she was "rather odd in affect, detached, with little rapport and very obsessed with symptoms, which endlessly occurred to her and were recorded in her diary". After the operation her mental state gradually returned to normal and when reviewed at 57 she was neither anxious nor depressed. Her main medical problem during the preceding four years had been painful feet, which had troubled her since 14. Depressive illness was associated with the onset of Cushing's syndrome.

CD 50

Cushing's disease was diagnosed at age 49 and treated by total adrenalectomy. Just before Cushing's syndrome was diagnosed she suffered from depression. This may have been associated with methyldopa therapy. Depression improved after the operation. She has been observed for 13 years.

CD 5I

Pituitary Cushing's disease was diagnosed at age 47 and treated by total adrenalectomy. Previous medical history included hypertension and osteoporosis. Increased skin pigmentation was noted since 56 and ACTH levels have been elevated at 3I9 ng/l, but the pituitary fossa remains normal. There is no history of depressive illness.

CD 52

Cushing's disease was diagnosed at age 37. He was treated by a pituitary implant, followed one year later by total adrenalectomy. In the referral letter the general practitioner commented on psychological and psycho-sexual difficulties since childhood, not thought to be related to endocrine dysfunction. One year before his first operation he had suffered weight gain, depression, headache and urinary symptoms, including frequency of micturition. A urologist diagnosed his urinary symptoms as psychogenic. Three years after the adrenalectomy he married but was impotent. Psychiatric referral was arranged but he did not attend for this. His wife was a social worker. The couple adopted a child and this brought much happiness to them.

CD 53

Cushing's disease was diagnosed at age 29. She remitted after a pituitary implant.

CD 54

Pituitary Cushing's disease was diagnosed at age 56. This responded to pituitary implantation. She was married with two daughters. At 36 tuberculosis was treated by thoracoplasty. When woken for a midnight cortisol estimation she became anxious and agitated and intractable to all reasoning, being disorientated in time and place. The clinical diagnosis was a steroid psychosis. After her first implant she remained anxious and depressed, mainly about the affairs of her daughter, rather than her own illness. When her Cushing's disease finally remitted, her depression became less.

CD 55

Cushing's disease was diagnosed at age 56. When her Cushing's disease occurred she became depressed and found it difficult to cope with her housework, for a period of two years. After a pituitary implant had caused successful remission, polymyalgia rheumatica was diagnosed and treated briefly with high doses of prednisolone. When Cushing's disease was active she was severely depressed, and this improved considerably as her Cushing's disease remitted.

CD 56

He was well until the age of 9 years, when his weight increased and he was found to have a blood pressure of I70/I30 and had Cushing's syndrome. At I2 he had a subtotal adrenalectomy, with a partial remission, and he gained 5 cm in height until his disease relapsed. He was referred for removal of the remaining adrenal tissue. Cushing's syndrome was obvious and he was described as alert and intelligent. After the operation he had a subphrenic abscess and a gastric fistula and pyrexia and he attributes feelings of depression to these problems. At 28 a pituitary tumour was diagnosed and treated by an implant. After this he became hypogonadal but this responded well to human chorionic gonadotrophin injections. His wife became pregnant twice, but had two miscarriages. In early childhood, he was evidently very intelligent and although he obtained a University degree, he felt that after treatment of his Cushing's syndrome that academically he achieved things " after a struggle".

CD 57

Cushing's disease was diagnosed at the age of I4 and treated by total adrenalectomy. Until he was II, he was one of the tallest in his class and did well academically and at sports. As Cushing's disease developed he became unable to play cricket and football.

He presented with low back pain and ankle pain, due to osteoporosis. He was seen before and after operation, which relieved Cushing's syndrome. He is an intelligent young man who coped well with severe physical illness. There were no features of depressive illness.

CD 58

Pituitary Cushing's disease was successfully treated by a pituitary implant at age 29. During her second pregnancy at 27 she developed the signs of Cushing's syndrome and her mood changed and she described herself as more tense and feeling as though everything was "too much effort". She was also depressed. She went into labour at 38 weeks spontaneously and delivered a girl weighing 2.9 Kg. Her menstrual periods became irregular, and then ceased 9 months before the pituitary operation. Three months after the pituitary operation her periods recommenced and her Cushing's syndrome was rapidly improving and her mood became normal. There is a striking series of photographs before and after treatment.

CD 59

Pituitary Cushing's disease was treated at 39 by total adrenalectomy. Previous medical history includes partial gastrectomy for duodenal ulcer, followed by

anaemia and malabsorption, hypertension and arthritis. After the adrenalectomy he developed a sub-phrenic abscess, paralytic ileus and a bronchopleural fistula and empyema, which required drainage. Cushing's disease remitted after adrenalectomy but arthritis became worse.

CD 60

Pituitary Cushing's disease was diagnosed at age 52. An attempted hypophysectomy was unsuccessful, and she was referred for external irrediation but there was no remission. She refused further investigations and treatment. One year later she had hypertension, diabetes mellitus and a cerebrovascular accident. Although severely disabled, she was still alive with signs of Cushing's syndrome 6 years after diagnosis.

CD 6I

She had two pituitary implants, then a bilateral adrenalectomy. The adrenalectomy was followed by deep venous thrombosis and pulmonary embolus, and a sub-phrenic abscess. At 54, carcinoma of the stomach was diagnosed and treated by a partial gastrectomy, and she has survived two years after this although a gasric fistula remains. She is one of I3 children, I0 of whom survived until adult life. Before Cushing's disease developed she described herself as shy and quiet. She had previously suffered from depression

and had taken one overdose. When re-assessed at age 56, Cushing's disease had remitted almost completely but she still had residual signs and it may be that her replacement dose of hydrocortisone 35 mg per day was slightly excessive and the plan was to reduce this. Her urinary free cortisol was 310 nmol per 24 hours while taking the above dose. When last assessed she admitted to mild depression which was less severe than when her Cushing's syndrome was most severe.

CD 62

Cushing's disease was diagnosed at age 67 and treated by a pituitary implant. During the three years before diagnosis she had become increasingly tired, lethargic, and anxious, and had cardiac failure. She was weak and depressed. She was too unwell for an adrenalectomy. Four months after the implant she was admitted with a lumbar disc lesion, and she rapidly deteriorated and died.

CD 63

Cushing's disease was diagnosed at age 23. She was treated by a right total and a left nine-tenths adrenalectomy. She worked as a shop assistant. Her parents were separated and she had one adopted brother. At the age of 20, Cushing's syndrome developed

and worsened over the next three years. The patient attributed her illness to an argument with her boyfriend and she did not leave the house because she became self-conscious about her appearance. There was a good clinical remission to the adrenal operation and she has been observed for 9 years. Her depression improved. However, when attempts to reduce her replacement cortisone acetate below I2.5 mg per day were made she reported "I have tried to do without my tablets... the first couple of days without any tablets at all was alright then I became very tired, my eyes and my head felt very heavy and I felt depressed and all that I wanted to do was to sleep and to cry, but I tried very hard to overcome this feeling until last Wednesday and then I just broke down at work....to top all this I have had the runs(diarrhoea) for three days ...I have gone off my food"- extract from patient's letter. Therefore, symptoms of depression occurred both when Cushing's syndrome was active , and when there was evidence of adrenal insufficiency.

CD 64

Pituitary Cushing's disease was diagnosed at the age of 46 and treated by total adrenalectomy. Nelson's syndrome was diagnosed at 5I and he was treated by external irradiation, followed by a pituitary implant

at 52. After the implant he had temporary diabetes insipidus, and permanent hypothyroidism.

CD 65

She was treated by a pituitary implant at age 47 but her Cushing's disease remained active. The total adrenalectomy was planned and as a first stage, the left adrenal gland was removed at 48. One month after the operation she developed headaches and a cerebrospinal fluid leak. Meningitis was diagnosed, complicated by a stroke paralysing her right side. Her conscious level deteriorated and in spite of intensive therapy she died. Post mortem examination showed a right adrenal gland weighing 10 gm (enlarged) and thrombosis of the cerebral venous sinuses. When Cushing's disease occurred she was depressed, and she attributed this to rejection by her husband on account of her obesity, despite all attempts to diet.

CD 66

Pituitary Cushing's disease was diagnosed at age 53 and treated by a pituitary implant. She complained of impaired memory and at 55 she was referred for psychiatric assessment. At age 54 she developed diabetes insipidus and epilepsy and hypertension. She has been followed for 8 years and remains very unwell.

CD 67

Pituitary Cushing's disease was diagnosed at age 67. He was treated with metyrapone and aminoglutethimide but medical treatment failed. He moved and was lost to medical follow-up.

CD 68

She was treated by a pituitary implant at age 61 with good remission and observed for eight years. On review at 69, Cushing's syndrome was in remission but she was being treated with amitriptyline for depression.

CD 69

She was treated by total adrenalectomy (two operations). When Cushing's disease was active she was weak, tired, and agitated. At 57 she developed dark skin, but her pituitary fossa showed no expansion and she is being observed.

CD 70

He was treated by a sub-total adrenalectomy at age 25 and Cushing's disease remitted until age 30 when the remaining adrenal tissue was removed. However, there must have been a further remnant since his Cushing's disease was still present at 35, when a pituitary implant was done with good clinical remission. He was a

draughtsman, married with one daughter. He has always suffered from anxiety and this became worse when his Cushing's syndrome was active. He suffered from moderate depression before his implant and his depression worsened three months after operation at a time when his steroids were being reduced, and his depression thereafter improved when he was given a regular replacement dose of prednisolone 7.5 mg and fludrocortisone 0.1 mg per day. He attributed depression and anxiety to the threat of redundancy.

CD 71

Pituitary Cushing's disease was diagnosed at age 28. She was treated by a pituitary implant with good clinical remission. She has worked as a hairdresser and shop assistant. Her previous history included ankylosing spondylitis. When Cushing's disease was diagnosed she had become depressed and irritable which she attributed to being obese, hirsute and tired. The depression improved one month after her operation when it became clear to her that the treatment was working. Therefore the development of Cushing's syndrome was associated with the onset of depression which was relieved with the successful pituitary implant.

CD 72

She was a single lady who worked as a nurse. At 26 Cushing's syndrome had been suspected, since she had irregular periods, hirsutism, and obesity (weight 82 Kg, height I66 cm). For several years tests were inconclusive but she had clear evidence of pituitary-dependent Cushing's disease with pituitary expansion at 35 and a transethmoidal hypophysectomy was successfully done. There was no past history of depression or other psychiatric abnormality and she was seen before and after her operation and she was not depressed.

CD 73

Pituitary Cushing's disease was diagnosed at age 55 and treated by total adrenalectomy.

CD 74

Pituitary Cushing's disease was treated at 23 by total adrenalectomy. There was remission and she became pregnant one year later and had a son. At 27 she had severe headache and pituitary apoplexy was diagnosed and haemorrhagic tumour was removed by transfrontal neurosurgery. After this operation she had transient diabetes insipidus. During the next five years she became deeply pigmented and her pituitary fossa

expanded and she had a transethmoidal pituitary operation at 33. There was a transitory sixth nerve palsy almost certainly associated with pituitary expansion at 3I. She has suffered from depression and anxiety for most of her adult life. These psychiatric symptoms worsened during the difficult treatment of her Cushing's and Nelson's syndromes.

CD 75

At the age of 27 she had been diagnosed by a Consultant Psychiatrist as suffering from paranoid schizophrenia, the symptoms of which fluctuated for several years. Pituitary Cushing's disease was diagnosed at age 45. Before operation she was noted to be "markedly psychotic". After the adrenalectomy Cushing's syndrome remitted but arthritis became worse, probably due to steroid withdrawal. At 47 there was an acute confusional state of unknown cause. She became deeply pigmented from the age of 49. She failed to attend for follow-up clinics and after several broken appointments she eventually re-attended at 59, when she had a grossly enlarged pituitary fossa and very dark skin. In spite of this she said she felt very well, and refused to have blood taken for ACTH estimation. She was only taking I2.5 mg per day of cortisone and this relatively low dose of glucocorticoids may have accelerated the

development of Nelson's syndrome. Further treatment is pending. . .

CD 76

Pituitary Cushing's disease was diagnosed at age 27 years. This was treated by attempted hypophysectomy, then external pituitary irradiation and metyrapone, which also failed, and she finally responded to total adrenalectomy at 29. She was married with two children. During the three years before Cushing's syndrome was diagnosed she became depressed and gained weight and periods became irregular. She was given diazepam. She described herself as nervous and introverted.She was depressed when interviewed when her Cushing's syndrome was active, and her depression improved considerably after the adrenalectomy.

CD 77

After adrenalectomy at age 43, she had a pulmonary embolus. Six months after the operation although her Cushing's syndrome had remitted she was noted to be very depressed but this has gradually improved. She has now been observed for I7 years.

CD 78

Cushing's syndrome remitted after a pituitary implant at age 50.

CD 79

Hypophysectomy, assumed to be total, was done at the age of 40 but Cushing's syndrome did not remit. Total adrenalectomy was done at 42. At 44, Nelson's syndrome was treated by external pituitary irradiation. She was married with four children and until recently worked as a machinist. She claimed that symptoms of depression came before any of the signs of Cushing's syndrome. When Cushing's syndrome was active she was noted to be depressed and subject to "explosive rages". She was seen by a psychiatrist who noted that she was severely and suicidally depressed and he was "not convinced that the psychiatric condition would be cured by curing her Cushing's syndrome". After the unsuccessful pituitary operation her main problem was profound depression with lethargy, irritability, feelings of guilt and self reproach and cognitive impairment with difficulty in memory. She was treated with nomifensine without benefit. After the adrenalectomy, she improved physically and mentally. She was still subject to depression, attributed to losing her job, injury of her daughter in a motor-cycle accident which required a spinal operation, illness affecting her mother(blind) and her father(in a geriatric hospital). She became very depressed and apprehensive when the need for external pituitary irradiation was explained.

Her life-long tendency to depression and anxiety was clearly worsened both by Cushing's syndrome and by life events.

CD 80

Pituitary Cushing's disease was diagnosed at the age of 42. She was successfully treated by total adrenalectomy and followed up for five years. Two years before adrenalectomy she became depressed and this was attributed to a reaction to a termination of pregnancy. After the operation she had a deep venous thrombosis and a pulmonary embolus. During follow-up she has been noted to suffer from nervous tension and depression and backache and "innumerable complaints".

CD 8I

Pituitary Cushing's disease was diagnosed at the age of 50. She has two children and is married to a successful executive. Ten years before Cushing's syndrome was diagnosed she had "a nervous breakdown" and this was attributed to the recurrent need for her husband to move house due to his job. At 49 she suffered an acute myocardial infarction with a ventricular arrhythmia and it was during convalescence from this that the physical signs of Cushing's syndrome were noted. She had severe depression and anxiety attributed to her

cardiac illness. Treatment by pituitary operation is pending and she is being prepared for surgery by metyrapone and aminoglutethimide; severe depressive illness anteceded development of Cushing's syndrome for many years.

CD 82

Pituitary Cushing's syndrome was diagnosed at age 39 and she was treated by total adrenalectomy. She developed renal failure and despite dialysis she died.

CD 83

Her presenting symptom at age 5I, was an ulcer on her left leg, caused by a dog bite one year previously. Treatment was with a pituitary implant, then a right frontal craniotomy was done, and the pituitary bed was packed with radioactive yttrium. There was still no remission, so she was treated with opDDD,up to 8gms per day which caused clinical remission but was associated with nausea, fever and weight loss. At 52, she slipped on ice and fractured her leg and was admitted to hospital, where she developed bronchopneumonia and died. On presentation with Cushing's disease she was noted to be anxious and depressed by several doctors and by the nursing staff. This was thought to be a life-long trait. She was seen by a psychiatrist when Cushing's

disease was active and he thought her depressed mood was explicable by her illness and also some marital difficulties. During the last months of her life she was noted to be depressed with loss of appetite and crying, and to be occasionally hallucinated. Post mortem showed adrenal necrosis attributed to opDDD.

CD 84

Cushing's disease was diagnosed at age 20. She has had four attempts to cure her Cushing's disease-total adrenalectomy, removal of adrenal remnant, pituitary implantation and a surgical hypophysectomy (which showed an empty fossa). At 42, she suffered avascular necrosis of the head of her femur, requiring hip replacement. At 44 she had a myocardial infarction. She is now in remission from Cushing's disease.

CD 85

Her tests were only mildly abnormal at I8, so she was observed for two years with slight deterioration both biochemically and physically. As her Cushing's syndrome worsened she became depressed and attributed this to the change in her appearance and obesity (97 Kg). On examination, she was shy and depressed. Further investigations and treatment are pending.

CD 86

Bilateral adrenalectomy was done, complicated by a left subphrenic abscess, a deep venous thrombosis, and a right sub-hepatic abscess. Five drainage operations were needed. Cushing's syndrome remitted. She was depressed when her Cushing's syndrome was active, during which time she became separated from her husband.

CD 87

She was treated by a pituitary implant at age 30. There was no depression associated with Cushing's syndrome, but she felt more energetic after treatment.

CD 88

Transethmoidal hypophysectomy was done at age 33, and her disease remitted.

CD 89

A subtotal adrenalectomy was done at age 23, followed by the removal of the adrenal remnant, and Cushing's syndrome remitted. At 28, he developed Nelson's syndrome, treated by surgical hypophysectomy, followed by external irradiation to the pituitary. He had partial third and fourth cranial nerve palsies and a visual field defect. A pituitary implant was then done (twice) and this

showed two distinct pituitary tumours, being a mixture of acidophil and mucoid cell types. Cyproheptadine and bromocriptine were tried without benefit. He has had severe psychiatric disturbances. He was depressed when Cushing's syndrome recurred after the subtotal adrenalectomy and he took a drug overdose after the adrenal remnant was removed. At 46 he had become darkly pigmented and although he is English, he was attacked by a racialist who mistook him for an Indian. Prospective employers also doubted his race. From 43, he had diminished libido and his marriage failed. When examined at 47, he was still moderately depressed. He has now been observed for 25 years.

CD 90

When aged I9, she was treated by total adrenalectomy. Cushing's disease remitted and she has had two pregnancies, and been observed for I2 years. She was depressed temporarily when divorced at age 23.

CD 9I

She was treated by a pituitary implant at the age of 32 and total adrenalectomy at 37. Nelson's syndrome was diagnosed at 42 and treated by surgical hypophysectomy. She was an intelligent lady, a good witness, and she denies any depression associated with Cushing's syndrome.

CD 92

She has a complicated psychiatric and social history. Her mother left home when the patient was five, and the father could not cope and the children were cared for by the Local Authority, where the atmosphere was stated to be regimented and free of affection. Later her father died of a myocardial infarction. The patient married at age I8. At 20 she was admitted to a psychiatric hospital with agitation, feeling that she was about to swallow her tongue and that she would die within a few days. She said" every thing which I have thought has happened" and " I am turning into a man". She was observed to have panic attacks when she would tremble and sweat. The patient was obsessed by the details of her past history stated above, plus the death of her twin sister from a road traffic accident when the patient was II, also the death of her brother, who fell from a rope and fractured his neck. There were paranoid thoughts concerning the medical and nursing staff at the psychiatric hospital. At 22 Cushing's syndrome was diagnosed. Throughout the interview she repeated her foreboding of death, of hearing voices, and she placed special significance on everyday activities, for example, a man in the street wore a black tie and she thought this meant that he was going to die. On seeing a dust cart go down the road she started to think about cremation, saying " ashes to ashes, dust to

dust". She was withdrawn and suspicious and took time to answer fairly simple questions. She was severely depressed on Hamilton ratings. She was given diazepam and thioridazine. It is planned to treat her with metyrapone and external pituitary irradiation. Clearly, she had many features in her life to make her depressed, but her depression became worse when Cushing's disease occurred. It is likely that she suffered a steroid psychosis.

CD 93

Cushing's disease was diagnosed at age 47. Treatments were external pituitary irradiation, pituitary implantation, then bilateral adrenalectomy. Three months after the adrenalectomy she died suddenly due to a pulmonary embolus. She was married with two children. She had severe mitral stenosis, and thalassaemia minor. She had severe Cushing's syndrome and was bed-ridden. The cause of her weakness and obesity was not appreciated and she was initially treated with prednisolone.

CD 94

At age 32 she had a two-stage adrenalectomy. At 45 she became depressed and suffered from headaches, and dark skin pigmentation was noted. At 47 Nelson's syndrome was treated by transethmoidal operation, followed by external pituitary irradiation.

CD 95

He was successfully treated by a pituitary implant at age I7, and has been observed for twelve years.

CD 96

A satisfactory clinical remission was induced by pituitary implants at age 4I. She had presented with a skin complaint (tinea versicolor rosacea) and was treated with prednisolone and then noted to have Cushing's syndrome. However, the signs of Cushing's syndrome persisted when prednisolone was discontinued. There was no previous psychiatric history and she was only slightly depressed before treatment and depression improved when Cushing's disease remitted.

CD 97

She was treated by pituitary implants. She was anxious and this was attributed to the need to live abroad with her husband.

CD 98

There was a clinical remission after bilateral adrenalectomy at age 47. Nelson's syndrome was treated at 52 by trans-ethmoidal hypophysectomy. After the adrenalectomy, she had a deep venous thrombosis and pulmonary infarction. She became depressed during the next twelve months and was treated with amitriptyline. Other medical

problems included hypothyroidism, hiatus hernia, vomiting after oral steroids and the need for maintenance on daily injections of hydrocortisone 50mg. With this supraoptimal dose she was obese at 105 Kg.

CD 99

Bilateral adrenalectomy was done at age 28 and she has been observed for thirteen years. At 29 she had a successful pregnancy. The depression which occurred with Cushing's syndrome improved after the adrenalectomy.

CD 100

Cushing's syndrome remitted after two pituitary implants at age 37. She was a nun who had worked as a teacher, both in England and Africa. Her symptoms may have been present for nine years when frontal baldness, weight gain and irregular periods began. Facial hair grew and she needed to shave daily. While her Cushing's syndrome developed she became more depressed and anxious and this may have been partly due to the worsening political situation in Africa. When Cushing's syndrome remitted she said " I didn't realise how rotten I have felt before" and she was better able to cope with life and commenced studying for a University degree in Arts at the Open University.

CD 101

He was treated by two pituitary implants at age 45. He became depressed just before Cushing's syndrome was diagnosed and remembers having insomnia, crying, anxiety, and feeling that life was not worth living, and that he was not in control of his thoughts. His memory became poor and he had difficulty in coping with his job as a builder. He left school at 13, unable to read and write. Later he became an apprentice, taught himself to read and write and built his own business, and employment meant much to him. He was distressed by the liquidation of his business when he became ill, about the impending marriage of his daughter, and he was afraid to make sexual approaches to his wife in case he aroused desire which he could not cope with. During follow up Cushing's syndrome remitted but he remained depressed, and this is no doubt due to life events.

CD 102

He had worked as a Physical Education Instructor but became weak and was admitted to hospital in diabetic hyperglycaemic coma at age 48. He bruised easily, gained weight, became too weak to continue his job and had a non-healing infection of his right index finger. He had severe depression, alternating with hypomania.

He would wake at night after only one to two hours sleep with ideas racing through his mind and his wife remembered that he was euphoric. While tests were being done he deteriorated and died of septicaemia. He had a severe form of Cushing's disease with enlargement of the pituitary fossa at diagnosis.

CD I03

She was treated with a pituitary implant at age 66 with remission.

CD I04

She was treated by bilateral adrenalectomy at age 37 with remission.

CD I05

She was treated successfully by a pituitary implant at age 60. She had often been depressed, about the death of her husband, the emigration of her only daughter,unhappiness in her job as a teacher, and arthritis of her hip. At 65, she said "I felt truly thankful when I was finally sent for to have my right hip replaced (at age 63), happy when I began to drive again, and very happy to visit the theatre every three weeks since". She also said " how you ever disentangle'feelings' caused by normal private reasons and any others baffles me".

CD 106

Symptoms and signs of Cushing's disease had been present since the age of nine, and she had been treated unsuccessfully with cyproheptadine and metyrapone. At 12, she was grossly obese at 59 Kg, height 139 cm. In two years she had changed from being the tallest and thinnest girl in her class to the shortest and fattest. She was very embarrassed about her appearance and her nick-name was "pork pie". Her parents were long suffering and helpful. Following a pituitary implant, Cushing's syndrome remitted for a few months, and then she started to gain weight again and to be weak and lethargic. Hypothyroidism was suspected and, surprisingly, this turned out to be primary hypothyroidism with serum thyroxine less than 15 nmol/l and TSH of 78 mu/l(normal <6). She was treated with thyroxine, and at 14 her weight was 44 Kg, and her height was 144 cm. Since five, she had suffered from asthma, which disappeared when Cushing's syndrome developed, but returned at 15. Her academic performance at school declined. She hoped to become a nurse but failed to obtain the necessary examinations. She was depressed when Cushing's syndrome was active.

CD 107

For 18 months he failed to grow in height, and became obese. He responded well to a pituitary implant at 14 years. He was observed on several occasions before and

after the operation and at all times he was cheerful and intelligent and there was no evidence of euphoria or depression. His academic performance was not affected and one follow-up visit was postponed so he could take part in a chess tournament.

CD I08

She was treated by total adrenalectomy at age 38, and her disease remitted. She was depressed when Cushing's syndrome occurred, partly due to separation from her husband. Four weeks after the adrenalectomy she took an overdose of tablets, from which she recovered.

CD I09

She was treated by total adrenalectomy at age 35. At 32 she had suffered a cerebrovascular accident. She died at 38.

CD II0

Biochemical tests were equivocal. An adrenal adenoma was suspected but Cushing's syndrome did not remit after unilateral adrenalectomy at age 53. Cushing's syndrome, now proven to be pituitary dependent, was then treated by external pituitary irradiation and metyrapone.She became depressed during the onset of Cushing's syndrome because her appearance had changed. During an interview before the operation there was no evidence of depression.

There were several life events, including a divorce at 5I, and adverse financial circumstances.

CD III

She was treated by bilateral adrenalectomy. At age 44 Nelson's syndrome was treated by external pituitary irradiation. She was married with two adopted children. When her Cushing's disease was active she had suffered intermittent mild depression, attributed to obesity and the change in her appearance. She also lost her temper with the children and had panic attacks. Cushing's syndrome remitted. At 43 she had depression and agoraphobia, and was given antidepressants. One year later she was no longer depressed.

CD II2

Before any treatment she was described as very co-operative but rather a frightened lady, always a worrier. At 39 she had recurrent depression and anxiety treated with medicines and later by electroconvulsive therapy which improved her mental state but she still had mood swings. During psychiatric treatment, features of Cushing's syndrome were noted at age 4I.She was treated by two pituitary implants, neurosurgery, right total and left subtotal adrenalectomy, and finally by removal of the left adrenal remnant.During these procedures she developed leakage of cerebrospinal

fluid, blindness in her left eye and a 5th cranial nerve palsy. At the age of 43, a Consultant Psychiatrist noted that her profound depression was attributed to her illness, the unsuccessful treatment, and partial blindness. In the final year of her life, aged 44 years, she wrote a very sad letter which showed a very brave person.

CD II3

She was treated by a pituitary implant at the age of 36, and by bilateral adrenalectomy at 37. At 3I, she had angina pectoris and at 35 she had a myocardial infarction. She died at 38 from another myocardial infarction. She was not depressed or anxious and she wrote very charming and kind letters of gratitude for her treatment.

CD II4

She was single and lived with her parents. She had always been a shy person, prone to anxiety and depression and these traits became worse when her Cushing's disease occurred.She was treated with chlordiazepoxide and imipramine. Before total adrenalectomy she was anxious and slightly depressed. A year later she had become less anxious, less self-conscious, and was not depressed.

CD II5

At the age of 58 she became very depressed and was admitted to a psychiatric hospital where the diagnosis of Cushing's syndrome was made. Symptoms of Cushing's

syndrome had been present for six years. She appeared to have had no adverse life events, being happily married, with a secure job, both for her husband and herself, a daughter and no financial worries. She could not remember when she had really felt happy and she had a tendency to "bottle-up" emotions. At interview she was anxious, severely depressed, and easily distracted. She had a variety of symptoms for which no organic cause could be found. A pituitary implant was done at age 58. When reviewed I2 months later, her depression was of moderate severity and Cushing's syndrome had remitted.

CD II6

She was treated with bilateral adrenalectomy at age 6I with clinical remission. At interview she was severely depressed and described herself as " always a nervous person, never a happy sort of person". The depression improved following adrenalectomy.

CD II7

She had a left adrenalectomy at age 29 and a right adrenalectomy at 36. She became pregnant at 37. At 50 her skin darkened but the pituitary fossa was normal. She has been followed for 26 years since her first operation. Although her Cushing's syndrome remitted clinically, she was depressed at the ages of 43 and 45 .

CD 118

Before Cushing's syndrome was diagnosed, she became severely depressed and anxious and was admitted to a psychiatric hospital at age 25 and given electro-convulsive therapy, which relieved her depression. She was then given "a short course of cortisone". The next year she had a second course of electro-convulsive therapy. The diagnosis of Cushing's syndrome was made four months later. One month after her first adrenalectomy she was still very depressed and required a third course of electro-convulsive therapy. She developed delusions that relatives were dead. She thought that she was changing sex and would lie in bed hiding from other patients and was mute. She was given a fourth course of electro-convulsive therapy two months after the second adrenalectomy and two months later there was marked mental and physical improvement. At 28 she was well, and able to cope with housework and to teach.

CD 119

Initial treatment was a sub-total adrenalectomy, followed by two pituitary implants, and her Cushing's disease remitted. She was depressed when she had Cushing's syndrome, and she attributed this to the change in her appearance. When Cushing's syndrome remitted the depression disappeared.

CD I20

He was treated by pituitary implant at age 52, followed by right total and then left subtotal adrenalectomy. He died two months after his last operation due to a myocardial infarction. When Cushing's syndrome occurred he became depressed and irritable, lost his libido, and was treated with testosterone.

CD I2I

He was treated by total adrenalectomy at age 28 and he was observed for seven years. There were no psychiatric abnormalities.

CD I22

She had a left total and right subtotal adrenalectomy at age 29 and remitted temporarily, but removal of the right adrenal remnant was required at age 32. She has been observed for 20 years. Nelson's syndrome was treated at 39 by a pituitary implant. Cushing's disease was diagnosed at the end of her second pregnancy when her weight had increased to 83 Kg. She was depressed when her Cushing's disease occurred, and she was irritable with her family and easily cried. This improved, but she became depressed again when Nelson's syndrome occurred. Depression improved after the pituitary implant.

CD I23

Cushing's disease was diagnosed at age 49. He responded to pituitary implants.

CD I24

Four years before diagnosis her periods stopped, and this was attributed to the emotional shock when her fiance died in a crash.She was treated in another country by partial left adrenalectomy, but her symptoms did not regress, so she was treated by a pituitary implant at age 27.After the pituitary implant she required replacement steroids. She then became anxious and depressed about infertility and after many investigations she became "fed up with temperature charts, bottles and doctors and wanted to forget the whole thing" (i.e. fertility). She adopted a baby and two years later the patient became pregnant and had a normal delivery, continuing to take prednisolone 5mg per day.

CD I25

She was born in Italy and had seven sisters. She married, moved to England and became the driving force behind the family retail business. One daughter was born when the patient was 27, and there was a miscarriage later on. At 47 diverticular disease was diagnosed and required a bowel operation with a temporary colostomy. The bowel was adherent to the uterus which was also removed. The hospital notes state that the patient had "boundless energy". At 48 she had anxiety, depression, and hypertension. Cushing's syndrome was suspected but tests were equivocal. Cushing's disease was confirmed at 49 and a total

adrenalectomy was done.Cushing's syndrome remitted but there were several social and psychiatric problems. She neglected her business, became very tense and anxious, ate very little and lost weight. Six months after the adrenalectomy she developed clinical and biochemical hyperthyroidism. She became euthyroid with carbimazole. One year after the adrenalectomy she was still depressed and having nightmares, and a psychiatric opinion was sought. Dothiepin was prescribed. Much of the depression stemmed from a decline in the family fortunes, and concern about the health of the patient's elderly mother. There was good evidence that during the development of Cushing's syndrome there was a bipolar illness with depression alternating with hypomania, and after successful treatment of Cushing's disease the dominant psychiatric illness was depression, at least partly due to life events.

CD I26

Cushing's disease was diagnosed at age nine, and treated by adrenalectomy. He became darkly pigmented at I5.ACTH levels were 3,000 ng/l and the pituitary fossa was enlarged. However the patient refused the recommended treatment on the grounds that this was inconvenient. When contacted at 23, the patient said he felt well and was able to continue working on a farm. He agreed that his skin was dark.

CD I27

She had been diabetic since the age of 49 and hypertensive since 56. Diabetic retinopathy was treated by laser photocoagulation. Two years before Cushing's syndrome was diagnosed she presented to psychiatrists with depression and inability to cope. Life events which contributed to her depression were the death of her boyfriend, who committed suicide, and abnormal behaviour of the patient's mother, who had a "nervous breakdown" and suffered from agoraphobia, and who used to threaten the patient with boiling fluids and a knife. The patient lived alone and had a phobia for men. At age 57 the clinical signs of Cushing's disease were mild. Treatment was pending.

CD I28

At the age of I7 the patient became a Christian Scientist. She taught ballet and married at 28. Her three children were born at home by natural methods. Physical ailments were successfully overcome by practising Christian Science. She declared the unreality of illness and strove for the true perfection of man's real being.Cushing's disease was diagnosed at 42. During the three years before this, she became subject to outbursts of temper and panic. She was unwilling to enter hospital for tests, and was unco-operative and resistant to the idea that treatment was necessary. She

had several delusional ideas, including the accusation that her mother was a murderess.Just before a pituitary implant, the patient spoke of committing suicide and begged to be given an overdose; later she claimed that the doctors were trying to murder her.A pituitary implant was followed by a temporary leak of cerebrospinal fluid, but she was unwilling to take antibiotics because of her religious beliefs, so management was a problem.She regretted the operation and she was impervious to reasonable argument, and a schizophrenic disorder was diagnosed. Three months after the implant she had lost weight and it was considered whether this was anorexia nervosa in an unusual context. Conversations with relatives showed that her interests shrank and that her mental condition was described as "a landslide loss of her faculties".There was constant talk of suicide and any talk of sunlight, flowers or things of beauty added to her unhappiness. Two years after the operation she was still mentally unstable and she was described as "grossly psychotic and preoccupied with her beliefs and refusal of food". Cushing's syndrome had remitted. She refused admission for psychiatric therapy. She then stopped using her right arm and right leg, claiming that they were paralysed, and she became incontinent of urine and faeces. There was marked antagonism to her mother. She slept for two hours per night, and the remaining time was taken up by a non-stop

monologue about mistakes that had been committed and of the mutilation and dreadful things done to her head. At 43, she emigrated to the United States and she began to improve both physically and mentally and commenced dancing. Nothing would persuade her to enter hospital for a check up.At 47 she was once again leading an active life, including teaching ballet, and she had taken no medicines for four years. She was found to be stimulating in company but was only sleeping for two hours at a time, when she would get up and seek an outlet for her restless activity.

CD I29

Before her illness, this lady was working as a singer and comedienne in a nightclub.She had two siblings by her father's first marriage, and four by his second marriage. Her parents separated when she was five and she remained with her mother. Periods commenced at the age of I0, but disappeared at I6, and signs of Cushing's syndrome developed over the next two years. At I7, she took her first drug overdose.Cushing's disease was diagnosed at the age of nineteen and treated by total adrenalectomy.At 2I, she was depressed and was referred to a psychiatrist who noted that she had attempted suicide on three occasions. She also admitted that she had omitted to take cortisone replacement therapy, and had deliberately misled the

nursing staff. This deliberate omission of tablets was regarded as a suicide attempt. At 26, Nelson's syndrome was diagnosed, and she was then depressed and anxious.A pituitary implant was done. She became hyponatraemic (plasma sodium 112 mmol/l) and hypothyroid and these abnormalities responded to treatment. One month after discharge following the pituitary implant, she attempted suicide again and was noted to be under pressure from financial and personal problems. A doctor wrote "the emotional overlay is enormous, and it is very difficult to obtain an adequate history". At 27, she complained of chest pains, shortness of breath, choking, indigestion and weakness of her left side. At 28 she had "almost every complaint possible" but she was "remarkably cheerful" about her problems. She took another over-dosage of analgesics. She regularly took thirty analgesic tablets per day for headache, backache, and a pain on her leg where she was hit by a saxophone. She complained of pains in the head which made her feel quite desperate "as if she could murder her child or anyone else". All the doctors who examined her noticed an extremely prominent emotional overlay. At 26 she had a child, and at 27 she left her husband to live with a man twice her own age. She continued her career in cabaret. At 29, she had a cerebral haemorrhage, and was critically ill, but made a good recovery. A Consultant wrote "my own growing conviction is that she will one day successfully

commit suicide. It is all so sad because she used to be a happy,charming, attractive, talented person". She died suddenly at 30. At autopsy neither adrenal nor pituitary tissue was found; there was a right frontal lobe infarction. Thus there was a severe depressive illness associated with Cushing's syndrome.

CD I30

He was treated by bilateral adrenalectomy at age 29.Nelson's syndrome was treated at 33 by pituitary implantation, and by neurosurgery. He also had primary hyperparathyroidism at age 32. He died at 47.

CD I3I

She was treated by total adrenalectomy at age 27. Nelson's syndrome was treated at 33 by pituitary surgery. She was depressed when Cushing's syndrome was active and returned to normal after the adrenalectomy. She wished she was dead when she had Cushing's syndrome.

CD I32

As a child she had been fostered and never knew her own parents. Later she married and had a child and was well until 60, when she was admitted to a psychiatric hospital with confusion and agitation. She was treated with chlorpromazine. Cushing's disease was diagnosed and

and treated at 6I by a pituitary implant. She died suddenly, two months after the pituitary operation. The onset of her Cushing's disease was difficult to determine, since photographs showed that she had been obese for many years.

CD I33

Pituitary Cushing's disease was treated at 47. Nelson's syndrome was diagnosed at 53 and treatment was pending. There was a past history of depression long before Cushing's disease was diagnosed. Three years after adrenalectomy, Cushing's syndrome remitted, but she required further antidepressant therapy.

CD I34

Cushing's disease was treated at 43 by total adrenalectomy. He died two weeks later, having suffered collapse of one lung, acute haemorrhagic pancreatitis and at necropsy these abnormalities were found together with left ventricular hypertrophy of the heart, scarred kidneys and an old cerebral infarct.

CD I35

Cushing's disease was treated at 35 by a pituitary implant. She was depressed during the development of Cushing's syndrome. Depression was relieved just after the operation, but recurred when she had adrenal insufficiency, which responded well to replacement steroids. Before treatment

for Cushing's disease she felt unhappy, cried, and had suicidal thoughts, but made no attempt to commit suicide. She felt self-conscious and consequently decreased her social activities.

CD I36

She was a widow who had suffered a stroke and was finding it difficult to cope at home alone. She was considered too frail for a total adrenalectomy or for pituitary surgery. After treatment with trilostane, then metyrapone, neither of which produced a satisfactory clinical result, she was referred for external pituitary irradiation, to which metyrapone was added.She was moderately depressed when interviewed both before and during treatment and this was due partly to physical infirmity and social circumstances.

CD I37

At the age of 32 she had a pituitary implant . She was happily married,but became depressed and embarrassed when her Cushing's disease developed. Both Cushing's syndrome and the associated depression remitted after the implant.

CD I38

Cushing's disease was diagnosed at age 25. Hypophysectomy failed due to excessive bleeding and was followed by transient paraplegia. After total adrenalectomy, Cushing's

syndrome remitted. At 27 he was darkly pigmented, and ACTH levels were increased, but the pituitary fossa was normal. A course of irradiation was given to prevent pituitary expansion. He has had bilateral renal calculi, osteoporosis and hypertension. During the onset of Cushing's disease he was emotionally disturbed and had sexual fantasies. After adrenalectomy his abnormal behaviour improved.

CD I39

Cushing's disease was treated at age 47 by pituitary implants. Eleven years later, Cushing's disease relapsed, and was successfully treated by another implant. She has never been significantly depressed.

CD I40

Cushing's disease developed after the birth of her first child at 23. She was treated by bilateral adrenalectomy but an adrenal remnant must have remained, and she required two pituitary implants before her disease remitted. She was depressed when her Cushing's syndrome occurred because " everything was an effort, and I felt people looked at my appearance, and I couldn't do things normally". Depression was noted after her implants when an attempt was made to reduce her steroids to zero and eventually she required replacement steroids. She was reviewed at the age of 28, and she was not depressed.

CD I4I

Cushing's disease was diagnosed at age 32. In preparation for trans-sphenoidal hypophysectomy, she was given metyrapone. When Cushing's syndrome occurred, she became depressed because she was unable to work on a farm. Before treatment she was moderately depressed, partly due to domestic problems.

CD I42

Cushing's disease was diagnosed at age 36. She was treated with trilostane without clinical or biochemical benefit. Her pituitary gland was then explored and although no tumour was found, and the biopsy showed normal pituitary tissue, there was a remission. She was depressed during her illness because her appearance had changed and she felt weak and unwell.

CD I43

Cushing's disease was diagnosed at age 49. She was treated by a pituitary implant with a clinical remission.

CD I44

She presented with psychiatric disturbance, saying that things seemed distant and unreal, and that she had lost her emotions and interest in her children. There was also a sense of suffocation and weakness, thirst and polyuria.Cushing's disease was diagnosed at age 34, in 1951, when replacement steroids were only just available.

The first treatment was left adrenalectomy, but Cushing's syndrome persisted, so external pituitary irradiation was given. After this there was a clinical remission, periods returned , and at 39 she had a normal pregnancy. After the operation she was disturbed and confused and did not believe that she had had an operation, and sedation was needed to prevent self-injury. Two months later she commenced a remarkable psychological and physical recovery. She was observed for five years.

CD I45

Cushing's disease was diagnosed at age 47 and treated by bilateral adrenalectomy. At 50 Nelson's syndrome was treated by pituitary surgery, plus external irradiation. When Cushing's disease developed, she became depressed and embarrassed about the change in her appearance, which included severe loss of scalp hair. She has been moderately depressed throughout eight years of observation.

CD I46

Cushing's disease was diagnosed at age 33. She was treated with bilateral adrenalectomy.

CD I47

She has a disturbed social background. Her parents separated when she was very young and her father was said to be

violent. Her disease may have commenced at 12 when she became very obese. From the age of thirteen she suffered intermittent depression. At age 18, she was grossly obese at 120 Kg. She was only slightly depressed. Her mood had improved since she learned that she had a treatable cause for obesity. Depression here could be related to social circumstances, or Cushing's disease. Treatment was commenced with external pituitary irradiation and metyrapone.

CD 148

Life events included the neo-natal death of her first child. Symptoms of Cushing's disease were present for nine years before the diagnosis was made at 52. During this time she had been very depressed and had had suicidal thoughts. She would cry for no reason. She became ill-tempered. There was a satisfactory remission with a pituitary implant and her depression disappeared and only returned for a short time when she became temporarily deficient of steroids.

CD 149

Cushing's disease was diagnosed at age 34. The first treatment was unilateral adrenalectomy but Cushing's disease persisted, so a pituitary implant was done.

CD I50

His past medical history included diabetes mellitus, hepatitis, arthritis and glomerulonephritis. When Cushing's disease occurred he was emotionally labile and had diminished libido. He was suicidal due to severe muscular weakness and compression fractures of his spine, and inability to walk.Cushing's disease was diagnosed at age 25. He was treated abroad by a right sub-total adrenalectomy, followed by a left total adrenalectomy, and Cushing's disease remitted, but recurred at 37. He was then treated by removal of the right adrenal remnant and a pituitary implant.Two months after the implant he improved greatly, joking with his medical attendants, and he was able to walk.

CD I5I

Cushing's disease, diagnosed at age 11, was treated by left adrenalectomy, and external pituitary irradiation at age twelve, and then by a pituitary implant at the age of I7. There was a satisfactory remission of Cushing's disease although his adult height was short. He was cheerful and co-operative. There was no evidence of depressive illness associated with Cushing's disease.

CD I52

Cushing's disease was diagnosed at age 33. He was treated

with bilateral adrenalectomy with clinical remission. His other medical problems included impotence, osteoporosis, low back pain, and gynaecomastia. At 36 he became more pigmented but his pituitary fossa was not enlarged.

CD I53

She presented with psychotic behaviour and had been treated with chlorpromazine and haloperidol at age 52. She was withdrawn and unco-operative, transferring her urine to the collection bottles of other patients. She refused to have investigations or treatment and she became lost to follow up.Life events included breakdown of her marriage.

CD I54

Cushing's disease was diagnosed at age 29. She was treated by a pituitary implant and observed for thirteen years.

CD I55

Her presenting symptom was secondary amencrrhoea. This was attributed to the psychological problems of emigrating and continuing her studies. Before operation she was a shy girl and was depressed about her lack of periods, change in appearance and the need for treatment. Cushing's disease was diagnosed at age I8. She was treated by a pituitary implant with an excellent clinical and bio-chemical and psychological remission.

CD I56

Cushing's disease was treated at 39 by bilateral adrenalectomy.At 49, Nelson's syndrome was treated by transethmoidal surgery. After the adrenalectomy she became depressed and was treated with tricyclic medicines.

CD I57

Cushing's disease was diagnosed at age 25 and treated by bilateral adrenalectomy. When Cushing's syndrome occurred he was anxious and depressed. There were social and personal factors which may have been relevant, and all these factors improved after the operation , and Cushing's syndrome also remitted.

CD I58

Cushing's disease was treated at 55 by bilateral adrenalectomy. The operation was complicated by a subphrenic abscess and a gastric fistula. She died seven weeks later.

CD I59

He failed to grow in height from the age of I2 and became obese. Until then he had been proficient at football and an extrovert, and for the next five years he became depressed about obesity, weakness, inability to play football, and his lack of a girlfriend.Cushing's disease was treated at age I7 by bilateral adrenalectomy. His

pituitary fossa was enlarged, so a prophylactic course of irradiation was also given. He made an excellent clinical response to treatment and depression disappeared.

CD 160

Cushing's disease was diagnosed at age 16. She was treated by bilateral adrenalectomy. She had stopped growing in height two years previously. Two years after adrenalectomy, Cushing's syndrome had remitted but she was depressed and referred for psychiatric assessment. At 24 she requested a termination of pregnancy. At 28 she again became depressed and tired and was again referred for psychiatric assessment. At 31, physical examination was normal and she was no longer depressed.

CD 161

Depression developed three months after the birth of her second baby with the onset of the signs of Cushing's syndrome. Cushing's disease was diagnosed at age 28. She was treated with metyrapone and external pituitary irradiation. Cushing's syndrome remitted and she became pregnant again.

CD 162

Cushing's disease was treated at age 30, by a pituitary implant. When Cushing's syndrome developed, she had rapid

changes of mood from depression to euphoria. Cushing's syndrome remitted after the operation. She was depressed when her Cushing's syndrome occurred because of change in her appearance and feeling weak and unwell, but she was also sad for no reason that could be identified. She was later depressed due to sciatica.

CD 163

The patient suffered a birth injury leaving him weak on the left side and with epilepsy. At the age of 14, he became violent. His intelligence quotient was rated at 59 at the age of 15. He was sent to a psychiatric hospital and treated with chlorpromazine, when Cushing's syndrome was diagnosed at age 17. During investigations he smashed windows on the ward and refused to have tests. He was seen by a Consultant Psychiatrist who noted the mood swings and outbursts of aggression. The emotional lability was apportioned partly to the brain damage, especially that affecting the temporal lobe, and partly as a complication of Cushing's syndrome. After a pituitary implant, the physical signs of Cushing's syndrome diminished and the patient became more manageable, but was still severely disturbed and was sent to a long-term psychiatric hospital. Weight reduced from 99 to 64 Kg. after the operation. The patient was visited by the author and interviewed.There were no physical signs of Cushing's syndrome, but he remained aggressive.

CD 164

Cushing's disease was diagnised at age 47. She was treated by bilateral adrenalectomy with clinical remission. She was an intelligent, co-cperative lady with no significant depression before or after treatment of Cushing's syndrome.

CD 165

Cushing's disease was diagnosed at age 33. She was treated by bilateral adrenalectomy and has been followed for fourteen years.

CD 166

He worked as a clerk. He became intermittently depressed and had a loss of libido. His other problem was urinary tract infections with renal calculi. Cushing's disease was diagnosed at age thirty-five and treated by a two stage total adrenalectomy.

ADRENAL ADENOMAS

AA 167

The patient had been a shop assistant, hair dresser, and part-time cleaner. She had one miscarriage and two live births. During her first pregnancy at 17, she developed hypertension, glycosuria and signs of Cushing's syndrome. During the next three years she was noted to be depressed, agitated and agoraphobic. One doctor wrote, " she seems to be on 20 different psychotrophic drugs at once ". She was admitted to a psychiatric hospital complaining of palpitations, anxiety, tremor, dry mouth, bloated up and feeling that her heart and her breathing would stop. She had a sense of impending doom, a phobia of cancer, and found herself unable to relax. Her appetite had diminished but her weight had increased by 10 Kg. She was having hot and cold flushes, and feelings of guilt about being unable to look after her handicapped sister. Psychiatric symptoms worsened after the death of her father in 1968 and of her mother in 1975, also the miscarriage in 1970. A psychiatrist thought that her recurrent anxiety and depression stemmed from these deaths. In 1970 she was very tearful and cried freely at an interview, she had early morning wakening, but no suicidal thoughts. In 1971, she had electroconvulsive therapy.She was assessed by a clinical psychologist in 1971, when standard progressive matrices gave an IQ of 90 and the Eysenck Personality Inventory showed Extraversion

of 15 and neuroticism 19. In 1975 she had suicidal thoughts and her handicapped sister had said "they would both be better off dead". In 1975 the husband was interviewed and felt that his wife was "playing up". In 1975, the patient was worried about an unpleasant smell about her person, and thought this meant she was going to die. She had auditory hallucinations. In 1976, Cushing's syndrome was recognised by the Consultant Psychiatrist and she was referred for endocrine assessment, which confirmed the diagnosis, due to a left adrenal adenoma. Before operation she was severely depressed with a Hamilton rating of 21. She rapidly recovered after this operation and came off all psychotropic drugs, and replacement steroids were not necessary due to normal functioning of the remaining adrenal gland. The Hamilton rating was zero, the Eysenck scale showed extraversion of 17, and neuroticism of 5. Therefore, her abnormal psychiatric behaviour was completely relieved by adrenalectomy.

AA 168

A left adrenal adenoma was removed at the age of 32. There were no features of a psychological illness.

AA 169

She had two daughters and her husband worked as a chargehand in a factory. Cushing's syndrome was diagnosed at age

44 and this was due to a benign left adrenal tumour, which was removed. The right adrenal gland did not resume activity after this operation, possibly due either to adrenal suppression, or to adrenal infarction during catheter studies. There was no depression noted before operation but afterwards she became depressed and lacking in confidence. Her husband did the shopping and housework in addition to his own work, and was found to be over-protective with the patient and would answer all the questions during an interview. There was a splendid clinical remission from Cushing's syndrome. During this period she was anxious about the impending marriage of her daughter. On contacting the general practitioner it was apparent that the patient had become depressed at the time when Cushing's syndrome was diagnosed by him.

AA 170

An adrenal adenoma was diagnosed at age 63 and treated by unilateral adrenalectomy. There was an excellent clinical remission and no evidence of depression.

AA 171

Cushing's syndrome was diagnosed at age 62 due to an adrenal adenoma. This was removed but her post-operative course was complicated with a left pleural effusion,

which was drained and later an empyema, which required surgical excision. Two years after the operation she was well on no replacement steroids. There was no history of depressive illness.

AA 172

Cushing's syndrome was diagnosed at age 25. She was treated by total adrenalectomy which showed a right adrenal adenoma with a suppressed left adrenal gland. She was depressed when her Cushing's syndrome was active, and for at least six months after treatment. An operation for gastritis and a duodenal ulcer was performed at 27, and cervical spondylosis was diagnosed at 29. Cushing's syndrome was cured but she still had "numerous psychological symptoms, mainly functional".

AA 173

Cushing's syndrome, due to a right adrenal adenoma, was diagnosed at 39. He was successfully treated by adrenalectomy.

AA 174

Cushing's syndrome was diagnosed at age 55. Biochemical results were typical for pituitary-dependent disease. A pituitary basophil adenoma was removed. However her Cushing's syndrome did not remit so bilateral adrenalectomy was done. Surprisingly there was a right adrenal adenoma with a suppressed left adrenal gland. After the adrenalectomy there was a deep venous thrombosis treated with anti-

coagulants. Two months after the operation the patient suddenly died at home, possibly from a pulmonary embolus. At 53, hyperthyroidism was treated with carbimazole. She was interviewed before and after treatment for Cushing's syndrome and she was always cheerful and extraverted.

AA 175

Bilateral adrenalectomy was done at age 30. There was a right adrenal adenoma and a suppressed left adrenal gland. She made an excellent clinical remission. She was married with one son. Four years before Cushing's syndrome was diagnosed she had severe depression treated by electro-convulsive therapy. She then weighed 61 Kg. Nine months later she weighed 73 Kg and Cushing's syndrome was probably present, but unrecognised. She then took a drug overdose and cut her wrists and depression and psychomotor retardation were diagnosed. Cushing's syndrome was not diagnosed for a further two years, when she had obvious physical signs. Before adrenalectomy she was slightly depressed. After the operation she had episodes of severe depression, in spite of adequate replacement with hydrocortisone and she became anxious and threatened her husband with violence. She was admitted to the psychiatric unit for several weeks and she recovered without psycho-tropic drugs. Eight months after adrenalectomy there was no psychological or psychiatric abnormality, and her weight had decreased to 58 Kg.

AA 176

She was treated by bilateral adrenalectomy at 34. There was a left adrenal adenoma and a suppressed right adrenal gland. She became pregnant at 35 and this was terminated at her request.

AA 177

A left adrenal adenoma was successfully removed at age 36 and Cushing's syndrome remitted. There was no depressive illness.

AA 178

Bilateral adrenalectomy was done at age 37. There was a left adrenal adenoma and an infarcted right adrenal gland. Cushing's syndrome remitted. When her Cushing's syndrome occurred she became depressed, and she retired from her job as a secretary because of facial hair. Depression improved as Cushing's syndrome remitted.

AA 179

A left adrenal adenoma was removed at age 52 and she remitted clinically. Her blood pressure was recorded at 250/160. At 56 she had a stroke and she remained unwell until her death at 59.

AA 180

Both adrenal glands were removed at age 40. The left had an adenoma and the right was suppressed. The post-operative course was complicated by pneumonia, a gastric fistula, and an arterial thrombosis to her left leg. She died two months later.

AA 181

She was married with one son, and she worked as a weaver. At 33 she had a nervous breakdown and was treated by electroconvulsive therapy. She did not become clinically depressed again until Cushing's syndrome developed. An adrenal adenoma was removed. She has been observed for three years and became very happy.

AA 182

A right adrenal adenoma was removed at 33. There was only mild depression when her Cushing's syndrome developed. She remitted clinically after the adrenalectomy. Her left adrenal gland had been suppressed and did not recover spontaneously, but she was maintained on ACTH injections for two years. When she had Cushing's syndrome she had boundless energy.

AA 183

Cushing's syndrome was due to a left adrenal adenoma which was removed. Three years later she had a successful pregnancy.

AA 184

At age 45 a left adrenal adenoma was removed. She was slightly depressed before the operation and severely depressed after the operation, and this improved when oral steroids were given. A few months later replacement steroids were discontinued and her depression disappeared.

ADRENAL CARCINOMAS

AC 185

Cushing's syndrome and severe depression were diagnosed at age 59. She was married and worked as a telephonist. She had auditory and visual hallucinations. There was a psychotic episode with paranoia and anxiety, and she required sedation. An urgent adrenalectomy was done and an adrenal carcinoma was found, most of which was removed. After the operation the paranoid features gradually diminished and she was seen by a psychiatrist who thought that impaired hearing and unfamiliar surroundings might have contributed to the psychiatric abnormalities. Five days after the operation, she remembered seeing the gates of heaven and could remember seeing silver and gold colours and hearing hymn music. Cushing's syndrome remitted after the operation, and both cortisol levels and her mental state became normal. She remained cheerful for one year until Cushing's syndrome relapsed. She had a stroke at 60 which paralysed her left arm and left leg, and her mood then varied between depression, frustration and aggression. The diagnosis was explained to her husband in the presence of the patient, and at first she was relieved to be told the truth, but in the next few weeks she became even more depressed and she required sedation. She died soon afterwards.

AC 186

Her husband was a publican but the patient drank very little alcohol. She had two children. Cushing's syndrome was

diagnosed at age 58 and previously there were no psychiatric abnormalities. Tests showed an adrenal tumour. Before the operation she was aggressive and the notes comment that she was "really toxic", "very restless and fidgety", and "becoming more psychotic". An adrenal tumour weighing 308 gm was removed. After the operation she was demanding and uncooperative but her behaviour gradually improved. Five months later she had a relapse and was re-admitted for tests that showed very high serum cortisol levels. Her behaviour was out of character for her previous personality and suggested hypomania. She was orientated in time and place. She had been observed to make telephone calls which involved purchases of equipment and property, which, although not beyond her means financially, were unnecessary. She gambled by telephone and made generous gifts. The change in her personality was confirmed by her relatives. Urinary free cortisol was 12,500 nmol/24 hours (normal less than 270). Chemotherapy with opDDD was commenced and increased to 8gms per day. This was well tolerated, and the signs of Cushing's syndrome and her behaviour improved slightly. Two months later she was admitted in a terminal state and post mortem examination confirmed a carcinoma of the adrenal with wide-spread peritoneal metastases. The brain was free of tumour. Therefore she had a steroid psychosis and was hypomanic at the time when cortisol levels were very high.

AC 187

An adrenal carcinoma causing Cushing's syndrome was diagnosed at age 48. As much as possible was removed but there were metastases in the liver and he died one year later. There was no depressive illness.

AC 188

She was married with one son and she presented at 47 with weight gain, hirsutism and deepening of her voice. Clinically she had Cushing's syndrome although there was no bruising and no muscle weakness. Blood pressure was 210/130. High blood pressure had been diagnosed 4 years previously. As much as possible of an adrenal carcinoma was removed. There was no improvement. There was no history of depression before Cushing's syndrome. The steroid pattern showed high levels of serum testosterone (16 nmol/l, mid-normal for a male). The tumour gradually enlarged and biochemically and clinically her Cushing's syndrome worsened but she remained free of depression until the last weeks of her life. She was a brave woman who received much psychological support from her family. She was treated with opDDD without clinical or biochemical benefit.

AC 189

A left adrenal carcinoma was diagnosed at the age of 31. A sub-total adrenalectomy was performed and then she was

treated with metyrapone. Cushing's syndrome did not remit and after the operation she was described as "psychotic" and was given electroconvulsive therapy for severe depression. She rapidly deteriorated and died.

AC 190

As much as possible of a right adrenal carcinoma was removed at age 73 and she was then treated with trilostane. She had two children and became widowed four years before Cushing's syndrome was diagnosed. At 72 an artificial left hip joint was inserted. She was only moderately depressed before and after adrenalectomy. She died two months after the operation and necropsy showed a large abscess by the left hip prosthesis, and the signs of infection were probably suppressed by the high endogenous cortisol levels.

AC 191

As much as possible of a left adrenal carcinoma was removed, but secondary tumour had already spread to the lymph nodes. When Cushing's syndrome occurred she was very depressed saying " I know what's going to happen- there is no cure for it. I have seen it on TV. I'll end up in a wheel chair. There is no reason for it. You see people going blind". During the interview she would become mute and stare straight ahead. One night she took off her night-dress and ran down the ward naked and tried to jump out of a window,

and commenced screaming. She was restrained and guarded carefully. She was suicidal and threatened to harm herself with scissors and said she " wanted to end it all". She was disorientated in time and place and had visual hallucinations of lights and of the presence of strange objects in her room. After the adrenalectomy her mental state improved and she remained depressed, but not suicidal. She was treated with aminoglutethimide and metyrapone and was allowed home.Three months after the operation she had backache, but her depression was much less. She died seven months after adrenalectomy.

AC 192

Cushing's syndrome was diagnosed at age 30. A right adrenal carcinoma was partially removed. Metyrapone was given but she deteriorated and died. She was an intelligent person with good initiative and there was no evidence of psychiatric abnormality.

AC 193

An adrenal carcinoma, causing Cushing's syndrome was diagnosed at 32. There were metastases in the lungs and bones. He also suffered from haemophilia. He was treated with aminoglutethimide and metyrapone but he deteriorated and died seven months later.

AC 194

For two years she had been depressed, agitated, confused, incontinent and bed bound, complaining of severe back pain. At age 68 she had only mild signs of Cushing's syndrome. She had very poor short term memory and mild nominal dysphasia with a labile effect. She was severely depressed. She had a massive right adrenal carcinoma which could not be removed, so she was treated with metyrapone. She rapidly deteriorated and died three weeks later.

ECTOPIC ACTH

EA 195

At age 66, she had a carcinoma of the bronchus secreting ectopic ACTH. Three years previously she had been depressed about the death of her mother. External radiotherapy to the brochial primary was commenced but she rapidly deteriorated and died within two months. She was only slightly depressed when Cushing's syndrome was active.

EA 196

He came from abroad and worked in England as a clerk. Diabetes mellitus was diagnosed at age 29 and treated with insulin. Two months later, Cushing's syndrome was diagnosed due to ectopic ACTH secretion from a primary tumour in the pancreas. The pancreatic tumour was partially removed, and both adrenals were removed. A secondary tumour was already present in the liver. After the operation, Cushing's syndrome improved. During his illness he became depressed, unco-operative and complained that the doctors were using him " as a guinea-pig". When the diagnosis was fully explained to him his personality changed and he was described as a model patient who became very pleasant and co-operative and his depression improved.

EA 197

Cushing's syndrome was diagnosed at age 53, due to ectopic

ACTH secretion from a thymic tumour. Plasma cortisol was very high being 1,800 nmol/l at both 09.00h and midnight. She rapidly deteriorated and died.

EA 198

She presented with diarrhoea, oedema of the legs and "psychosis". She had Cushing's syndrome with plasma cortisol of 1,600 nmol/l and serum potassium of 2.1 nmol/l. She had a carcinoid tumour of the ileum with secondary tumour in the liver and raised urine values of 5 hydroxy-Indole-acetic acid. She was treated with spironolactone and potassium supplements and her psychosis was treated with chlorpromazine. She died soon after presentation.

EA 199

Cushing's syndrome due to ectopic ACTH secretion from a lung primary was diagnosed at the age of 70. He was an unreliable historian who was confused and very unwell. Serum potassium at diagnosis was only 1.5 mmol/l. He rapidly deteriorated and died. At post-mortem he had a carcinoma of the bronchus with metastatic disease in the lungs, liver, and adrenal glands together with broncho-pneumonia. The immediate cause of death, however, was peritonitis due to diverticular disease and the symptoms of this were probably suppressed by the high cortisol levels. Although he was unwell physically there were no features of depressive illness.

EA 200

Ectopic ACTH from an oat cell primary tumour of the bronchus was diagnosed at age 52. She rapidly deteriorated and died.

EA 201

At age 29 she had ectopic ACTH secretion from an oat cell carcinoma of the bronchus. Plasma ACTH was 2,000 ng/l and plasma cortisol ranged from 3,500 to 7,600 nmol/l. She responded slightly to a course of metyrapone,and radiotherapy to the primary lesion, but later relapsed and she died within a year.

EA 202

She had ectopic ACTH secretion from a carcinoid tumour of the bowel. At 59 a small bowel tumour had been removed and she was well for many years. At 73 she presented with right-sided heart failure, tricuspid valve disease and an enlarged liver. She was treated with parachloro-phenylalanine without benefit. She was depressed and confused and she had extensive malignant disease, from which she rapidly died.

EA 203

At age 70, she deteriorated in personal cleanliness and became confused in the few months before diagnosis.She had ectopic ACTH secretion from a lung tumour. The primary

tumour was treated with external irradiation. She rapidly deteriorated and the necropsy showed an oat cell carcinoma of the bronchus with bilateral adrenal hypertrophy. There was cerebral atrophy, but no secondary tumour in the brain. The peritoneum contained faecal material so the endogenous production of cortisol disguised the signs of perforation of the large bowel.

OTHER CUSHING'S

OC 204

Menstrual periods started at the age of 13 and stopped at 14. During the next two years she developed signs of Cushing's syndrome. At 16, she took 8 'O' levels and during her 'A' level course Cushing's syndrome was diagnosed. She used to be near the top of her form in Grammar School until she entered the sixth form when her academic performance started to deteriorate. At 14 she became depressed and would cry "for hours on end for no particular reason". She was found to have a rare form of Cushing's syndrome due to nodular hyperplasia and there was an excellent clinical remission to removal of both adrenal glands in a two-stage operation. She was never hypomanic. She was interviewed before and after her treatment for Cushing's syndrome and her depression improved and a series of photographs confirmed the clinical improvement. She successfully passed her 'A' level examinations and could have gone to University but she preferred to work for the family business. The development of Cushing's syndrome was clearly linked to the onset of a depressive illness.

OC 205

Alcoholic pseudo-Cushing's syndrome was diagnosed at age 62. He was married, worked as an accountant and had been a

Squadron Leader. He has been married twice and his second wife committed suicide. He was not depressed.

OC 206

At the age of 38 he had Cushing's syndrome attributed to his grossly excessive intake of alcohol. Despite obesity, weakness, hypogonadism and asthma, and life events which included losing his job and looking after elderly, frail parents, he remained remarkably cheerful. For a while he abstained from alcohol and the signs of Cushing's syndrome diminished, but later he relapsed and said " I drink as much as possible- I'll drink 'til I run out of money".

OC 207

Signs of Cushing's syndrome were noted at the age of 49, and attributed to his large intake of alcohol. He also had osteoporosis.

OC 208

He was of above average intelligence and ability and although he left school early, he obtained a University degree as an external student, and worked as a scientific officer for the Civil Service. Eczema had been present from childhood and from the age of 30 he suffered from asthma. Treatment with ACTH and steroids was given intermittently for the next 20 years and he developed obvious signs of

Cushing's syndrome. During this time he became depressed and cried but was not suicidal. He used to wake early in the morning and lost interest in his work and hobbies. Under supervision exogenous steroids and ACTH were gradually withdrawn and his muscle power increased, signs of Cushing's syndrome diminished and he became less depressed. At 50, he developed Peyronie's disease of the penis, which made him unhappy about his sex life and a course of steroids was recommended by a Consultant Urologist. His sister is a qualified psychiatrist who wrote saying "my brother is depressed by his condition and by the continuing physical and psychological disability which it imposes". When steroids were eventually reduced to zero orally, and only topical steroids were given, he developed severe joint pains and non-steroidal anti-inflammatory drugs were given, to good effect. When steroid levels were high, his depression was very severe.

OC 209

He was treated with bilateral adrenalectomy at age 70. Symptoms and signs and biochemistry followed a cyclical pattern. While being investigated he developed diarrhoea and colicky abdominal pain. A pelvic abscess was drained and a temporary colostomy was made. Psychologically he was normal before and after treatment of Cushing's syndrome, in spite of the disability due to Cushing's syndrome, and life events which included a burglary.

The White Rabbit put on his spectacles.
"Where shall I begin, please your Majesty?" he asked.
"Begin at the beginning", the King said, very gravely,
"and go on till you come to the end: then stop".

Lewis Carroll 1865
Alice's Adventures in Wonderland.

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CUSHING'S SYNDROME DUE TO ADRENOCORTICAL CARCINOMA – A COMPHRENSIVE CLINICAL AND BIOCHEMICAL STUDY OF PATIENTS TREATED BY SURGERY AND CHEMOTHERAPY

By

W. F. Kelly, A. J. Barnes, J. Cassar, M. White, K. Mashiter, S. Loizou, R. B. Welbourn and G. F. Joplin*

ABSTRACT

Four post-menopausal women had Cushing's syndrome due to adrenal cortical carcinomas. Comprehensive analyses of blood and urinary steroids showed that although the steroid profiles differed between patients, the pattern in each patient remained almost constant as the disease progressed, or remitted due to therapy. Elevations of serum testosterone and oestradiol were commensurate with the extent of virilisation, and the urinary output of aldosterone was associated with the severity of hypertension. A new finding was that all had substantially increased urinary free deoxycorticosterone. Complete surgical removal of the primary tumours was impossible but when most of the tumour tissue was removed, full clinical and biochemical remissions were obtained for a short time in 2 patients. One patient obtained a clinical and biochemical remission from op'DDD. In another patient the drug caused reduction both in blood pressure and in urinary aldosterone excretion, but there were unpleasant side effects. A third patient could not tolerate op'DDD. Metyrapone therapy produced neither clinical nor biochemical improvement in 3 patients. The mean duration of survival was 17 months after the first symptoms and 10 months from the date of operation. Despite advances in drug therapy, adrenal cortical carcinoma remains a lethal disease. Biochemical screening of multiple steroids offers a means of early diagnosis and disease monitoring. Extensive surgical removal of the tumour offers the best chance of a clinical and biochemical remission.

Correspondence to G. F. Joplin

Primary carcinoma of the adrenal cortex is extremely rare, affecting only 2 people per million. Most published data concern isolated case reports, although there have been some large series, usually assembled from multiple sources (*MacFarlane* 1958; *Hutter & Kayhoe* 1966*a*). The disease is usually swiftly fatal, and the diagnosis is suggested by the rapid onset of Cushing's syndrome with elevated cortisol and suppressed plasma ACTH concentrations. The important differential diagnosis is from Cushing's syndrome due to an adrenal adenoma, which has an excellent prognosis after the removal of the tumour. One of us has operated on 9 such patients without mortality, and the first 6 (*Welbourn et al.* 1971) are now alive and well from 10 to 23 years after operation.

Treatment of adrenal cortical carcinoma is by complete removal of the primary tumour, and by giving drugs such as op'DDD where further operations are not feasible (*Montgomery & Welbourn* 1975). Chemotherapy of adrenal carcinoma was introduced following an observation by *Nelson & Woodard* (1949) that the insecticide DDT caused necrosis of the adrenal cortex in dogs. This led to purification of the compound op'DDD (ortho-para prime DDD) i. e. 1-1 dichloro-2-(0-chlorophenyl)-2-(p-chlorophenyl)-ethane, which had been present in small amounts in the original insecticide. Trials in man (*Bergenstal et al.* 1960; *Montgomery & Welbourn* 1965; *Hutter & Kayhoe* 1966*b*) demonstrated examples of regression of metastases, necrosis of adrenal tumours, and decrease in urinary steroid metabolites. Later, metyrapone was found to inhibit steroid 11β-hydroxylase, and thus curtail the conversion of 11-deoxycortisol to cortisol, and deoxycorticosterone to corticosterone (a precursor of aldosterone) (*Liddle* 1974). Since cortisol and aldosterone are more potent biologically on a molar basis than their precursors, enzyme inhibition may be clinically useful.

Formerly, biochemical assessments of adrenal carcinoma and its response to treatment were based on non-specific urinary metabolites such as 17-oxogenic and 17-oxosteroids, but specific and sensitive assays for steroids in blood and urine are now available, and enable us to define in detail the pattern of steroids excreted.

We therefore report 4 recent patients of our own with multiple endocrine investigations to define the metabolic pathways leading to the synthesis of cortisol, aldosterone and the sex hormones, initially and after surgical procedures and chemotherapy with op'DDD and metyrapone. All patients were followed with serial measurements in which the same laboratory methods were used.

METHODS

Hormone measurements

Normal ranges are shown in Table 1. The following methods were used:

Serum (or plasma) cortisol. – ***Murphy*** (1967); 11-deoxycortisol (compound S): as cortisol, except for additional extraction with dichloromethane and carbon tetrachloride; testosterone: *Kjeld et al.* (1976*a*); oestradiol-17β: *Kjeld et al.* (1976*b*); luteinizing hormone (LH): *Marshall et al.* (1972); deoxycorticosterone (DOC): *Cope & Loizou* (1975) and aldosterone (*Cope & Loizou* 1973). Plasma ACTH was measured by Dr. L. Rees and 17 α-hydroxyprogesterone by Dr. G. Groom.

Urine. – Free cortisol: *Beardwell et al.* (1968); the inhibition of binding relative to cortisol in this assay is: 11-deoxycortisol 90 %, DOC 48 %, cortisone 17 % and testosterone 11 %; free DOC (*Cope & Loizou* (1975); total aldosterone: *Cope & Loizou* (1973); 17-oxogenic steroids (17-OGS) and 17-oxosteroids (17-OS): *Medical Research Society Committee* (1963); pregnanetriol: *Fotherby & Love* (1960).

Stimulation tests

"Synacthen Depot" (CIBA Laboratories) 1 mg im daily for 2 days; gonadotrophin releasing hormone (GnRH) 100 μg iv with measurements of LH at zero, 30 and 60 min; chorionic gonadotrophin ("Gonadotraphon LH", HCG, Paines & Byrne Ltd), 2000 units im daily for 2 days with blood samples for cortisol, testosterone and oestradiol for a further 2 days; metyrapone ("Metopirone" CIBA Laboratories) 750 mg orally every 4 h for 24 h with measurements of urine 17-OGS and serum 11-deoxycortisol.

Suppression tests

Dexamethasone 2 mg orally 6 hourly for 72 h, with measurements of urine free cortisol and 17-OGS over the last 48 h.

RESULTS

Patient 1

This 59 year old lady was first investigated by us in March 1975. Typical clinical signs of Cushing's syndrome (with only mild hirsutism) had developed during the previous 13 months, and her blood pressure was 140/100. She had had no treatment whatsoever.

Biochemistry (Table 1)

There were increased concentrations of serum cortisol, and plasma ACTH was suppressed. Plasma 11-deoxycortisol was increased basally, with a 4-fold rise one day after metyrapone. Serum testosterone was increased to that of normal adult males, and there was also a large increase in serum oestradiol; serum LH was undetectable both basally and after GnRH. HCG caused no further

Table 1.
Adrenal cortical carcinoma patients. Results of tests when first assessed[1]).

	Patients				Normal range[2])
	1	2	3	4	
Blood					
a) Steroids and hormones					
Cortisol (nmol/l)					
09.00	770	681	974	1525	100–550
24.00 h	570	600	770	1311	< 150
ACTH (ng/l)	< 10	< 15	–	< 10	< 10–80
11-Deoxycortisol					
Basal	182	71	161	177	28–84
With metyrapone[3])	710	–	–	–	
DOC (pmol/l)	–	–	–	2010	85–610
Aldosterone (pmol/l)	–	–	–	1550	30–130
Testosterone (nmol/l)[4])	17	16	2.6	2.3	1.0–3.2
Oestradiol (pmol/l)	1335	232	67	156	21–59
Luteinizing hormone (μg/l)					
Basal	< 1	1.1	–	1.8	> 15
Peak after GnRH[3])	< 1	–	–	2.1	> 35
b) Other					
Potassium (mmol/l)	4.2	4.0	1.9	2.9	3.5–5.5
Glucose (mmol/l):					
Fasting	4.2	4.7	7.1	–	3.5–5.5
After glucose orally[5])	9.6	–	15.2	16.2[6])	

rise in serum cortisol or testosterone. Plasma potassium was normal, and a 50 g oral glucose tolerance test showed only mild diabetes mellitus. Urinary free cortisol, which was greatly increased, failed to suppress with dexamethasone; urinary 17-OGS were three times the upper limit of normal, and again there was no suppression with dexamethasone; however, there was a 50 % increase in urinary 17-OGS with metyrapone, and together with the rise in serum 11-deoxycortisol mentioned above, this suggested that metyrapone might be effective in blocking cortisol synthesis. Basal urinary DOC was greatly increased, while urinary aldosterone was subnormal.

Table 1 (cont.).

	Patients				Normal range[2]
	1	2	3	4	
Urine – 24 h					
Free cortisol (nmol)					
Basal	1540	866	12 500	18 280	< 270
Dexamethasone[3]	1160	–	–	–	–
17-OS (μmol)	132	279	137	108	< 50
17-OGS (μmol)					
Basal	152	240	268	303	< 50
Dexamethasone[3]	184	–	–	–	–
Metyrapone	224	–	–	–	–
Pregnanetriol (μmol)	–	7.2	6.3	21	< 6
Free DOC (pmol)	2187	2354	1410	1325	45–242
Aldosterone (nmol)	1.4	464	40	13	14–55
Blood pressure	140/100	210/130	170/90	180/100	

1) Results quoted here are those when first assessed at Hammersmith Hospital; blood samples at 09.00 h unless otherwise stated.
2) Normal ranges are for post-menopausal women.
3) See text for full details.
4) Normal male range is 10–28 nmol/l.
5) Blood sample taken 120 min after glucose 50 g orally.
6) Random sample at another hospital just before insulin commenced.

These preliminary investigations suggested an adrenal tumour, so the patient was readmitted in May 1975 for localisation studies and with a view to adrenalectomy. She had deteriorated rapidly over the intervening 2 months with the development of proximal muscle weakness, hypokalaemia (3.2 mmol/l), hypertension (BP 210/120) and a steroid psychosis.

Localisation studies

A plain radiograph of the abdomen was normal. Arteriography and venography both showed a right adrenal tumour, confirmed by adrenal scanning

with [^{131}I]19-iodocholesterol with the best delineation at 7 days. Venous sampling of serum cortisol levels correctly localised the tumour, but simultaneous estimations of serum testosterone were unhelpful.

Operation June 1975

Most (428 g) of a large right adrenal tumour was removed by one of us (RBW). Complete excision was not possible and the tumour had already invaded the local veins. The left adrenal was free from tumour.

Post-operative progress (Figs. 1 and 2)

There was initially good progress with a rapid return to normal of the mental

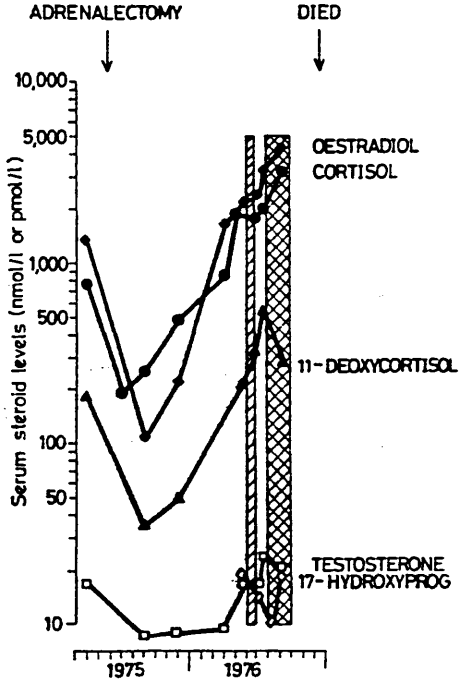


Fig. 1.

Patient 1. Effect of operation and chemotherapy on serum steroids. See Table for normal ranges.

● —— ● Cortisol nmol/l
▲ —— ▲ 11-deoxycortisol nmol/l
□ —— □ Testosterone nmol/l
◆ —— ◆ Oestradiol pmol/l
◇ —— ◇ 17-alpha-hydroxyprogesterone nmol/l (normal < 18)
▨ op'DDD
▩ Metyrapone

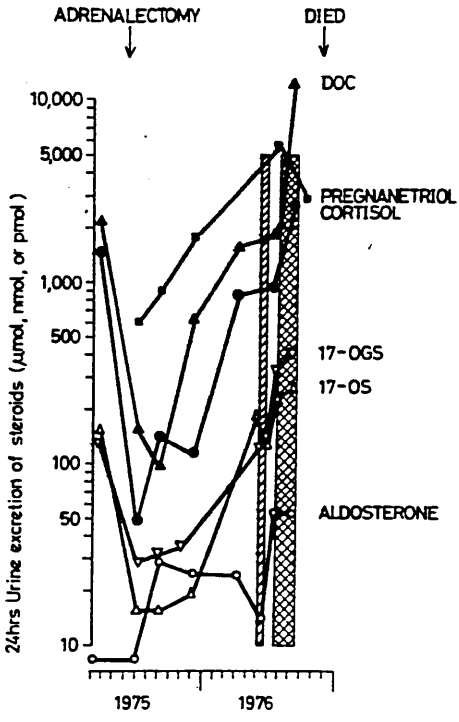


Fig. 2.

Patient 1. Effect of operation and chemotherapy on urinary steroid excretion. See Table for normal ranges.

● —— ● Free cortisol nmol
▲ —— ▲ Free DOC pmol
o —— o Aldosterone nmol
■ —— ■ Pregnanetriol nmol
▽ —— ▽ 17-OGS μmol
△ —— △ 17-OS μmol
▨ op'DDD
▩ Metyrapone

state and the blood pressure and plasma potassium, and the disappearance of the physical signs of Cushing's syndrome. Serum cortisol became normal at 09.00 h (257 nmol/l) and increased to 698 nmol/l with insulin-induced hypoglycaemia, showing a normal response. Serum 11-deoxycortisol and urinary free cortisol, 17-OGS, 17-OS and DOC also became normal. The patient remained well for nearly a year until April 1976, when there was a recurrence of facial plethora, accompanied by significant increases in the concentrations of all the serum and urinary steroids that had initially been high. Treatment with op'DDD ("Mitotane", Calbiò Pharmaceuticals) was commenced, and the dose was increased to 8 g/day. There was neither clinical nor biochemical improve-

ment, and on the 10th day therapy was stopped owing to severe systemic symptoms and an extensive rash. In July 1976 metyrapone ("Metopirone" CIBA Laboratories) was started, increasing the dose to 1.5 g/day. There was no objective improvement, and serum and urinary steroid values continued to increase. There was progressive deterioration with worsening of the physical signs, a cerebrovascular accident and severe depression. The patient died in December 1976.

Patient 2

This lady had been hypertensive since the age of 43, and her periods ceased at age 45 years. In August 1975, aged 47 years, Cushing's syndrome was diagnosed with symptoms of weight gain and hirsutism of 4 months duration. The diagnosis was confirmed biochemically and an excretion urogram indicated a left adrenal mass. At operation 400 g of an adrenal carcinoma were removed (Mr. J. S. Mously) but complete ablation was impossible. There was no change in symptoms, and the patient was referred to us for further treatment. On examination, the striking features were hirsutism, powerful muscles and hypertension (BP 210/130). There was slight facial plethora but there were no bruises, and no striae, and skin thickness was normal.

Biochemistry (Table 1)

There were increased serum concentrations of cortisol with undetectable plasma ACTH. Serum testosterone was within the normal male range; serum oestradiol was also increased, but not markedly so. There was no increase in serum testosterone or cortisol after "Synacthen Depot". Plasma potassium and fasting blood glucose were normal. The urinary free cortisol was greatly elevated, but not so much as in the other 3 patients. Urinary 17-OS, 17-OGS, pregnanetriol and free DOC were all clearly increased.

Skull and chest radiographs were normal, but a second excretion urogram demonstrated a left adrenal mass.

Progress

The risks of a second operation on the primary tumour exceeded the probable benefits, so treatment with op'DDD was commenced, gradually increasing to 8 g/day. The drug had to be stopped on two occasions because of diarrhoea, nausea and vomiting. At the end of one month, there was biochemical improvement, with progressive reduction in serum cortisol and most of the urinary steroids (Figs. 3 and 4). However, most of these soon started to rise again, and there was no response to 2 further courses of op'DDD. Although the blood pressure fell, there was no response to op'DDD in any other clinical aspect.

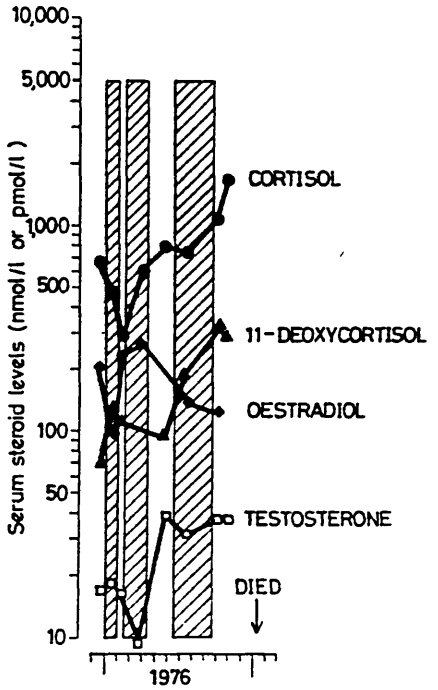


Fig. 3.
Patient 2. Effect of op'DDD on serum steroids.
See Table for normal ranges.
● —— ● Cortisol nmol/l
▲ —— ▲ 11-deoxycortisol nmol/l
□ —— □ Testosterone nmol/l
◆ —— ◆ Oestradiol pmol/l
▨ op'DDD

The patient deteriorated and progressively developed enlarged hard cervical lymph nodes and hepatomegaly, suggesting carcinomatosis. Metastases, first shown on the chest radiograph in May 1976, continued to increase in size. The patient died in January 1977.

Patient 3

This 58 year old lady had had typical symptoms of Cushing's syndrome for 4 months in July 1975 when the physical signs and biochemical tests confirmed the diagnosis. A plain radiograph of the abdomen showed downward displacement of the left kidney and calcification above it. In July 1975 as much as possible of an adrenal carcinoma was removed (Mr. J. S. Mously). The specimen weighed 308 g and had areas of haemorrhage and necrosis. There was clinical and biochemical remission for 3 months after which the patient started

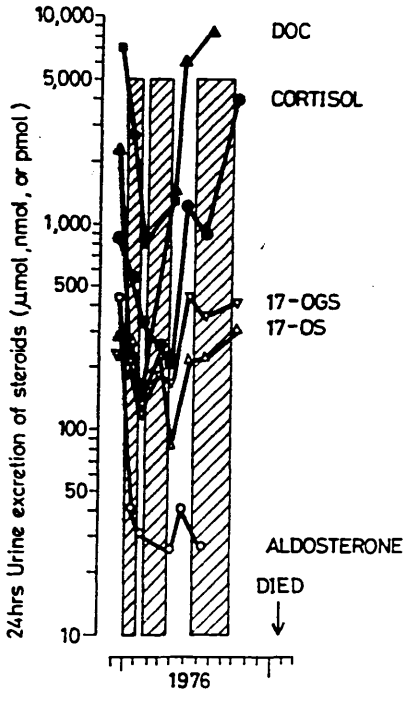


Fig. 4.
Patient 2. Effect of op'DDD on urinary steroid excretion.
See Table for normal ranges.

● —— ● Free cortisol nmol
▲ —— ▲ Free DOC pmol
o —— o Aldosterone nmol
■ —— ■ Pregnanetriol nmol
▽ —— ▽ 17-OGS μmol
△ —— △ 17-OS μmol
▨ op'DDD

to relapse. In November 1975 she was referred to us for further management. On examination, typical features of Cushing's syndrome were found, but hirsutism was only slight, the blood pressure was 170/90.

Biochemistry (Table 1)

Serum cortisol and 11-deoxycortisol were increased, but testosterone and oestradiol were normal. HCG failed to produce increases in serum cortisol, testosterone or oestradiol. Plasma potassium was low and the 50 g oral glucose tolerance test showed diabetes mellitus. Urinary free cortisol, 17-OS, 17-OGS and free DOC were all increased, but urinary aldosterone was normal.

Progress

op'DDD was commenced in November 1975, was increased to 8 g/day, and was well tolerated. Within 2 weeks, the clinical signs of Cushing's syndrome started to regress and the plasma potassium became normal, but the blood pressure remained unchanged. In January 1976 the patient was reassessed while taking 8 g/day of op'DDD. There were obvious improvements in facial plethora, obesity (weight reduction of 4 kg) and conjunctival oedema. There were progressive decreases in urinary free cortisol, 17-OGS, 17-OS and pregnanetriol (Fig. 5). There was no significant change in urinary DOC but aldosterone excretion was diminished. Serum cortisol fell from 974 to 756 nmol/l, and 11-

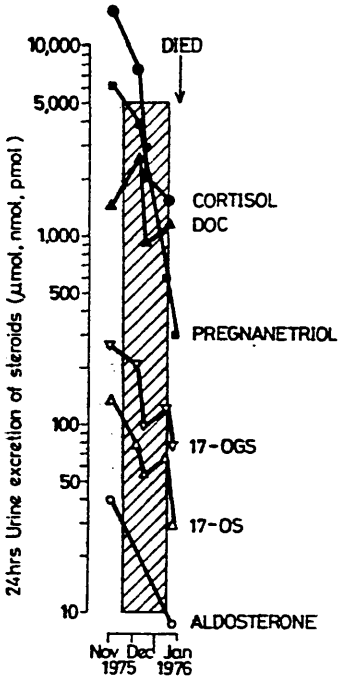


Fig. 5.
Patient 3. Effect of op'DDD on urinary steroid excretion.
See Table for normal ranges.

● —— ● Free cortisol nmol
▲ —— ▲ Free DOC pmol
o —— o Aldosterone nmol
■ —— ■ Pregnanetriol nmol
▽ —— ▽ 17-OGS μmol
△ —— △ 17-OS μmol
▨ op'DDD

deoxycortisol from 161 to 107 nmol/l, while there were no significant changes in serum testosterone or oestradiol. The final deterioration was swift, and the patient died in January 1976.

Post-mortem examination

This showed a left adrenal tumour 14 x 11 x 5 cm, with peritoneal metastases. The liver, lungs, bone, brain and right adrenal gland were all free from tumour. The pituitary gland was normal except for hyaline changes in corticotrophin-producing cells (Crooke's cells).

Patient 4

This 68 year old lady was admitted to hospital in February 1978 complaining of weakness and back pain. She had been treated for mild hypertension for the previous 5 years. Her health had deteriorated from November 1977, when she became agitated and depressed. The diagnosis of Cushing's syndrome was suggested in February 1978 by central obesity, muscle weakness, hypokalaemia (potassium 1.3 mmol/l), hyperglycaemia (glucose 16.2 mmol/l) and hypertension (BP 180/100). The physical signs of Cushing's syndrome were minimal, and hirsutism, facial plethora and "mooning", striae, easy bruising and conjunctival oedema were all absent initially.

Biochemistry (Table 1)

Serum cortisol was the highest of the 4 patients, and plasma ACTH was undetectable. Serum testosterone was normal but serum oestradiol was slightly increased; serum LH was low, and there was no significant increase after GnRH. Plasma potassium remained subnormal. Urinary free cortisol was extremely high, and urinary 17-OS, 17-OGS and pregnanetriol were increased. Urine free DOC was increased, but urinary aldosterone was not.

Radiographs of the pituitary fossa and chest were normal, but the lumbar spine showed severe osteoporosis, as indicated by vertebral collapse.

Localisation studies

Plain radiographs of the abdomen and an excretion urogram were normal. The site of the adrenal tumour on the right side was correctly located by ultrasound (which also showed an abnormal mass in the liver). An arteriogram sugggested that the circulation to the right adrenal gland was abnormal, but the appearances were not definite. Hence venous sampling was attempted but this failed to localise the tumour since the right adrenal vein could not be entered, and samples from other sites were uniformly high. An isotopic liver scan showed an abnormal mass.

Progress

Metyrapone was commenced in March 1978 and was increased to 2.5 g/day. The effects were observed for 2 weeks; there was no clinical benefit and blood pressure remained elevated. There was no consistent reduction in serum or urinary cortisol values, and serum 11-deoxycortisol concentrations did not change. However, there was a 10-fold rise in urinary DOC excretion, without a change in urinary aldosterone; serum DOC increased 4-fold but serum aldosterone did not change. The condition of the patient deteriorated with drowsiness and severe back pain.

Operation March 1978

The abdomen was opened anteriorly (RBW). The liver contained a large mass of tumour in the right lobe, which concealed the right adrenal tumour, and there were many small hepatic metastases. No palliative procedure was possible and the patient died 3 days later.

Post-mortem examination

There was a right adrenal carcinoma weighing 20 g, and a tumour-free left adrenal of 3 g. The massive hepatic secondary tumour (15 x 10 x 10 cm) was at the site shown by ultrasonic and isotopic scans. The multiple hepatic metastases were each less than 1 cm in diameter. The lungs, bone and brain were free from metastases, and the pituitary gland was normal except for Crookes' changes.

DISCUSSION

These patients illustrate several interesting features concerning the nature and treatment of functioning adrenal cortical carcinomas. The diagnosis was suggested initially in all by the short history of the signs of Cushing's syndrome (mean of 6 months) and in patient 2 by significant virilisation. The physical signs were least apparent in patient 4, despite the fact that she had the highest cortisol values, suggesting that there was insufficient time for all the signs to develop.

The biochemical features of adrenal carcinoma were the very high amounts of cortisol excretion in 3 patients when first seen by us (and in the 4th patient later), since values exceeding 1500 nmol/24 h are exceptional in the commoner pituitary-dependent disease (*Burke & Beardwell* 1973). Moreover, greatly elevated values of serum oestradiol, testosterone and 11-deoxycortisol are not usual in the benign types of Cushing's syndrome (*Liddle* 1974). Urinary DOC and aldosterone are usually close to normal in pituitary-dependent Cushing's syn-

drome (*Cope & Loizou* 1976) whereas all our patients with adrenal carcinomas had very high values for urinary DOC, and patient 2 also had substantially increased urinary aldosterone. The elevations in urinary DOC without corresponding increases in urinary aldosterone, and the increase in serum 11-deoxycortisol suggest that relative insufficiency of 11-hydroxylation of steroids may be a feature of these adrenal carcinomas, as noted by *Lipsett & Wilson* (1962) and by our own group (*Dennis et al.* 1967). If 11-hydroxylation is a rate-limiting step, then therapeutic efficacy of metyrapone might be anticipated. This metabolic block was not total since metyrapone caused further increases in urinary and plasma DOC values. However, urinary and plasma aldosterone values remained unchanged, and metyrapone neither reduced blood pressure nor alleviated the physical signs of Cushing's syndrome.

Correlation between the biochemical and clinical features was interesting. Only patient 2 suffered from severe virilisation, and this was probably due to the very high level of serum testosterone unopposed by a very high serum concentration of oestradiol; in contrast patient 1 (without virilisation but with equally high serum testosterone levels) was perhaps protected by the very high concentration of oestradiol.

Suppression of pituitary gonadotrophins in these post-menopausal females was possibly due to increased serum concentrations of sex steroids.

At our first assessment, only patient 2 had severe hypertension and this may have been due to her very high output of aldosterone. Patients 1, 3 and 4 all had milder hypertension, responding (in patient 1) to removal of most of the tumour. The relative roles of DOC and cortisol in the genesis of hypertension could not be distinguished. since treatment affected these steroids similarly.

Severe hypokalaemia was found in patients 3 and 4 who had the highest cortisol values; it is interesting that patient 2 who had the highest urinary excretion of DOC and aldosterone did not have such severe hypokalaemia. We interpret these results by considering that despite the relatively weak mineralocorticoid action of cortisol, it can cause hypokalaemia if present in enormous concentrations.

Functioning adrenal carcinomas are usually autonomous (*Welbourn & Sellwood* 1969; *Liddle* 1974), and we confirm this since dexamethasone, HCG and "Synacthen Depot" produced no significant changes in steroid levels.

Localisation studies correctly predicted the sites of tumours in all patients. In patient 3 a plain radiograph of the abdomen, and in patient 2 an excretion urogram were adequate for diagnosis. Ultrasound was the most useful method in patient 4 since it correctly identified both the tumour, and the large hepatic metastasis. Arteriography and venography both gave one definite and one inconclusive result, and we prefer the non-invasive methods.

Immediate treatment by removal of as much cancer tissue as possible is worthwhile. In patients 1 and 3 this resulted in several months of complete

clinical and hormonal remission, but patient 2 showed no improvement even though, like others, she showed no evidence of metastases at the time of operation. Palliation was impossible in patient 4 since she presented in a terminal state.

In the largest series of patients with adrenal carcinoma, op'DDD therapy was said to have caused clinical improvement in a third, regression of malignant tissue in a third, and reduction of high steroid levels in about two thirds (*Hutter & Kayhoe* 1966*b*). If a further operation to remove tumour is not feasible, then op'DDD is worth a trial; patient 3 in our series obtained an impressive clinical and biochemical remission for 2 months, but patients 1 and 2 could only tolerate limited courses of therapy.

Biochemical monitoring of disease activity in our patients showed that steroid levels tended to change in parallel, the hormonal pattern remaining relatively constant. Therefore, to check for disease reactivation, we recommend that sequential measurements are made of several steroids including those which showed the most severe initial abnormalities. We did not observe the change reported by *Temple et al.* (1969) that, in Cushing's disease, op'DDD could be used to reduce selectively the serum cortisol levels, without a concomitant reduction in aldosterone.

In our group, the mean duration of survival after the onset of symptoms was 17 months, and that after operation was 10 months. Short survival after diagnosis is typical of adrenal carcinoma and agrees with our experience of 8 other patients (amalgamating the results of *Welbourn & Sellwood* 1969; *Welbourn et al.* 1971). *MacFarlane* (1958) reported the mean survival after diagnosis of 9 untreated patients as 4 months. However, with operations and op'DDD some patients have survived much longer (*Hajjar et al.* 1975; *Becker & Schumacker* 1975; *Ostuni & Roginsky* 1975).

In conclusion, functioning adrenal cortical carcinoma remains a lethal condition despite advances in chemotherapy. Biochemical screening to measure multiple steroids as described in this paper is helpful both for diagnosis, and for monitoring the response to therapy. Immediate surgical ablation of the tumour offers the best chance of palliation, and if an operation is impossible then op'DDD should be used.

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Cushing's Syndrome, Tryptophan and Depression

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SUMMARY Fifteen patients with active Cushing's syndrome have been compared with 15 other patients who had been treated successfully for Cushing's syndrome and with 13 patients with other pituitary tumours. Depression was the main psychiatric diagnosis made by the CATEGO programme after Present State Examinations. Patients with active Cushing's syndrome were significantly more depressed (Hamilton Rating Scores), than were the other patients. Compared with the control patients, those with active Cushing's syndrome had slightly lower plasma concentrations of total tryptophan, though the concentrations of freely diffusible tryptophan were not significantly changed.

Cushing's syndrome may provide a biological model for the study of depressive illness, since depression has been described in many patients with Cushing's syndrome (Cushing, 1932; Spillane, 1951; Trethowan and Cobb, 1952; Hurxthal and O'Sullivan, 1959; Furger, 1961). However, most of these studies were retrospective in design and did not use modern measures of psychiatric morbidity or adrenocortical function. None of the studies used control groups of patients with other illnesses even though depression is a common symptom in medically ill patients (Stewart *et al*, 1965; Schwab *et al*, 1967; Maguire *et al*, 1974; Moffic and Paykel, 1975). In most of the early studies little consideration was given to the possibility that patients with Cushing's syndrome might be selectively referred if they were also depressed.

To overcome some of these problems a prospective study was designed to be completed at Hammersmith Hospital where there are specialized facilities for performing pituitary ablation (Joplin *et al*, 1965). Patients are referred to this endocrine unit regardless of the presence or absence of psychiatric illness. As well as patients with Cushing's syndrome the unit admits patients with other pituitary tumours for similar investigations and treatment. This latter group provides a control for the psychosocial effects and biases of illness, referral, investigation and treatment. We also studied a second control group of patients who had been successfully treated for Cushing's syndrome, and who were being reassessed. If depressive illness is precipitated in patients with Cushing's syndrome, then the patients with active Cushing's syndrome should be depressed more frequently and more severely than the control patients.

At the same time a biochemical mechanism has been tested whereby Cushing's syndrome might cause depression. Cortisol at pathological levels can increase the activity of the enzyme tryptophan oxygenase (l-tryptophan: oxygen oxidoreductase, EC 1.13.1.12) (Knox and Auerbach, 1955; Altman and Greengard, 1966). As a result there will be more oxidative metabolism of tryptophan so that less may be available for uptake into the brain and for the subsequent conversion to 5-hydroxy-tryptamine (5-HT). Under these conditions brain 5-HT concentrations fall (Curzon and Green, 1971). Such a deficit of brain 5-HT is postulated as a possible factor in some depressive illnesses (Asberg, 1979; van Praag, 1979). We tested the hypothesis that in Cushing's syndrome depression might be precipitated by induction of tryptophan oxygenase, so causing a deficit of brain 5-HT; plasma concentrations of total and freely diffusible tryptophan were measured in patients with Cushing's syndrome and in patients with other pituitary tumours. The hypothesis predicts that those patients with active

Cushing's syndrome should have low plasma concentrations of total and free tryptophan.

Methods

1. *Patients*

All patients were investigated in the Endocrine Unit, Hammersmith Hospital in 1977 and 1978 during the routine evaluation of their disease. All gave informed consent to interview. Active Cushing's syndrome was defined by increased excretion of urinary free cortisol, and was always associated with the presence of some of the physical signs described by Cushing (1932).

Of the 15 patients with active Cushing's syndrome, in 12 this was due to Cushing's disease, that is an excessive production of ACTH from the pituitary gland, one had an adrenal carcinoma (case 1), one had ectopic ACTH production from a bronchogenic carcinoma

TABLE I

Details of patients

Endocrine syndrome	Age	Sex	UFC	CATEGO diagnosis	HRS score	Tryptophan	
						Total	Free
Active Cushing's							
1.	68	F	6,025	O ? N +	18.5	49	10.2
2.	70	M	4,390		4.5	50	8.9
3.	66	F	1,959		2.0	53	5.6
4.	48	M	1,737	N +	14.5	57	18.2
5.	50	M	1,490	R +	15.5	62	7.3
6.	32	F	1,300		–	55	9.6
7.	58	F	1,000	N +	27.5	51	2.7
8.	14	M	965		–	52	3.8
9.	46	F	786		–	42	2.5
10.	59	F	600	R +	12.5	71	10.3
11.	18	M	436	N +	5.0	86	24.0
12.	37	F	406	N +	10.0	74	9.0
13.	35	M	388	N ?	5.0	69	11.0
14.	45	F	372		3.0	59	10.5
15.	48	F	361		0.0	123	13.7
Mean	46.2		1,481		9.83	63.5	9.82
SD	16.9		1,628		8.14	20.0	5.70
Treated Cushing's							
16.	50	F	270	N +	3.0	56	7.2
17.	49	M	251	R +	9.5	47	5.5
18.	50	F	232	N +	8.5	84	16.9
19.	60	F	196	N +	3.5	58	–
20.	64	F	181		0.5	106	13.6
21.	33	F	151		0.0	57	6.6
22.	56	F	149	R +	8.0	56	–
23.	18	F	71		4.5	74	19.4
24.	58	F	62		0.0	69	10.1
25.	30	F	43		2.0	77	7.5
26.	53	F	43	N +	3.5	57	–
27.	43	F	23		1.5	98	17.1
28.	31	F	20		0.0	77	7.6
29.	56	F	19		0.0	43	5.5
30.	49	F	–		3.0	93	11.7
Mean	46.7		122		3.16	70.1	10.7
SD	13.1		92		3.22	19.0	4.9

TABLE I continued

Other pituitary tumours							
31.	19	F	260		1.5	88	11.6
32.	54	F	247		1.0	66	12.4
33.	53	F	242		0.5	76	8.5
34.	26	F	218		1.0	73	6.3
35.	40	F	206	N +	4.5	97	11.9
36.	34	F	160		0.5	60	7.1
37.	29	F	128		1.5	101	14.8
38.	55	F	118	A +	2.5	79	24.9
39.	31	F	93		0.0	65	6.5
40.	65	F	78		2.5	68	9.5
41.	26	F	39		0.0	69	6.1
42.	46	F	–		1.0	65	12.1
43.	48	F	–		0.0	73	12.3
Mean	40.5		163		1.27	75.4	11.1
SD	14.1		76		1.28	12.7	5.0
Normal Values			<270			69–101	6–15

N = neurotic; R = retarded depression; A = anxiety state; D = other psychosis
UFC = urinary free cortisol, nmol/24 hours
CATEGO = diagnosis from Present State Examination, Wing *et al* (1974)
HRS = Hamilton (1967) Rating Score
Tryptophan = plasma concentration in μmol/litre normal values from Bender and Bamji (1974).

(case 3) and in one patient high doses of ACTH had been given for asthma and eczema (case 5). The 15 patients who had been successfully cured of Cushing's syndrome included 13 treated by pituitary ablation, and 2 by removal of adrenal glands (case 18 for bilateral hyperplasia and case 21 for an adrenal adenoma). Four patients (i.e. cases 16, 26, 27 and 30) had previously had Nelson's syndrome, that is expansion of a pituitary tumour secreting ACTH following adrenalectomy. The 13 patients with other pituitary tumours included 6 with acromegaly (i.e. cases 32, 33, 38, 40, 41 and 43) and 7 with prolactin-secreting tumours which caused amenorrhoea, galactorrhoea and infertility (Kelly *et al*, 1978). Like those with Cushing's syndrome these other patients knew that an operation on the pituitary gland might be needed. Because of the disfigurement of acromegaly, and the endocrinological results of raised serum prolactin, these other patients might be considered to have a priori causes for depression. All patients were admitted to the same Metabolic Unit and given a normal diet. Blood samples for tryptophan assays were taken between 0800 and 0930 hours and patients were supervised to ensure that no food had been taken since the previous midnight. Some patients were already taking a variety of medications, including hypnotics (usually diazepam), analgesics (usually paracetamol) and some took antibiotics and appropriate replacement corticosteroids. No patient was taking major tranquillizers, aspirin, oral contraceptives, anti-depressants or l-tryptophan. Urine was collected for free cortisol estimation. Where assays were not performed immediately, plasma, serum or urine samples were stored at −20°C. It was usually possible for blood samples to be taken at the beginning or end of the 24 hour periods during which urine was collected and psychiatric evaluation made.

2. *Assays*

Plasma total tryptophan was measured by the method of Denckla and Dewey (1967), and binding to albumin as described by Bender *et al* (1975), allowing calculation of the concentration of diffusible or 'free' tryptophan. Plasma total amino acid concentration was measured by the method of Maeda and Tsuji (1973). Normal ranges ± two standard deviations based on 67 persons aged 22–62 years are shown in Table I (Bender and Bamji, 1974): there was no effect of age or sex on plasma tryptophan. Urinary free cortisol (UFC) is a sensitive index of overactivity of the adrenal cortex (Cope, 1972) and

the method of Beardwell *et al* (1968) was used, taking 270 nmol/24 hours as the upper limit of normal. Where a value for UFC is not provided (cases 30, 42 and 43), normal adrenocortical function was assumed since plasma cortisol values were normal, and physical examination was also normal. Plasma ACTH was kindly measured by radioimmunoassay by Professor Lesley Rees.

3. *Psychiatric assessment*

Patients were assessed at an interview at which were administered the Present State Examination (Wing *et al*, 1974) and the Hamil-

TABLE II

Comparison between 3 groups of patients

1. Mann-Whitney U-tests

Active Cushings and Treated Cushings	
Cortisol	$P < 0.001$*
Depression	$P = 0.011$*
Total tryptophan	$P = 0.2$
Free tryptophan	$P = 0.8$
Active Cushings and other pituitary tumours	
Cortisol	$P < 0.001$*
Depression	$P < 0.001$*
Total tryptophan	$P = 0.013$*
Free tryptophan	$P = 0.4$
Treated Cushings and other pituitary tumours	
Cortisol	$P = 0.2$
Depression	$P = 0.2$
Total tryptophan	$P = 0.4$
Free tryptophan	$P = 0.9$

2. Spearman's tests

	Pairs	Correlation coefficient	P
Active Cushings			
Cortisol v. Depression	12	0.43	0.17
Cortisol v. Total tryptophan	15	−0.68	0.005*
Cortisol v. Free tryptophan	15	−0.37	0.18
Depression v. Total tryptophan	12	−0.37	0.24
Depression v. Free tryptophan	12	−0.28	0.38
Treated Cushings			
Cortisol v. Depression	14	0.56	0.035*
Cortisol v. Total tryptophan	14	−0.13	0.65
Cortisol v. Free tryptophan	11	−0.06	0.86
Depression v. Total tryptophan	15	−0.15	0.59
Depression v. Free tryptophan	12	0.23	0.46
Other pituitary tumours			
Cortisol v. Depression	11	0.14	0.68
Cortisol v. Total tryptophan	11	0.24	0.48
Cortisol v. Free tryptophan	11	0.25	0.45
Depression v. Total tryptophan	13	0.53	0.063
Depression v. Free tryptophan	13	0.49	0.086

* Denotes significant result.

ton rating scale for use in depression (Hamilton, 1967). Three patients who did not speak English (cases 6, 8 and 9) were excluded from the psychiatric but not the biochemical assessments. Inter-observer reliability based on 15 independent assessments by W K. and S.C. using the Hamilton Rating Scale gave a correlation coefficient of 0.87 ($P < 0.001$).

4. *Statistics*

Data for urinary free cortisol and Hamilton scores were not normally distributed, and we used non-parametric methods. Comparisons between the three groups of patients were made by the Mann-Whitney U test at a reduced significance level of 0.017 (Table II). Within each group the correlation between variables was measured by Spearman's rank correlation (Table II).

Results

The mean ages of the patients with active Cushing's syndrome, treated Cushing's, and other pituitary tumours were 46, 47 and 41 years respectively; in all groups females outnumbered males, although the variables measured did not appear to be related to sex.

Depression

CATEGO diagnoses of neurotic depression (N?, N+) or retarded depression (R? or R+) were made in 8 of the 12 English-speaking patients with active Cushing's syndrome, in 6 of 15 patients with treated Cushing's syndrome and in only 1 of the 13 patients with other pituitary tumours (Table I). The only other CATEGO diagnosis to be made in a patient with active Cushing's syndrome (possible other psychosis) was an acute organic reaction in a lady who was terminally ill with metastases from an adrenal carcinoma. One patient with acromegaly and a long standing agoraphobia received a CATEGO diagnosis of an anxiety state (A+). As all other psychiatric diagnoses were of depression, we used Hamilton Rating Scores (HRS) to measure depression in all patients (Hamilton, 1967). Using this measure the patients with active Cushing's syndrome were significantly more depressed than the patients who had been treated successfully for Cushing's syndrome (rho = 2.54; $P = .011$). The patients with active Cushing's syndrome were also more depressed than the patients with other pituitary tumours (rho = 3.37; $P < .001$). However, only one patient (case 7) was severely depressed.

Total tryptophan

Plasma concentrations of total tryptophan were slightly lower in 15 patients with active Cushing's syndrome (mean 64 μmol/l) than in either the 15 treated patients (mean 70 μmol/l, rho = 1.26, $P = 0.2$) or in the 13 patients with other pituitary tumours (mean 75 μmol/l, rho = 2.49, $P = 0.013$). In the active Cushing's group there was a significant negative correlation coefficient (rho = −0.68, $P < 0.005$) between cortisol excretion and plasma total tryptophan (Table II).

Free tryptophan

Overall, no significant differences were found in plasma free tryptophan concentrations comparing active Cushing's patients with those treated, or with other pituitary tumours (mean values 9.8, 10.7 and 11.1 μmol/l respectively) although there was a trend similar to that found for total tryptophan. These values for concentration of free tryptophan were determined by equilibrium dialysis at 4°C, without control of pH (Bender *et al*, 1975), rather than by ultrafiltration, a technique which was agreed as a standard method after the present study had commenced (meeting on the uptake of tryptophan into tissues, Lausanne, July 1978). Results obtained by the equilibrium dialysis technique agree well with those reported by various workers using ultrafiltration techniques (Baumann and Perry, 1977).

Total amino acids

The plasma concentrations of amino acids did not differ significantly between the groups, and were not related to the cortisol values.

Discussion

It is difficult to compare the present study with earlier series which were often retrospective and which used neither control groups nor standardized measures of psychiatric morbidity.

Carroll (1976) has reviewed these case reports and considers that about half contained evidence of depressive illness. However depression is common in medical patients (Stewart *et al*, 1965; Schwab *et al*, 1967; Maguire *et al*, 1974; Moffic and Paykel, 1975) and it remains to be shown that depression is more common in patients with Cushing's syndrome.

The present study was prospective in design. The Present State Examination (Wing *et al*, 1974) was used as a standardized screening instrument to cover a wide range of possible psychiatric diagnoses. The Hamilton (1967) Rating Scale was used to measure the severity of depressive symptoms. Two control groups were used. The first included patients with other pituitary tumours who were admitted to the same unit for similar investigations and treatment. The second included patients who had previously been treated for Cushing's syndrome and who were being investigated as part of their routine follow up.

Under these conditions depression was the main psychiatric diagnosis to be found in the patients with active Cushing's syndrome: one patient also had an acute organic reaction in the setting of a terminal illness. The patients with active Cushing's syndrome were significantly more depressed than were the patients in each of the control groups. Thus we have demonstrated association between Cushing's syndrome and depression in a controlled quantitative study. However the present data do not imply any causal connection between the two conditions. To clarify this issue we are at present measuring sequential changes in mood and cortisol excretion following the successful correction of the Cushing's syndrome. So far six patients have been followed up at one year and all are less depressed than when they had active Cushing's syndrome.

We also tested the hypothesis that in Cushing's syndrome depression occurs by the induction of tryptophan oxygenase and the consequent depletion of brain 5-hydroxytryptamine (5-HT). Green and Curzon (1968) have shown that in experimental animals injection of cortisol leads to an increase in tryptophan oxygenase activity and a decrease in brain concentrations of tryptophan and 5-HT (Curzon and Green, 1971; Green *et al*, 1975). We tested the possibility that a similar effect occurs in patients with Cushing's syndrome. It was predicted that compared with the control patients those with active Cushing's syndrome would have lower plasma concentrations of total tryptophan and this has been demonstrated. Patients with active Cushing's syndrome also tended to have slightly lower concentrations of plasma free tryptophan than controls, although this difference was not statistically significant. Therefore we have detected changes in tryptophan metabolism in patients with Cushing's syndrome. However for the following reasons it would be premature to conclude that the observed changes in tryptophan will alter brain 5-HT and so cause depression. Firstly, the effects were small and in the case of free tryptophan not statistically significant. This latter point is important as it is generally accepted that the concentration of free tryptophan regulates brain tryptophan uptake and 5-HT synthesis (Knott and Curzon, 1972; Tagliamonte *et al*, 1973; Curzon and Knott, 1974), although Fernstrom and co-workers (1976) have shown correlations between total tryptophan concentrations in plasma and brain. Secondly, even if a change in free tryptophan were found it could be an effect rather than a cause of depression.

The uptake of tryptophan into the brain is also influenced by plasma concentrations of neutral amino acids (Kiely and Sourkes, 1972; Pardridge, 1977) although these may not be affected in the patients with Cushing's syndrome, since we found normal plasma concentrations of total amino acids. Non-esterified fatty acids displace tryptophan from binding sites on albumin (McMenamy and Oncley, 1958; Curzon and Knott, 1974) but this effect was not measured in our study. To investigate further the triangular relationship between cortisol, tryptophan and depression we have commenced a longitudinal study of patients treated for Cushing's syndrome; although only 6 patients have so far been reassessed at one year there have been consistent increases in plasma total tryptophan following correction of adrenocortical over-activity.

Finally the present study also suggests a new way of examining the role of endorphins in

mental illness. β-endorphin and ACTH may both be derived from a common pro-hormone (Smyth, 1978); patients with Nelson's syndrome secrete exceptionally large quantities of ACTH; they may also secrete large quantities of β-endorphin (Nakai *et al*, 1978). It is therefore important to note that none of the four patients who had been treated for Nelson's syndrome in the present series met our criteria for diagnosing depression.

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HYPERMINERALOCORTICISM WITHOUT EXCESSIVE ALDOSTERONE SECRETION: AN ADRENAL CARCINOMA PRODUCING DEOXYCORTICOSTERONE

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SUMMARY

A 51-year-old female was thought to have Conn's syndrome because she had hypertension, hypokalaemia and low plasma renin activity. The cause was not aldosterone excess, but there was an adrenal cortical carcinoma producing 11-deoxycorticosterone (DOC) in extremely large quantities, with ineffective 11β-steroid hydroxylation. Plasma and urinary aldosterone levels were within the normal range. Blood levels of other steroids including those on the pathways of formation of glucocorticoids and sex steroids were unaffected. The tumour was cultured *in vitro* and shown by high performance liquid chromatography (HPLC) to produce predominantly DOC from tritiated pregnenolone, with no detectable aldosterone, in agreement with the *in vivo* results.

11-deoxycorticosterone (DOC) is a normal, albeit minor, product of the adrenal gland where it is a precursor of corticosterone and aldosterone (Ayres *et al.*, 1960). Excessive serum levels of both DOC and aldosterone cause hypertension, sodium retention, and potassium loss (Kahn *et al.*, 1966; Ross, 1975).

Excessive production of aldosterone by adrenal glands has been recognized since 1954 as a cause of hypertension, hypokalaemia and tetany (Evans & Milne, 1954; Conn, 1955 a, b; Mader & Iseri, 1955; Foye & Feichtmeir, 1955). Suppression of plasma renin activity favours the diagnosis of mineralocorticoid excess, and usually excludes renal artery stenosis, but the two diseases can occur together (Mills *et al.*, 1980). Although primary aldosteronism is rare, there have been several hundred patients reported in the literature including benign and (rarely) malignant tumours (Ross, 1975).

A similar clinical condition can arise from excessive production of DOC, with normal aldosterone levels. However, individual patients with adrenal tumours causing hypermineralocorticism, without excessive production of aldosterone or cortisol, such as those

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reported by Powell-Jackson *et al.* (1972) and Kondo *et al.* (1976) are exceptional. Therefore we present detailed studies of a patient with an adrenal carcinoma producing large amounts of DOC but not excessive aldosterone, and without signs of Cushing's syndrome.

CASE REPORT

Mrs M., aged 51 years was referred to us in June 1980, when she complained of general malaise, nocturia, abdominal pain, and weakness. Hypertension (blood pressure 215/100 mmHg) had been discovered 18 months previously, and when blood pressure was measured she developed tetany. Despite hypotensive therapy (which did not include spironolactone) blood pressure remained elevated. Plasma potassium was 2·9 mmol/l (re-checked) in April 1979 and despite potassium supplements plasma potassium remained low. The past medical history included mild hypertension during a pregnancy at the age of 35 in 1964, menopause at the age of 49, and myocardial infarction at 50 years.

On examination (June 1980) blood pressure was 200/110 mmHg, and the pulse rate was 84/min. The liver was enlarged 6 cm below the right costal margin but no other abdominal masses were palpable. There were no clinical signs of Cushing's syndrome.

She remained hypertensive, blood pressure averaging 180/100 mmHg. Treatment with vasodilators and diuretics was gradually withdrawn, but potassium supplements (180 mmol/day) were continued and plasma potassium was, on average, 2·1 mmol/l. Samples for steroid and other assays were taken under basal conditions and then treatment with spironolactone (Aldactone, Searle) 200 mg/day was commenced. Plasma potassium became normal within 48 h, and it was possible to reduce potassium supplements to 60 mmol/day. To obtain a diagnosis a laparotomy was done on 2 July 1980 and a large adrenal carcinoma with liver metastases was found. No palliative procedure was possible, and the patient deteriorated and died 1 week later.

METHODS

Serum or plasma was stored at −20°C until assayed. Serum DOC (Fraser *et al.*, 1975) and corticosterone (Fraser, unpublished) were measured by radioimmunoassays. Urinary free DOC and total aldosterone (pH1 hydrolysate) were measured by radioimmunoassays by the methods of Cope & Loizou (1973, 1975). Plasma cortisol was measured by fluorimetry (Mattingly, 1962), a method which may measure substances other than cortisol (James *et al.*, 1967). Plasma cortisol was also measured by a specific method using gas liquid chromatography with electron capture detection (Mason & Fraser, 1975). Urinary 17-oxogenic and 17-oxosteroids were measured by conventional methods (Medical Research Council, 1963). Serum FSH, LH and PRL were measured by radioimmunoassays at St Mary's Hospital, Manchester. All steroids not previously mentioned were measured by Dr D. Bu'lock in the Regional Steroid Laboratory, Hope Hospital, Salford. The cross reactions of steroids in radioimmunoassays were negligible. Synacthen (250 μg) was given i.v. and LHRH (100 μg) was given (on another day) and the 60-min cortisol and gonadotrophin values are shown in Table 1.

Tissues from the primary adrenal and secondary hepatic tumours were sent immediately at 0°C to the Ludwig Institute for histological and ultrastructural examination, and for preparation of cell cultures according to previously described methods (Neville &

Table 1. Urinary biochemistry (24 h)

	Patient	Normal range
11-Deoxycorticosterone (pmol)	34 530	42–242
Aldosterone (nmol)	3	14–55
17-oxogenic steroids (μmol)	70	20–60
17-oxosteroids (μmol)	22	15–55
Sodium (mmol)	97	100–250
Potassium (mmol)	117	40–120
Normetadrenaline (μmol)	2	<6

O'Hare, 1978). Steroid biosynthetic activity *in vitro* was then studied by adding trace amounts (1 μCi, 36 ng) tritiated pregnenolone, incubating the culture for 24 h, and separating radiometabolites by reversed phase HPLC (O'Hare *et al.*, 1976). Steroid metabolizing activity was studied before and after addition of both ACTH and dibutyryl cyclic AMP to replicate cultures for 7 days; these conditions cause both quantitative and qualitative changes in steroidogenesis by normal adult human adrenal cells (Neville & O'Hare, 1978).

RESULTS

Biochemistry

Pre-operative blood steroid levels are shown in Fig. 1. The most significant increases were in the metabolic pathway from pregnenolone (15 nmol/l, 1·6 times the normal

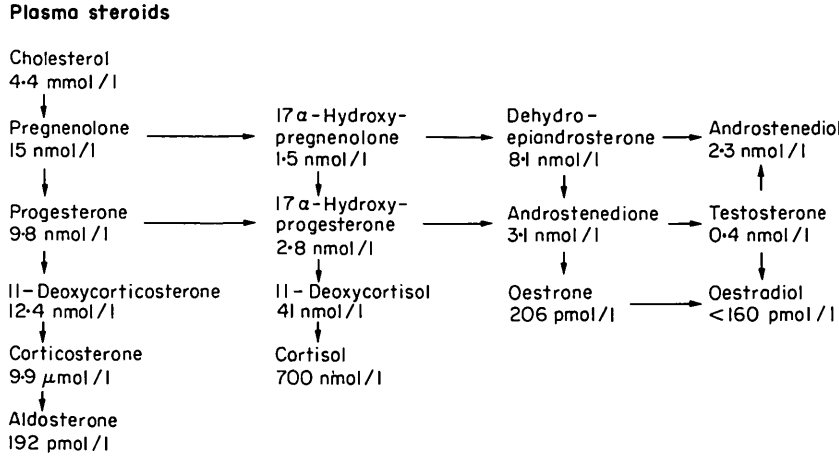


Fig. 1. Plasma steroids, results shown individually. Normal ranges (±2 SD): cholesterol, 3·6–7·2 mmol/l; pregnenolone, 4·1–15·3 nmol/l; progesterone, 0·7–2·7 nmol/l; 11-DOC, 100–500 pmol/l; corticosterone, 2·3–23 μmol/l; aldosterone, 100–500 pmol/l; 17α-hydroxypregnenolone, 1·6–25 nmol/l; 17α-hydroxyprogesterone, 0·1–2·5 nmol/l; 11-deoxycortisol, <35 nmol/l; cortisol 200–600 nmol/l; DHEA, 12–40 nmol/l; androstenedione, 3·6–8·6 nmol/l; oestrone, 117–195 pmol/l; androstenediol, 6–17 nmol/l; testosterone, 0·3–2 nmol/l; oestradiol, <160 pmol/l.

Table 2. Plasma biochemistry

	Patient	Normal range
Sodium (mmol/l)	142	132–144
Potassium (mmol/l)	2·3	3·5–5·0
Chloride (mmol/l)	92	95–105
Renin recumbent (ng/ml/h)	<0·5	1–6
ambulant (ng/ml/h)	1.7	2–9
Aldosterone recumbent (pmol/l)	192	100–500
ambulant (pmol/l)	177	100–500
ACTH 09.00 h ($n=4$) (ng/l)	32	<10–80
Cortisol 24.00 h (nmol/l)		
Fluorimetry ($n=2$)	222	<200
Cortisol 09.00 h (nmol/l)		
Fluorimetry ($n=4$)	652	200–600
Specific assay ($n=1$)	275	200–550
Cortisol response to Synacthen		
Fluorimetry before ($n=2$)	676	200–600
after ($n=2$)	1237	700–1300
LH basal (iu/l)	39	>25 Post-
after LHRH (iu/l)	>50	>50 menopausal
FSH (iu/l)	12	>20 females
SHBG (nmol/l)	30	40–110
PRL (mu/l)	323	<425

Plasma cortisol results shown as mean of several samples. Fluorimetry denotes method of Mattingly (1962); specific assay denotes method of Mason & Fraser (1975).

mean), to progesterone (9·8 nmol/l, 5·8 times the normal mean), and 11-deoxycorticosterone (41 times the normal mean). Corticosterone and aldosterone levels were both slightly less (0·8 and 0·6 times respectively) than the mean normal levels. Both pregnenolone and progesterone were elevated relative to their 17α-hydroxylated products.

Urinary steroid levels are shown in Table 1. There was a large increase in urinary free DOC, whereas urinary total aldosterone was low.

Other blood tests including electrolytes, ACTH and gonadotrophins are shown in Table 2. The Synacthen test was normal, and the gonadotrophin concentrations were normal for a post-menopausal female.

Radiology

Plain antero–posterior radiology of the abdomen showed a mass in the right flank. Ultrasound showed an irregular mass between the liver and the right kidney. An isotope scan suggested metastases in the liver.

Histology

Light microscopy of the biopsy sample taken at surgery showed an adrenocortical carcinoma (Fig. 2). The tumour had wide areas of necrosis, oedema and calcification, and the cells were compact with eosinophilic lipid-poor cytoplasm and some with enlarged,

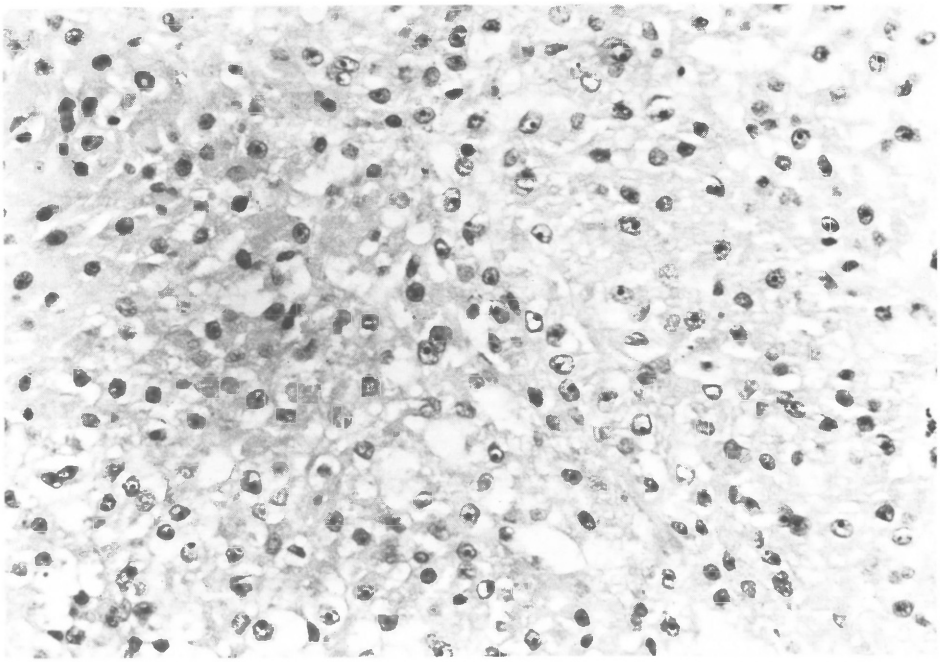


Fig. 2. Light microscopy of right adrenal carcinoma. ×225.

vesicular nuclei. There was evidence of capsular invasion. The appearances were distinct from those of both benign and malignant aldosterone-producing adrenal lesions, but were similar to those producing glucocorticoids or sex hormones (reported by Professor A. Munro Neville). The appearances of the lesions in the liver were consistent with metastases from the primary adrenal tumour. Electron microscopy (Fig. 3), of the primary tumour, showed what is, in our experience, an unusual appearance in adrenal cortical tumours with a marked development of saccules of rough endoplasmic reticulum with dilated cisternae which tended to envelop the mitochondria. The latter showed features typical of steroidogenic cells, including vesicles, and resembled those seen in many types of adrenal tumours (O'Hare *et al.*, 1979).

Biosynthetic studies in vitro

Studies *in vitro* (Fig. 4) showed that when tritiated pregnenolone was added to the cultured cells from the adrenal tumour, both progesterone and DOC were formed. The yields of 17-hydroxycorticosteroids such as 11-deoxycortisol and cortisol were negligible, and neither corticosterone nor aldosterone were detected, showing the absence of effective 11β- and 17α-hydroxylase activity. There were no changes in patterns of (^{3}H) pregnenolone metabolism or morphological responses after chronic (7 days) stimulation with $ACTH_{1-24}$ (1 μg/ml) or separately with dibutyryl cyclic AMP (0·5 mmol/l). Endogenous ultra-violet absorbing steroid production by the cultures was however too low (<1–2 ng/day/10^5 cells) for direct measurement by HPLC. This contrasts with normal adrenal cortex which produces 2–5 μg/day/10^5 cells with ACTH stimulation (Neville & O'Hare, 1978).

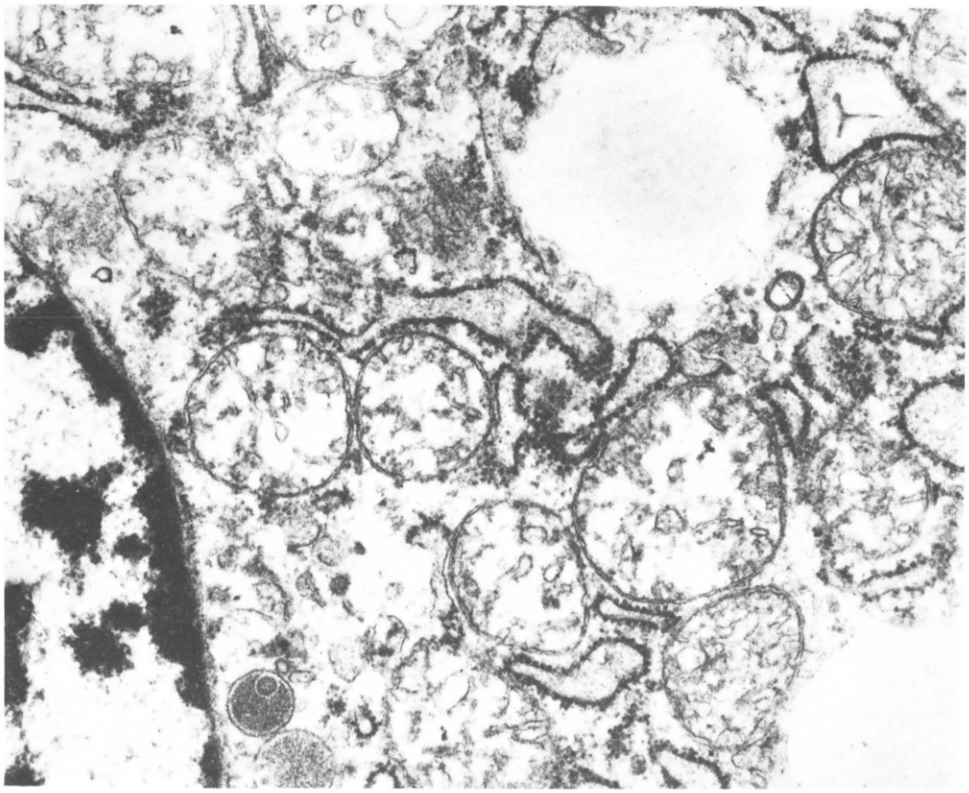


Fig. 3. Electron microscopy of right adrenal carcinoma. ×21 000.

Post-mortem examination

Post-mortem examination revealed a right adrenal tumour weighing 810 g. The weight (12 g) and microscopic appearances, with compact cell changes, of the left adrenal gland were consistent with stress-induced ante-mortem changes in a non-suppressed adrenal gland. The liver weighed 3·5 kg (normal 1·4 kg) and contained large tumour deposits. There were small (< 1 cm diameter) nodules in the lungs. The pituitary fossa and gland were normal. There was generalized atheroma together with enlargement of the left ventricle of the heart. There was no evidence of renal artery stenosis.

DISCUSSION

The clinical presentation with hypertension, hypokalemia and low plasma renin activity and the response of hypertension and hypokalemia to spironolactone in this patient suggested a diagnosis of primary aldosteronism (Conn, 1955b). When Conn *et al.* (1964) reviewed the presenting symptoms of 103 patients with primary aldosteronism they found muscle weakness (73%), polyuria and nocturia (72%), tetany (21%), and fatigue (19%), all of which were experienced by our patient. The increased levels of DOC in plasma and urine with plasma aldosterone concentrations in the normal range, together with *in vitro*

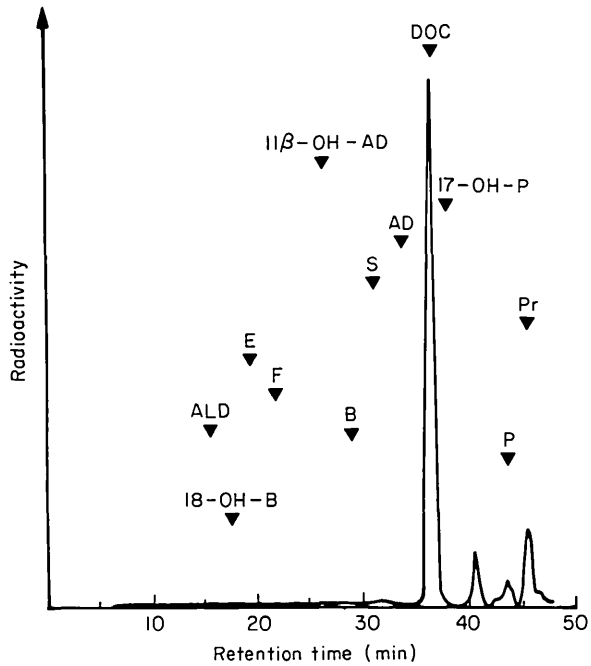


Fig. 4. HPLC scan. Radiometabolites formed from (^{3}H) pregnenolone by culture of adrenal tumour cells from biopsy of primary lesion, separated by reversed-phase HPLC, using a methanol:water gradient. Arrows indicate retention times of standards. AD = androstenedione; ALD = aldosterone; B = corticosterone; DOC = 11-deoxycorticosterone; E = cortisone; F = hydrocortisone; P = progesterone; Pr = pregnenolone; S = 11-Deoxycortisol.

studies, showed that the adrenal tumour in our patient was producing large amounts of DOC. Although DOC is not as potent as aldosterone, when the levels of DOC are greatly elevated, then hypertension with hypokalaemia can occur, confirming the suggestion of Cope & Loizou (1975). There were no signs of Cushing's syndrome in our patient, and the basal cortisol and ACTH levels, the diurnal rhythm of cortisol and the response to Synacthen were all normal. The tumour was correctly localized by the plain radiograph of the right supra-renal region. However, the other scans gave more definite information, including the probability of hepatic metastases. The post-mortem examination confirmed the localization and nature of the adrenal tumour.

The plasma aldosterone concentration was within the normal range, but the urinary excretion of total aldosterone was low. This apparent discrepancy may be due to episodic fluctuations in steroid production by the tumour. The total secretory pattern cannot be calculated from isolated blood levels of steroids, and without additional knowledge of the clearance rates, production rates cannot be deduced. In addition, the low urinary aldosterone excretion may be due to altered hepatic metabolism of aldosterone due to the metastatic tumour tissue.

The light microscopic appearance of tumour was compatible with an origin from the zona fasciculata. If this were true, then the tumour may later have become deficient in the 17α-hydroxylase activity of this part of the adrenal. The other possibility is that the

tumour arose from the zona glomerulosa, and therefore never possessed 17α-hydroxylase activity, but later changed in morphological appearance.

The *in vitro* results showed that the primary adrenal tumour was producing DOC but without significant amounts of aldosterone or cortisol, in agreement with the *in vivo* results. The failure of the tumour cells to respond to ACTH and cyclic AMP *in vitro* is a feature noted in many malignant, as opposed to benign, adrenal tumours (O'Hare *et al.*, 1979).

Adrenal adenomas, and bilateral adrenal hyperplasia with excessive production of aldosterone are rare, although Conn himself had collected 103 cases by 1964. However, malignant lesions of the adrenal causing primarily a syndrome of mineralocorticoid excess are very rare. Thus only twenty-nine cases of carcinomas with good evidence of excessive aldosterone secretion had been reported by 1980 (Neville & O'Hare, 1982); patients with excessive DOC production without concurrent hypercortisolism such as that reported here, are even rarer than this. Powell-Jackson *et al.* (1974) reported a patient similar to our own, with hypertension, hypokalaemia, and excessive secretion of DOC but not of aldosterone, whose symptoms were improved by removal of an adrenal cortical carcinoma, only to recur 4 years later when a metastasis was found in bone. A benign DOC-producing tumour was described by Kondo *et al.* (1976), but their period of follow-up was short. Excessive DOC secretion is not confined to tumours of the adrenal cortex. Thus, Brown *et al.* (1972) studied thirty-one hypertensive patients with normal aldosterone excretion, and found that plasma DOC was persistently moderately raised (range 0·5–2·8 nmol/l, normal 0·1–0·5) in six patients; none of these had adrenal tumours or the ectopic ACTH syndrome in which DOC levels may also be elevated (Brown & Strott, 1973). Isolated DOC excess was also described by Kahn *et al.* (1966) but follow-up details are not available. The urinary excretion of DOC and aldosterone in fifteen patients with Cushing's syndrome was studied by Cassar *et al.* (1980). Very high levels of DOC were found in each of three patients with adrenal carcinoma, all of whom had some clinical and biochemical evidence of Cushing's syndrome. However, our patient did not have Cushing's syndrome clinically or biochemically.

The large size of the primary tumour and the bad prognosis are typical of patients with malignant adrenal tumours (Hutter & Kayhoe, 1966; Kelly *et al.*, 1979). The hopes for the future are that use of the DOC assay will enable the diagnosis to be made earlier, when surgical cure may be possible, and that *in vitro* studies may be developed so that potential anti-tumour drugs can be tested. Clearly, the opportunities are fleeting for studying such interesting but rare patients in life.

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Cushing's Syndrome and Depression—A Prospective Study of 26 Patients

WILLIAM F. KELLY, STUART A. CHECKLEY, DAVID A. BENDER and KEITH MASHITER

Summary: Of 26 patients with active Cushing's syndrome assessed before and at three and 12 months after treatment, 21 had pituitary-dependent disease. Median urinary free cortisol values (per 24 hours) were 680, 180 and 200 nmol at zero, three and 12 months (normal <270 nmol), with significant improvement ($P < 0.001$) at three and 12 months. Depression on the Hamilton rating scale was significantly less at three months ($P < 0.01$) and at 12 months ($P < 0.001$). We have already demonstrated that some patients with Cushing's syndrome have PSE diagnoses of depression and are more depressed than patients with other pituitary tumours. This is the firmest evidence to date that when Cushing's syndrome occurs it commonly causes depressive illness.

Cushing's syndrome and depression were linked in Harvey Cushing's original descriptions (1913; 1932). A *causal* connection, however, has yet to be established, as previous studies have been uncontrolled, qualitative and retrospective (Spillane, 1951; Trethowan and Cobb, 1952; Hurxthal and O'Sullivan, 1959). When we examined a series of patients with various pituitary tumours including some patients with Cushing's syndrome, depression was the main diagnosis to emerge from the analysis of the Present State Examination (PSE), and as measured by the Hamilton rating (Hamilton, 1967), patients with active Cushing's syndrome were significantly more depressed than either those previously successfully treated for Cushing's syndrome or those with other pituitary tumours (Kelly *et al*, 1980). This quantitative and controlled study demonstrated an association between Cushing's syndrome and depression.

We now wished to ascertain whether or not Cushing's syndrome caused depression, and also to measure plasma tryptophan concentrations in a longitudinal study, since we had found slightly lower plasma total tryptophan concentrations in new active cases and lowered tryptophan has been linked with lowered brain serotonin.

Methods

Patients

All patients had biochemically proven Cushing's syndrome and were assessed between 1977 and 1981 during the routine evaluation of their disease. The series was unselected, and the only patients excluded from the study were three who did not speak English and four patients (three with adrenocortical carcinomas) who died within three months of entry.

Active Cushing's syndrome was defined by the increased urinary excretion of free cortisol (Beardwell *et al*, 1968), and was always associated with the presence of the physical signs described by Cushing (1932). There were 7 men (aged 18–70, mean 39 years) and 19 women (aged 19–63, mean 39 years), with a median urinary free cortisol of 680 nmol/24 hours (range 355–4,390). The cause of the syndrome and the methods of treatment are shown in Table I. For three patients, basal urinary free cortisol values were not available but the diagnosis of Cushing's syndrome was in no doubt since plasma cortisol levels were elevated and there was loss of diurnal rhythm of plasma cortisol. The protocol included clinical and biochemical reassessment three and 12 months after therapy. All patients gave informed consent to interview during which the Hamilton rating scores (Hamilton, 1967) were obtained. Fasting blood samples for tryptophan were taken with the precautions described previously (Kelly *et al*, 1980).

Assays

Urinary free cortisol (Beardwell *et al*, 1968) and plasma total and free tryptophan (Denckla and Dewey, 1967) were measured by methods described previously (Kelly *et al*, 1980).

TABLE I

Details of patients: aetiology and treatment

Diagnosis	Total	Bilateral adrenal-ectomy	Unilateral adrenal-ectomy	Pituitary implant	Neurosurgical hypo-physectomy	Metyrapone	Reduction of synacthen
PC	21	8+1*	0	7	2	0+3*	0
Ectopic ACTH	2	1	0	0	0	1	0
Ad. ad.	1	0	1	0	0	0	0
NAH	1	1	0	0	0	0	0
IC	1	0	0	0	0	0	1
	26	10+1	1	7	2	1+3	1

* Also had pituitary irradiation.

PC—pituitary dependent Cushing's disease; Ad ad—adrenal adenoma; NAH—bilateral nodular adrenal hyperplasia; IC—iatrogenic Cushing's syndrome.

Statistics

Tryptophan values were normally distributed and Student's paired t-test was used. Cortisol values were log-transformed. Non-parametric tests were used where appropriate (Siegel, 1956).

Results

All 26 patients improved clinically after treatment with diminution of the physical signs of glucocorticoid excess. There were significant reductions in cortisol excretion ($P < 0.001$, Student's paired t-test) at both three and 12 months (Fig 1). Median values of urinary free cortisol excretion were respectively 680, 180 and 200 nmol/24 hours before, at three months and at 12 months after therapy (normal <270 nmol/24 hours). By three months 17 of 23 (three quarters) had normal cortisol excretion, and this improved to 19 of 23 at 12 months. Urinary cortisol excretion was not available for three patients, but they showed improvements in plasma cortisol.

Comparing ratings obtained before and after treatment (Fig 2), there were significant improvements in depression at three months ($P < 0.01$ Wilcoxon) and at 12 months ($P < 0.001$ Wilcoxon). Only one patient was severely depressed (Hamilton score $27\frac{1}{2}$) before treatment, and although there was substantial improvement, she remained the most severely depressed at 12 months (Fig 2). At three months there were improvements in depression ratings in 20 patients (with deterioration in four, no change in one and no details in one); when reassessed at 12 months there were improvements in depression ratings in 25 patients (the other patient scored zero on all three occasions). Comparing initial ratings with those after therapy, there were no significant correlations between changes in cortisol and depression at either three months (Kendall's test, $T = 0.05$, $n = 22$, $P > 0.10$) or 12 months ($T = -0.12$, $n = 21$, $P > 0.10$). There were no significant correlations between severity of depression and any of these parameters: cortisol excretion, age, plasma free tryptophan or plasma total tryptophan (Kendall's test). Depression was not correlated with the sex of the patient (Mann-Whitney U test).

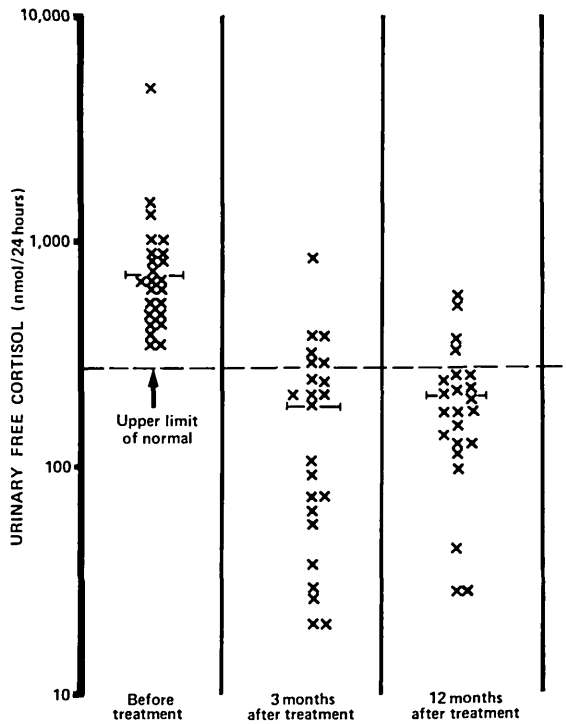


FIG 1.—Urinary free cortisol excretion before and after treatment. Note: Decrease after treatment is significant ($P < 0.001$ at 3 and 12 months).

Plasma tryptophan concentrations and the normal ranges are shown in Table II. Plasma total tryptophan

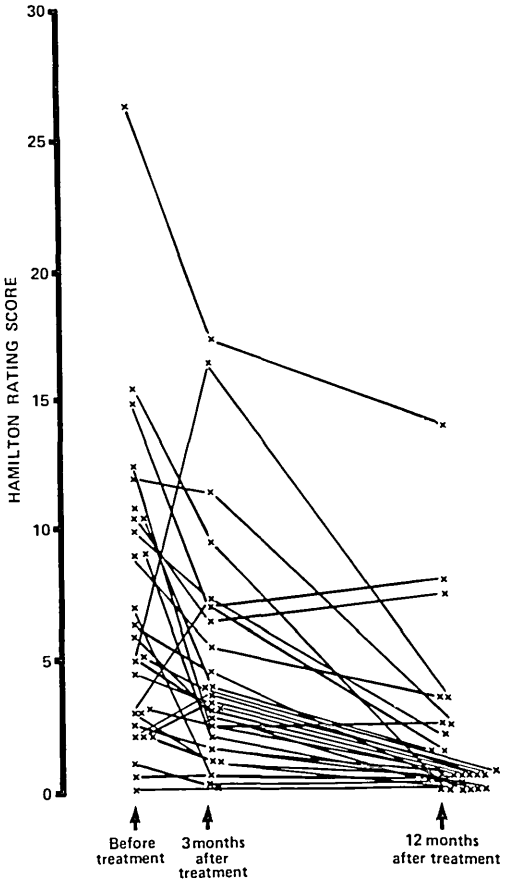


FIG 2.—Depression scores by Hamilton Scale before and after treatment. Note: Decrease after treatment is significant ($P < 0.01$ at 3 months and $P < 0.001$ at 12 months).

concentrations were low before treatment for Cushing's syndrome, and there was a small increase at 12 months, but the changes were not significant (Student's paired t-test). Plasma free tryptophan concentrations were normal throughout the period of the study, and there were no significant changes (Student's paired t-test).

Discussion

We have previously shown that patients with Cushing's syndrome receive PSE diagnoses of depression and are more depressed than are patients with other endocrine diseases, including some with pituitary tumours (Kelly *et al,* 1980). The present prospective and quantitative study additionally shows that correction of the Cushing's syndrome alleviates the associated depression. Two other groups, who did not measure the severity of depression, also reported an alleviation of depression following the successful treatment of Cushing's syndrome (Jeffcoate *et al,* 1979; Cohen, 1980). The simplest explanation for these various observations is that where Cushing's syndrome develops it commonly causes depressive illness.

TABLE II

Plasma total and free tryptophan concentrations

	Number of patients	Mean ± SD	Range	
Total:				
Before treatment	23	56±14	32–86	μmol/l
At 3 months	21	55±15	27–76	
At 12 months	16	63±16	43–83	
	Normal:	85± 8	69–101	
Free:				
Before treatment	23	12± 5	3–24	μmol/l
At 3 months	20	13± 5	6–28	
At 12 months	14	13± 5	6–23	
	Normal:	11± 2	6–15	

No significant change in plasma total or free tryptophan occurred comparing pre-treatment values with those at 3 and 12 months (Student's paired t-test). Normal values from Bender and Bamji (1974).

The evidence that Cushing's syndrome can cause depression suggests an animal model for studying the pathogenesis of depression. Cushing's syndrome can be reproduced in animals in whom the effects of cortisol upon neurotransmission can be studied. If changes are found in animals, then the same changes can be sought in patients with Cushing's syndrome. In this way the pathogenesis of depression can be investigated much as the role of dopamine in the pathogenesis of schizophrenia has been investigated following the description of the amphetamine psychosis (Connell, 1958).

In animals, treatment with cortisol causes an increased activity of the enzyme tryptophan oxygenase (Green and Curzon, 1968). As a result, tryptophan metabolism is diverted along the kynurenine pathway leading to falls in plasma tryptophan concentration and brain tryptophan and serotonin concentrations (Curzon and Green, 1971; Green *et al,* 1975). To test whether or not a similar mechanism might operate in patients with Cushing's syndrome, we earlier measured plasma concentrations of free and total tryptophan in them and found a significantly lower plasma concentration of *total* tryptophan than in the control patients; however, this difference was slight

and no difference was found in free tryptophan (Kelly *et al*, 1980). The present findings are more clearly negative: neither the free nor the total plasma tryptophan concentrations changed significantly as Cushing's syndrome was corrected. It is therefore most unlikely that in this syndrome depression results from a deficiency of tryptophan, and hence of serotonin.

While this study was in progress, Mobley and Sulser (1980) showed that adrenal corticosteroids reduce the sensitivity of receptor-coupled adenylate cyclase in rat brain, a biochemical model of the ß-adrenoceptor. Whether or not similar changes occur in patients can now be tested by measuring adrenoceptors on lymphocytes.

The most important factor in relieving the depression associated with Cushing's syndrome is to remove the primary cause of cortisol excess. In this respect all of the several methods used were effective. In summary there is now good clinical evidence that Cushing's syndrome can cause depression. This finding opens up a new type of animal model with which to investigate the pathogenesis of depression.

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Cushing's Disease Treated by Total Adrenalectomy: Long-term Observations of 43 Patients

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SUMMARY

Forty-three patients were treated by total adrenalectomy for pituitary-dependent Cushing's disease. The median period of observation was 10 years (range one to 20 years). Thirty-eight patients (88 per cent) had rapid and lasting remissions. Of the 38 in remission, 21 became pigmented but without pituitary enlargement, 11 became pigmented with evidence of further pituitary expansion (Nelson's syndrome) and six neither became pigmented nor showed pituitary expansion. Pituitary expansion was associated with high plasma ACTH values, and treatment of pituitary tumours by surgery or radiotherapy gave poor results. However, when compared with alternative methods of treatment, total adrenalectomy for Cushing's disease is still satisfactory for many patients, despite advances in pituitary surgery, and has advantages over 'medical adrenalectomy' with drugs.

INTRODUCTION

The treatment of pituitary-dependent Cushing's disease remains controversial. The most rapid way to achieve remission of the features of glucocorticoid excess is bilateral adrenalectomy, but this carries a significant immediate morbidity and mortality (1, 2) and the long-term risk of developing an invasive pituitary adenoma secreting ACTH. In this article the term Nelson's syndrome defines a patient with pituitary dependent Cushing's disease who had been treated by total adrenalectomy, and who later developed pituitary expansion, with increased plasma concentrations of ACTH (corticotrophin), and increased brown pigmentation of the skin. The syndrome was first reported by Nelson *et al.* in 1958 (3) and has been observed since by others (4–10). By compressing adjacent cranial nerves, expansion of the pituitary gland can cause visual field defects, blindness and diplopia.

Surgery to remove an ACTH-secreting adenoma without damaging other pituitary functions seems the ideal method of treatment but the cure rate of pituitary surgery, and the side effects, are often disappointing (8, 11), possibly due to the presence of multiple microadenomas (12). Medical treatment acting primarily on the adrenal using metyrapone (13), aminoglutethimide (10) and opDDD (14, 15), or on the hypothalamus and pituitary using cyproheptadine (16), have been advocated, but Cushing's disease usually relapses after treatment stops (10, 17). External irradiation (18–20), heavy particle therapy (21) and

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internal irradiation with radioactive implants into the pituitary (22) all have advantages and disadvantages. Since there are many alternative treatments advocated, we report a large series of patients treated by total adrenalectomy, and observed for many years. No patient had prophylactic pituitary irradiation beforehand.

PATIENTS

The medical records of 70 patients with Cushing's syndrome diagnosed during the last 20 years were scrutinized, and Cushing's disease (pituitary-dependent Cushing's syndrome) was found in 56. There were 10 adrenal adenomas, two adrenal carcinomas, and two patients with ectopic ACTH production. The primary treatments given to the 56 patients with Cushing's disease were: bilateral adrenalectomy (48 patients), subtotal adrenalectomy (two patients), pituitary implant with ^{90}yttrium (two patients), surgical hypophysectomy (two patients), and metyrapone with external pituitary irradiation (one patient). Because of old age and only mild manifestations, one patient was not treated. We report details of 43 patients (34 female) treated by surgical removal of both adrenal glands, for whom there was both clinical and biochemical evidence of Cushing's disease, with histology showing either diffuse bilateral hyperplasia or nodular hyperplasia and who were then observed for at least one year. The 43 patients all had the physical signs described by Harvey Cushing in 1932 (23).

METHODS

The biochemical tests used to confirm the diagnosis of pituitary-dependent Cushing's disease are summarized in Table 1. The tests included dexamethasone suppression (24), metyrapone stimulation (25) and absence of diurnal rhythm of plasma cortisol. Urinary 17-oxogenic and 17-oxosteroids were assayed by conventional methods (26). Plasma cortisol was measured by fluorimetry (27) and plasma ACTH by radioimmunoassay (28). The stated concentrations of plasma ACTH before adrenalectomy were the means of several values between 09.00 and

TABLE 1. *Urinary and plasma steroid levels before and after removal of both adrenal glands. Normal ranges under basal conditions are: urinary 17 OS 30–80 μmol/24 hours, 17 OGS 30–70 μmol/24 hours, free cortisol < 270 nmol/24 hours; plasma cortisol 09.00 hours 200–600 nmol/l and at 24.00 hours < 200 nmol/l; plasma ACTH < 80 pg/ml. n = number of patients tested. p values by Student's t-test*

	At diagnosis Median	After adrenalectomy Median	
Urine 24 hour collection			
17 OS μmol	57 ($n = 42$)	19 ($n = 12$)	$p < 0{\cdot}01$
17 OGS μmol:			
Basal	88 ($n = 41$)	60 ($n = 12$)	$p < 0{\cdot}01$
Dexamethasone 2 mg/day	47 ($n = 22$)		
Dexamethasone 8 mg/day	24 ($n = 28$)		
Metyrapone 4·5 g/day	216 ($n = 21$)		
Free Cortisol nmol	548 ($n = 4$)	215 ($n = 7$)	$p < 0{\cdot}05$
Plasma			
Cortisol 24.00 hours nmol/l	560 ($n = 31$)	85 ($n = 1$)	
Cortisol 09.00 hours nmol/l:			
Basal	660 ($n = 33$)	167 ($n = 14$)	$p < 0{\cdot}01$
Dexamethasone 2 mg/day	566 ($n = 13$)	55 ($n = 8$)	
Dexamethasone 8 mg/day	196 ($n = 10$)	—	
ACTH pg/ml	56 ($n = 7$)	239 ($n = 38$)	

11.00 hours, and after adrenalectomy the ACTH concentrations were the means from blood taken at one and two hours after hydrocortisone (20 mg) was given orally at 09.00 hours. At presentation coned lateral and antero-posterior radiographs of the pituitary fossa were obtained and where necessary air encephalograms, and recently, computerized axial tomograms and metrizimide cisternograms were also done to detect upwards extension or the empty sella syndrome. Patients later had computerized tomography scans during follow-up assessments. From 1960 to 1978 adrenalectomy was done by the anterior approach (39 patients) but from 1979 the posterior approach was preferred (four patients).

RESULTS

(a) *Early post-operative period*

There were two deaths occurring at 10 days (pancreatitis and pneumonia) and 42 days (subphrenic abscess, pneumonia and pulmonary embolus). Three other patients developed subphrenic abscesses which recovered after drainage. Three patients were not cured, two achieving partial remissions with recurrence of Cushing's disease within two years. All three were treated subsequently with pituitary irradiation.

TABLE 2. *Long-term observations of 38 patients with Cushing's disease treated by total adrenalectomy. ACTH levels are at latest assessment, but before neurosurgery or irradiation in group C. Replacement therapy has been converted to terms of hydrocortisone equivalents. In normal subjects weight of both adrenal glands is less than 14 g. Urinary steroids have been converted on the assumption that 1 mg is equivalent to 3.3 μmol*

	Group A	Group B	Group C
	Median values		
Number of patients	6	21	11
Increased pigmentation	No	Yes	Yes
Increase in pituitary fossa size after adrenalectomy	No	No	Yes
Age at adrenalectomy (years)	38	33	45
Duration of symptoms before adrenalectomy (years)	2·5	2	5
Pituitary fossa size before adrenalectomy:			
Normal	6	19	10
Enlarged	0	2	1
Urinary steroids (μmol/24 hour) before adrenalectomy			
17 OS	50	63	53
17 OGS	75	86	91
Combined weight of adrenals (g)	15	26	22
Years of observation after adrenalectomy	7	10	11
Plasma ACTH (pg/ml) after adrenalectomy	60	162	>240
Latest replacement therapy (mg/day)			
Hydrocortisone	30	30	35
Fluorocortisone	0·1	0·1	0·1

(b) Long-term observations

Thirty-eight patients had lasting clinical remissions. The remissions were confirmed biochemically in all those patients who were retested (Table 1). During the period after removal of the adrenal glands, the patients were allocated to three groups (Table 2). Six patients had normal skin pigmentation (Group A), 21 patients developed increased pigmentation (Group B) and 11 patients developed increased pigmentation and further pituitary expansion (Nelson's syndrome, Group C). Details of age at the time of diagnosis, duration of symptoms before adrenalectomy and initial investigations are given in Table 2. Thirty-seven of these 38 patients are still alive; one Group C patient died of chronic renal failure 10 years after adrenalectomy.

In Group C, five patients had suprasellar extensions, two with visual field defects. Seven patients in Group C had nine operative attempts to remove pituitary tumours, and six also had radiotherapy to the pituitary. The results of these procedures were poor and ACTH levels have remained elevated in all group C patients.

The plasma ACTH levels when last assessed after adrenalectomy (but before pituitary irradiation or neurosurgery) are shown on Fig. 1. In Group C the interval between adrenalectomy and the detection of further expansion of the pituitary fossa in the 11 patients was from three to 13 years (median six years).

The age at operation of Group C patients (median 45 years) was greater than Group B (median 33 years) and Group A (median 38 years). Comparing Group B with Group C this

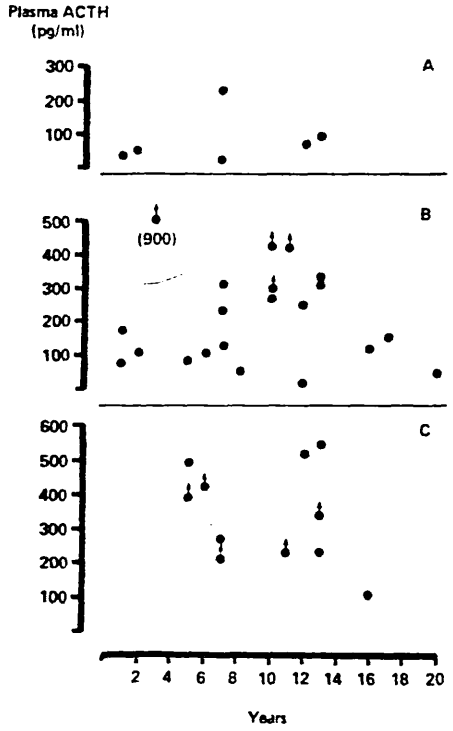


FIG. 1. Plasma ACTH at latest assessment in 38 patients with Cushing's disease treated by total adrenalectomy. Group A = Normal pigmentation. B = increased pigmentation. C = increased pigmentation plus further pituitary expansion (Nelson's syndrome). ACTH levels are before neurosurgery or irradiation in group C. Circles with arrows indicate that ACTH exceeded the value indicated.

TABLE 3. *Cushing's disease. Incidence of abnormal pituitary radiology at presentation and after treatment. ADX = total adrenalectomy; NS = neurosurgery.*

Authors	Radiological evidence of pituitary expansion				Treatment primarily by:
	On presentation		After treatment		
	Number	%	Number	%	
This paper	3/43	7	11/38	29	ADX
Cohen (9)	1/21	5	10/21	48	ADX
Hopwood (7)	1/31	3	8/31	25	ADX
Salassa (4)	8/122	6	13/122	10	
Welbourn (1)	6/60	10	11/43	26	ADX
Nabarro (8)	3/42	7	6/34	18	ADX
Bigos (32)	14/24	58			NS
Tyrell (34)	12/20	60			NS

was not significant ($p > 0{\cdot}18$, Wilcoxon rank sum test). Symptoms were present before operation for longer in Group C patients (median five years) than Group B (median two years) and Group A (median two-and-a-half years). Comparing Group B with Group C this was not significant ($p = 0{\cdot}07$). Plasma ACTH levels were higher in Group C (median > 240 pg/ml) than Group B (median 162 pg/ml) and Group A (median 60 pg/ml). ACTH levels > 240 pg/ml were significantly more common in Group C (10 of 11) compared to Group B (9 of 21) ($p < 0{\cdot}02$, Fisher's exact probability test).

There were no significant differences between the groups in pre-operative urinary steroid excretion, weight of adrenals, or replacement doses of adrenal steroids (Table 2).

DISCUSSION

This is one of the largest series from a single centre of patients treated primarily by adrenalectomy; it may be compared with other series in Table 3. The two early post-operative deaths, two of 43 (< 5 per cent), in our series, may be compared with the figure of 4 per cent quoted by Welbourn *et al.* (1) and 12 per cent quoted by Hasner (2). It should be borne in mind that unwell patients are being subjected to a major surgical procedure. We now prepare patients with metyrapone for several weeks before operation, to reduce the severity of the clinical and biochemical features and aid wound healing. The posterior approach to the adrenals is now used, as recommended for hyperplastic adrenal glands (29), and we are optimistic that operative morbidity and mortality can be reduced further. The rate of remission obtained by total adrenalectomy in this series is very impressive and from a survey of the literature, is achieved more rapidly and reliably than with any other form of treatment. The three patients who did not have lasting clinical remissions may have had ectopic adrenal tissue (30, 31).

The incidence of a pituitary adenoma on radiological grounds at presentation has varied from 3 to 60 per cent in the recent literature (Table 3) and was 7 per cent in our series. These variations probably reflect the different radiological techniques used, and the treatment available. Initially, pituitary adenomas may not be apparent radiologically. Bigos *et al.* (32) reported the results of trans-sphenoidal surgery on 24 patients and confirmed the presence of a tumour detected radiologically in 14. In addition pituitary adenomas were found in seven patients considered to have normal pituitary radiology. Their study suggests that pituitary adenomas may be present at diagnosis in up to 88 per cent of patients with Cushing's disease.

When patients have been treated primarily by total adrenalectomy and observed for several years, pituitary adenomas have been detected with increasing incidence since the original description by Nelson (3). The detection rate of Nelson's syndrome has varied from 10 to 48 per cent in five recent series (Table 3). Some pituitary tumours become apparent many years after adrenalectomy (6, 8)—up to 13 years in our series, and that quoted by Moore *et al.* (6). Prior external irradiation of the pituitary has been given to some patients before adrenalectomy (18), but this has not always prevented Nelson's syndrome (6, 7, 33), although it may have delayed the onset. Analysis of data is complicated by the occurrence of spontaneous pituitary infarction which may cause remission of Nelson's syndrome (8) and the absence of controlled clinical trials assessing the role of pituitary irradiation before adrenalectomy. The increase in pigmentation without evidence of pituitary expansion occurred in 21 of 38 (55 per cent) of our patients (Group B), and it is possible that some of these will eventually develop invasive pituitary adenomas. Our present policy is to review such patients every six months and to maintain a close liaison with the neurosurgeons. In our experience the results of treatment in patients with progressive pituitary expansion (Group C, 11 of 38 or 29 per cent) were disappointing, since in no patient were ACTH levels returned to normal.

Because the primary abnormality in Cushing's disease does not occur in the adrenal, it is reasonable to seek alternative methods of treatment. Cyproheptadine appears to help some patients (16) but not others (35). Metyrapone can restore cortisol levels to normal but increases hirsutism (13) and requires careful monitoring. Metyrapone causes ACTH levels to increase (13) and it may cause further pituitary expansion. Cushing's syndrome usually relapses after withdrawal of metyrapone (10), but this may not always be the case (17). Some patients treated with metyrapone also had external pituitary irradiation which makes analysis of the results difficult (13). Sustained remission of Cushing's disease with *Mitotane* (opDDD) and pituitary irradiation has been claimed (15); out of 36 patients there were 29 clinical and biochemical remissions, but 12 of these 29 relapsed after withdrawing *Mitotane*, so the success rate was only 39 per cent.

It is logical to remove a pituitary adenoma secreting ACTH, leaving normal pituitary tissue, and this has been the aim of several workers. Bigos (32) reviewed trans-sphenoidal microsurgery in 24 patients over a 15-year period. The best results were obtained in patients with a normal radiograph of the sella, in whom a microadenoma could be identified. No tumour was detected in three of 24 patients, so alternative treatment was necessary. None of three patients with significant upwards extension were cured, and two apparent cures relapsed after 10 and 30 months respectively. Tyrell *et al.* (34) cured 17 of 20 patients by trans-sphenoidal resection of pituitary microadenomas, but most needed glucocorticoid replacement and the period of follow up was short, from six months to three-and-a-half-years. Fahlbusch (36) reported on the surgical management of 35 patients with Cushing's disease. Twenty-one were reported to be in remission, with eight failures and six 'undecided', and the eight failures were referred for bilateral adrenalectomy. There are other reports of failure to cure Cushing's disease despite removal of a microadenoma (12) or attempted total hypophysectomy (11). Treatment by implantation of radioactive gold or yttrium seeds gave a 60 per cent cure rate, the best results occurring in patients with normal pituitary radiographs (22); 50 per cent of these patients became hypogonadal, and many required replacement glucocorticoids and thyroxine. Cassar *et al.* (37) report good results of treatment of eight patients with Nelson's syndrome by this implant technique. Heavy particle therapy to the pituitary gland has been used (21) with complete remission reported in about 60 per cent of patients. The equipment is not generally available and about 7 per cent of patients go on to develop cranial nerve palsies or permanent pituitary failure though recent advances in the technique suggest that there may be improvement in the future (38).

In conclusion we report a series of 43 patients with Cushing's disease treated by adrenalectomy and observed for up to 20 years. Clinical remission was achieved in 38 of the 43 patients (88 per cent). Eleven of the 38 patients (29 per cent) in prolonged remission went on to develop expansion of the pituitary fossa. In favour of total adrenalectomy is the guarantee of rapid cure, but against this must be weighed the immediate surgical morbidity, the need for replacement therapy, and risks of later pituitary expansion. In favour of pituitary surgery is the lower early morbidity and mortality, but these must be balanced against the slightly lower cure rate, and the risk of partial or total pituitary failure. Current opinion favours pituitary surgery, but our experience shows that bilateral adrenalectomy is still a satisfactory form of treatment for many patients with Cushing's disease.

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AN EVALUATION OF PLASMA EXCHANGE FOR GRAVES' OPHTHALMOPATHY

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SUMMARY

Eighteen patients with ocular manifestations of Graves' disease were treated by plasma exchange. Detailed clinical, ophthalmological and orthoptic assessments were made including computerized axial tomography and A + B scan ultrasound of the orbits. Seventeen different ocular parameters were separately rated for each patient. The changes recorded were small, statistically insignificant, and no patient was cured of ocular disease. There were no significant correlations between the ocular changes recorded and age, sex, duration of ophthalmic symptoms, the presence of thyroid antibodies, the number of exchanges, or the concurrent administration of azathioprine.

Graves' disease is frequently associated with ophthalmopathy, but this is severe in only about 3% of hyperthyroid patients (Hamilton *et al.*, 1967). The ophthalmopathy is characterized by exophthalmos, diplopia, ophthalmoplegia, chemosis, peri-orbital oedema, lid retraction and lag, corneal exposure and pain (Gorman, 1978; Havard, 1979). The cause of this 'thyroid eye disease' is still uncertain and one theory implicates an exophthalmogenic role for a fragment of thyroid stimulating hormone (Kohn & Winand, 1971); others have suggested that there is a defect in antibody synthesis (Solomon *et al.*, 1977) or in cell mediated immunity (Volpé, 1977) or both (Havard, 1979; Wall *et al.*, 1973). Medical treatment includes ocular lubricants, systemic glucocorticoids, guanethidine eye drops, diuretics and immunotherapy (Gorman, 1978). Surgical treatment may include orbital decompression and reinsertion of eye muscles. Orbital irradiation has also been used (Teng *et al.*, 1980). However, there is no uniformly satisfactory treatment and few patients return to normal. Plasma exchange has been reported to benefit a patient with thyroid eye disease (Dandona *et al.*, 1979a) but this was not confirmed by others (Lewis *et al.*, 1979). The initial reports were limited to single patients and there is increasing evidence for the value of plasma exchange in many other conditions (Anon.,

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1978 and 1980). Therefore we performed a clinical trial of plasma exchange for Graves' ophthalmopathy and now report details of 18 patients.

PATIENTS AND METHODS

Eighteen patients were studied between August 1979 and March 1981 (Table 1). There were 16 females and 2 males. The mean age at plasma exchange was 52·4 years (±SD 12·3; range 35–73 years). The mean body weight of males and females was 80 kg and 59 kg respectively. All patients had Graves' ophthalmopathy with varying degrees of exophthalmos, ophthalmoplegia, diplopia and chemosis. The mean duration of eye symptoms was 19·1 months (range 1–132 months). There were eight patients who had ocular symptoms for 6 months or less. Ocular symptoms preceded, accompanied or succeeded other thyroid symptoms in three, four and 11 patients respectively. The mean duration of other symptoms of thyroid disease was 46·2 months (range 3–228 months). Four patients had pre-tibial myxoedema, and one of these also had digital clubbing (thyroid acropachy). One patient had diabetes mellitus, and one had pernicious anaemia; there was a family history of thyroid disease in the first degree relatives of five patients. Previous treatments for thyrotoxicosis included anti-thyroid drugs (usually carbimazole) in 10 patients, radioactive iodine in six patients and partial thyroidectomy in four patients; some patients had received more than one form of treatment. Two patients were taking thyroxine. By the time of plasma exchange all patients had been rendered clinically and biochemically euthyroid (mean serum thyroxine 106±SD 39 nmol/l, normal range 50–150); just before plasma exchange was started eye symptoms and signs were stable in 15 patients, but there were three (numbers 1, 2 and 3 on Table I) in whom the eye signs were deteriorating.

Plasma exchange was carried out using a Haemonetics 30 cell separator. The mean number of plasma exchanges was 4·4 per patient (range 3 to 11) and at each exchange a mean of 2·52 (±SD 0·59) litres of plasma was removed, and replaced by 5% albumin solution. Plasma exchange was usually done on alternate days, but no exchanges were done at weekends; for example, patient 12 had 11 sessions of plasma exchange over 30 days, and patient 14 had 8 sessions over 17 days. Complications and side effects of plasma exchanges were allergic rash (2 patients), hypotension (3 patients), tiredness (3 patients) and anxiety (2 patients), but generally the procedure was well tolerated. Azathioprine 150 mg/d was given to 13 patients before and during plasma exchange and to another patient afterwards. No patient took glucocorticoids during the period of plasma exchange, but prednisolone was given to eight patients afterwards.

Assessment of the severity of the ocular disease was made clinically and orthoptically. Exophthalmos was measured on a Hertel exophthalmometer. A control series was obtained from 50 patients (36 females) who were in hospital for a variety of medical conditions, but who had no personal or family history of thyroid disease; the mean age of these controls was 60·8 years (±SD 15·6). The 95% confidence limits for measuring exophthalmos were ±1·5 mm. A four point scoring system (0 = normal to + + + = maximum severity) was used to rate puffiness of eyelids, conjunctival chemosis and superficial punctate keratopathy. Accurate measurements were made of the vertical palpebral apertures, and the incompleteness of lid closure. Note was taken of the appearance of the optic discs. The intraocular pressures were measured in the primary position and in attempted upwards gaze. Orthoptic evaluation included a Hess Chart and fields of

Table 1. Details of patients and treatment

Number	Sex	Age (yrs)	Exophthalmos (mm)	Onset of symptoms before plasma exchange (months) Eyes	Other thyroid	Thyroid antibody titre Microsomes	Thyroglobulin	Number of exchanges	Total volume exchanged (litres)	Notes
1	M	56	29	18	8	+6,400	+320	3	5·7	A,B,C,D
2	F	37	24	23	30	−100	−10	4	8·6	A,D
3	F	44	21	3	3	+100	−10	3	8·8	A,D
4	F	46	26	7	20	+400	−10	4	7·6	B,D
5	F	30	25·5	3	132	+4,000,000	+20	7	20·8	B
6	F	42	24	2	13	−10	−10	5	10·1	D
7	F	59	23·5	36	18			8	21·6	
8	M	47	22·5	4	8	−100	−10	3	6·2	D
9	F	65	22	18	96	−100	−10	3	8·1	D
10	F	56	21	16	228	−10	−10	3	8·2	
11	F	68	21	6	6	+25,600	+1,280	3	7·5	D
12	F	35	20	4	6	+400	−10	11	31·4	
13	F	45	20	11	48	−10	−10	3	6·9	D
14	F	73	17·5	35	35	+600	−10	8	21·0	
15	F	62	16·5	21	13	+25,600	−10	3	6·8	D
16	F	67	12	4	8	+6,500,000	+5,120	3	7·8	B, D
17	F	56		1	29	+102,400	−10	3	6·9	D,E
18	F	56		132	132	−100	+320	3	7·7	D,E

Exophthalmos readings stated are mean for both eyes. Mean readings 21·6 ± SD 4·1 mm, $n = 32$ eyes (mean for normal subjects 11·8 ± SD 2·1 mm, $n = 100$ eyes).

Thyroid antibodies positive (+) or negative (−) at the titres shown.

A, eyes deteriorating just before plasma exchange (stable in other patients). B, pretibial myxoedema. C, finger clubbing. D, azathioprine before and during plasma exchange. E, exophthalmos readings not available before exchange; after exchange 16 mm for patient 17 and 16·5 mm for patient 18.

binocular single vision where possible. Enlargement of the extraocular muscles was assessed by computerized axial tomography using horizontal and coronal scans. Assessments of scans were made independently by one of us (RF) and also by an experienced colleague, with the dates of the scans covered. The widths of selected extraocular muscles, usually the medial and inferior recti, were assessed using the Kretz A—Scan ultrasound machine. Assessments were made before and immediately after each session of plasma exchange. Changes were rated as significant as follows: visual acuity at least one line change on Snellen chart, exophthalmos > 1·5 mm change, binocular single vision by measuring area on chart by planimetry, lid and conjunctival changes as 50% or greater change on the four-point scale, intraocular pressure as ⩾2 mm Hg change, Hess chart as overall change, ultrasound as ⩾0·5 microsecond change in the echo representing muscle thickness, and CT scan as change based on a scoring system (0 = normal to + + + = severe enlargement) for each external ocular muscle. Statistical significance of results was assessed by conventional tests (Siegel, 1956).

RESULTS

Results of plasma exchange

Visual acuity improved in 2 patients, from perception of light to counting fingers (patient 1) and from 6/24 to 6/18 (patient 6); no patient deteriorated and for the other 16 patients there were no changes in visual acuity (NS, sign test).

Exophthalmos ranged from 12 to 29 mm (mean 21·6, $n = 32$ eyes) before plasma exchange, and from 12 to 28 mm (mean 20·8) after treatment (NS, Wilcoxon's signed rank test); there were two patients who did not have exophthalmos recorded before plasma exchange; nine eyes improved, 21 were unchanged and two became worse (NS, sign test). For comparison, the exophthalmometer readings in control patients ranged from 8–17 mm (mean 11·8 ± SD 2·1, $n = 100$ eyes $P < 0{\cdot}01$ compared to thyroid patients, Student's t test).

Fields of binocular single vision improved in seven patients, deteriorated in three and were unchanged in one (NS, sign test). Due to strabismus, fields of binocular single vision could not be obtained in seven patients.

Intraocular pressure looking ahead ranged from 10–22 mm Hg (mean 18·1) before plasma exchange, and from 10–24 mm Hg (mean 17·1) afterwards (NS, Wilcoxon); there were improvements in eight and deterioration in two, no changes in three and no details in five patients.

Intraocular pressure looking upwards ranged from 14–32 mm Hg (mean 24·3) before plasma exchange and from 15–26 mm Hg (mean 21·9) afterwards (NS, Wilcoxon); there were improvements in seven patients and two deteriorated.

The optic discs showed less congestion in one patient (number 11) others showing no changes (NS, sign test).

Hess charts improved after plasma exchange in eight patients, deteriorated in two and were unchanged in five (NS, sign test).

Ultrasound showed decrease in size of eye muscles in six patients and increase in two patients after plasma exchange (NS, sign test).

Computerized tomography scanning showed decrease in eye muscle thickness in two patients, increase in one and no change in seven patients after plasma exchange (NS, sign test).

Patients 1, 2 and 3 had deteriorating eye disease just before plasma exchange was done. The greatest clinical response of eye disease occurred in patient 1, who also had pretibial myxoedema and finger clubbing; the improvement in this patient was obtained as follows: visual acuity from perception of light to counting fingers, improvements in all these: fields of binocular single vision, lid puffiness, lid retraction, lid closure, chemosis, and corneal superficial punctate keratosis; intraocular pressure looking ahead improved from 22 to 14 mm Hg, intraocular pressure looking upwards from 22 to 18 mm Hg, improvement in ultrasound from 7·1 to 5·7 microseconds, and there was a decrease in orbital muscle thickness on CT scan; exophthalmos changed from 29 to 28 mm in both eyes; there were no changes in lid lag, palpebral aperture, or optic discs, and a Hess chart was not obtainable. Patient 2 had improvement in fields of binocular single vision, and exophthalmos diminished from 24 to 21 mm. There was however no change in the exophthalmos of patient 3.

The overall response for each parameter was also calculated (Fig. 1). Pretibial myxoedema and finger clubbing were unaltered after plasma exchange. There were no significant correlations between the 17 parameters measured before and after plasma exchange and the age or sex of the patients, the titre of anti-thyroid antibodies, or the concurrent administration of azathioprine (Table 1). Serum immunoglobulins G, A and M measured before plasma exchange were normal; immediately after plasma exchange there were mean reductions by 66, 63 and 64% respectively. Immunoglobulin levels then gradually rose again.

Clinical follow up after plasma exchange

After plasma exchange had been completed, and assessments made, patients were followed up for a mean of 13 months (range 4–29). The mean number of visits for

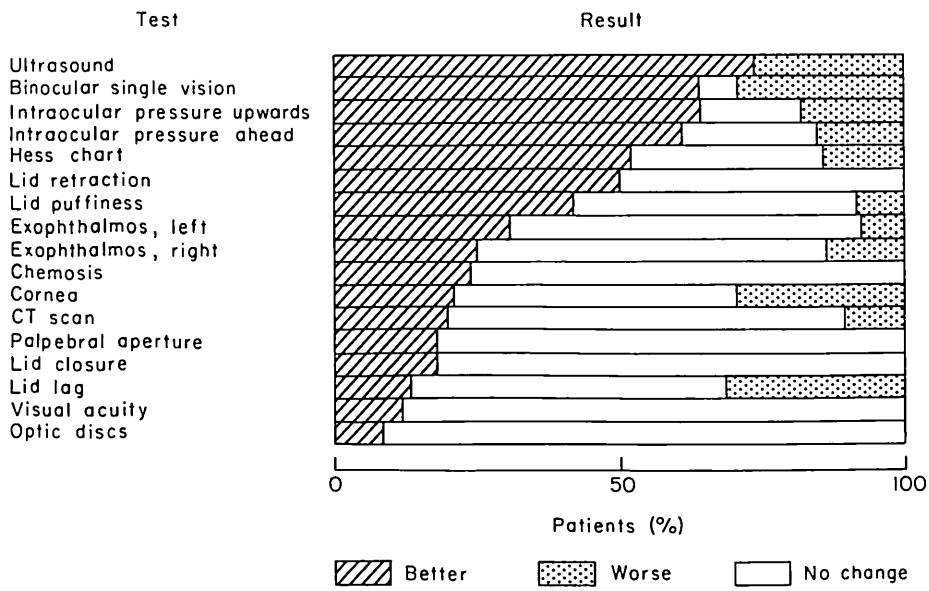


Fig. 1. Ocular assessments after plasma exchange.

reassessment was 9 (range 2–17 visits). The details of treatment and the exophthalmometer readings are shown in Table 2.

Prednisolone up to 80 mg/day was given to eight patients, all of whom concurrently received azathioprine. Five of these eight patients had subjective improvement in ocular symptoms when taking high doses of prednisolone, but improvement in exophthalmos of 2 mm. or more occurred in only two patients (numbers 6 and 11). Side effects of steroids were weight gain (mean of 8 kg in five patients), exacerbation of peptic ulcer (two patients) and diabetes mellitus (one patient); two patients (numbers 8 and 17) are still taking prednisolone, and the doses that produce symptomatic benefit also cause signs of Cushing's syndrome. Three patients refused to take prednisolone because of potential side effects.

Azathioprine 150 mg/day was given to 14 patients, eight of whom concurrently had prednisolone (see above). There were no significant changes in the eye disease of the six

Table 2. Follow up details after plasma exchange

Treatment	Number of patients	Exophthalmometer reading (mm) mean ± SD	
		After plasma exchange	Latest
All patients	18	19·0 ± 2·7	19·6 ± 2·7
Prednisolone	8	19·3 ± 2·2	20·2 ± 2·4
No prednisolone	9	18·7 ± 3·0	19·6 ± 3·2
Azathioprine	14	19·5 ± 2·5	19·8 ± 2·8
No azathioprine	3	16·8 ± 2·4	18·5 ± 2·0

Latest assessment made 4–29 months (mean 13 months) after plasma exchange.

Measurements were both before and after plasma exchange in patients 1–16 by JN. Measurements were made after plasma exchange to latest follow up in all 18 patients by WK.

Patient 15 treated by orbital decompression; patients 8 and 17 still taking prednisolone; patient 1 still taking azathioprine.

No changes are statistically significant (Student's *t* test & Wilcoxon signed rank test).

patients taking azathioprine alone. There was a significant increase in the red cell mean corpuscular volume in patients taking azathioprine (from 90 to 97 cubic microns, normal range 80–97, $P < 0{\cdot}05$, Student's *t* test).

Surgical treatment was as follows: patient 15 had orbital decompression which decreased exophthalmos by 2 mm. Patients 7 and 9 are awaiting orbital decompression operations. Patients 9, 13 and 18 have had re-insertion procedures on eye muscles, and patients 4 and 9 have had tarsorrhaphies.

The results in Table 2 show a small overall increase in exophthalmos from 19·0 ± SD 2·7 mm after plasma exchange to 19·6 ± SD 2·7 mm (NS, Wilcoxon) at latest assessment in the

18 patients. There were no significant changes in the groups of patients treated with or without prednisolone or azathioprine.

DISCUSSION

All our patients had thyroid eye disease, but there was a striking variability in the clinical history, the physical findings and the thyroid antibody titres. At the time of plasma exchange all patients were euthyroid. Most of our patients had severe Graves' ophthalmopathy, since the protrusion of eyes exceeded that in control subjects by 9·8 mm (i.e. difference between mean values of 21·6 and 11·8 mm respectively). For comparison, the excess protrusion of eyes of patients with Graves' disease in a large series was only 2·7 mm (Amino *et al.*, 1980). The clinical response to plasma exchange was variable and was usually small. Improvement in visual acuity which occurred in two of our patients has not previously been reported. The improvements in exophthalmos in our patients were small, and were not statistically significant. A decrease of 2 mm in exophthalmos is due to a diminution of orbital volume by 1·3 ml, a change of only 5%, assuming an orbital volume of 26·1 ml (Rundle & Pochin, 1944). Improvements in exophthalmos have been reported after plasma exchange (Dandona *et al.*, 1979a,b), but others have reported no change (Lewis *et al.*, 1979). Improvements in areas of fields of binocular single vision, which occurred in some of our patients, have not previously been reported after plasma exchange.

The mean decrease in intraocular pressure in our patients was not significant, although others noted a temporary reduction in one patient (Lewis *et al.*, 1979). The changes in the size of eye muscles assessed by ultrasound and computerized tomography scans were small. These techniques were difficult to reproduce and were mainly useful to confirm the diagnosis of Graves' ophthalmopathy by excluding other causes of exophthalmos (Fledelius & Gyldensted, 1978). Clinical assessment of patients, although valuable, is subjective. To make clinical assessments as accurate as possible we used the same ophthalmologist, orthoptist and endocrinologist for all patients. The most useful and reproducible objective parameters were measurements of exophthalmos and intraocular pressure. Fields of binocular single vision were also valuable, but could only be assessed in two-thirds of patients.

Assessment of Graves' ophthalmopathy has been made by others using an ophthalmopathy index (Teng *et al.*, 1980; Werner, 1969); since we measured 17 different parameters, which is more than previous workers have used, we devised our own rating scheme (Fig. 1). The 17 parameters were not all independent, and some would be related measurements of the same basic abnormality. The ratings obtained were both objective and clinically useful, and usually agreed with the subjective experiences of the patients. The only comparable series of patients treated by plasma exchange showed improvement in four and no change in three of seven patients (Dandona *et al.*, 1979b). Unlike these workers, we found no correlation between the ophthalmic changes after plasma exchange and the duration of symptoms. The reason for using plasma exchange is the removal of circulating toxic substances, and there is some evidence that these are immunoglobulins (Gorman, 1978). We demonstrated a mean reduction after each plasma exchange by two-thirds in IgG, A and M. Immunosuppression delayed this subsequent rise in immunoglobulin, and was associated with clinical improvement in one patient (Dandona *et al.*, 1979a).

Glinoer and co-workers (1981) reported no changes in thyroid stimulating immunoglo-

bulins or exophthalmogenic immunoglobulins in two patients treated by plasma exchange; in both patients, however, there were improvements in ocular symptoms described as 'spectacular and rapid', but no objective measurements are stated (Glinoer *et al.*, 1981). There were no changes in pretibial myxoedema in our patients, in agreement with Lewis *et al.*, 1979.

There is no uniformly satisfactory medical treatment for Graves' ophthalmopathy. Prednisolone in large doses was effective in reducing subjective symptoms; however, the objective benefits were small, the side effects were considerable, and on reducing the dose there was worsening of the ophthalmopathy. These benefits and problems with high doses of glucocorticosteroids have been noted by others (Hoffenberg and Jackson, 1958; Wall *et al.*, 1981). We found azathioprine alone to be ineffective, in agreement with Burrows *et al.*, 1970, and in contrast to the report of Wall *et al.*, 1973. Plasma exchange may have avoided the need for urgent surgical decompression in three of our patients with deteriorating eye disease. The greatest clinical benefit occurred in a patient who had thyroid acropachy. A method of predicting which patients will benefit from plasma exchange would be valuable, and further studies are needed. It is not known whether plasma exchange alters the natural history of Graves' ophthalmopathy, but this seems unlikely in theory, unless plasma exchange is combined with long-term immunotherapy, which has substantial disadvantages. Our follow up data (Table 2) deals with small numbers of patients treated in several different ways, and there is no treatment that emerges as clearly superior. Therefore, since plasma exchange is expensive, potentially hazardous, and relatively ineffective, we recommend that it should be considered in patients with deteriorating eye signs only if conventional medical treatment, including high dose glucorticosteroids, has failed. We conclude that there is no treatment yet available which is simple, safe and effective for this enigmatic disease.

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