results when the initial urinary steroid excretion (17-KGS, 17-OHCS) is low. The response may be negative in patients with myxœdema, liver disease or pregnancy or when certain drugs are given such as œstrogens, anabolic steroids or chlorpromazine. Further, because of the marked diurnal sensitivity to metyrapone administration it is most important that a suitable dose be given at midnight and at 4 a.m. or a false negative result may be obtained.

Insulin hypoglycæmia is of great value in testing the hypothalamic-pituitary-adrenal axis but it must be carried out with due attention to its limitations. It is important that the fasting plasma glucose is reduced to at least 40% of its initial value within twenty to thirty minutes of the administration of the insulin. Hypoglycæmia of less intensity may fail to elicit a response. Patients with obesity and Cushing's disease may be unresponsive as are patients who have previously received glucocorticoids. The test must be carried out under skilled medical supervision and otherwise is unsuitable as a screening procedure.

Lysine-8-vasopressin administration is a useful test of pituitary function and is best carried out by intramuscular administration of 10 units of the synthetic peptide. The test should be performed in the afternoon rather than in the morning because of the greater sensitivity at this time. False negative responses are found sometimes without apparent explanation but often when patients have been given glucocorticoids before. The test is not without risk and should not be carried out on patients suspected of coronary insufficiency.

Dr Barbara E Clayton
(Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London)

Assessment of Pituitary-adrenal Function in Children

During infancy marked changes occur in the adrenal gland. Involution of the fœtal cortex and progressive development of the adult type of cortical tissue are associated with changing patterns in steroid secretion.

The response of the 'normal' child to adrenocorticotrophic hormone and the measurement of his cortisol production rate have been reasonably well standardized. These tests can be used to investigate pathological conditions.

The use of the metyrapone test in children has been evaluated, and it has been concluded that it is unsatisfactory.

The use of pyrogen and lysine vasopressin to stimulate the pituitary-adrenal axis will be discussed.

Dr M Friedman
(Pædiatric Department, University College Hospital, London)
and
Dr F C Greenwood
(Division of Chemistry & Biochemistry, Imperial Cancer Research Fund, London)

The Effects of Prolonged ACTH or Corticosteroid Therapy in Children on Growth and on Pituitary-adrenal and Pituitary Function

The results of a study comparing the effects of long-term corticosteroids, a combination of corticosteroids and ACTH, and ACTH alone on the growth velocity of children is described. Growth velocity is decreased by corticosteroids leading to stunting of growth whereas ACTH, in sufficient doses to control the signs and symptoms of the disease being treated, increases the growth velocity.

The plasma cortisol response to insulin-induced hypoglycæmia has been investigated in a group of normal adults, patients on long-term steroids and children on long-term ACTH: (*a*) Only 3 of 24 patients on long-term corticosteroids had a normal plasma cortisol response to intravenous insulin; the response obtained is dose dependent. (*b*) Twelve of 13 children on long-term ACTH gave a normal response in plasma cortisol following intravenous insulin; previous steroid therapy affected the maximum level of plasma cortisol attained after insulin. From this study we conclude that ACTH does not suppress the pituitary-adrenal axis to the same extent as long-term corticosteroids. Anabolic adrenal steroids which are suppressed on corticosteroid therapy may be secreted on ACTH therapy.

The plasma growth hormone response to insulin-induced hypoglycæmia has been studied in a group of normal adults, patients on long-term corticosteroids and patients on ACTH. (*a*) Corticosteroids inhibit the plasma growth hormone response and the effect is partly dose dependent. (*b*) Children on long-term ACTH have a plasma growth hormone response which falls within the normal adult range. (*c*) The growth hormone response is independent of the cortisol response to insulin induced hypoglycæmia. (*d*) ACTH *per se* does not stimulate growth hormone secretion. The difference in growth hormone response to insulin-induced hypoglycæmia may be a factor in accounting for the difference in growth velocity observed between the groups treated with ACTH and with corticosteroids.

A radioimmunological method was used to detect antibodies to porcine ACTH in children on long-term therapy with porcine ACTH. Thirteen of 19 children had detectable antibodies to porcine

ACTH and none was detected in normal children. The specificity of the antisera was directed to the species-specific portion of the porcine ACTH molecule. The presence of circulating antibodies was not associated with resistance to ACTH therapy, allergy or hypersensitivity reactions. There was no correlation between the duration of ACTH therapy, the total dose of ACTH given and the antibody titres obtained. The adrenal responses to pharmacological doses of porcine ACTH or of the pituitary-adrenal axis to intravenous insulin was not related to antibody titre. Thus the development of antibodies to ACTH therapy is variable and without clinical significance.

Dr M Hartog, Dr G F Joplin, Dr K Fotherby, Dr D Mattingly and Professor T Russell Fraser
(Departments of Medicine and Steroid Biochemistry, Royal Postgraduate Medical School of London)

The Assessment of Patients with Cushing's Syndrome before and after Pituitary Implantation

Results of measurements of urinary 17-OGS and plasma free 11-OHCS in 43 patients with Cushing's syndrome (in 6 due to an adrenal tumour) were presented. Abnormally high values for the midnight plasma free 11-OHCS and failure of normal suppression of the urinary 17-OGS with dexamethasone 2 mg/day were found in all the patients. Two patients with pituitary-dependent Cushing's syndrome failed to show the expected fall of urinary 17-OGS with dexamethasone 8 mg/day, and one other patient failed to show a rise of urinary 17-OGS with metyrapone given in a dose of 500 mg three-hourly. The patients included 10 with overt pituitary tumours (on either clinical or radiological grounds) whose preoperative corticosteroid measurements were no different from those of the other patients with pituitary-dependent Cushing's syndrome.

Thirty-six of the patients with test evidence of pituitary-dependence were treated by pituitary implantation of radioactive sources (usually ^{90}Y). Post-operative assessment showed that some of the patients, who had been judged to have a satisfactory remission, still had abnormally elevated values for the midnight plasma free 11-OHCS and an abnormal diurnal rhythm. In all the patients who sustained a satisfactory remission, the response to metyrapone was blunted with no patient showing a rise of urinary 17-OGS of more than 10 mg/24 hours. By contrast the urinary 17-OGS rose by more than 10 mg/24 hours in the majority of the patients who sustained only a partial remission or who showed no improvement following the operation.

Dr R L Ney, Dr D N Orth and Dr G W Liddle
(Vanderbilt University, Nashville, Tennessee, USA)

Evaluation of Pituitary-adrenal Function in Man

Pituitary ACTH secretion in normal man is governed by three known variables: circadian periodicity, feed-back inhibition by cortisol, and stress. Evaluation of the first two of these variables has proved useful in the diagnosis of disorders of pituitary-adrenal function. In Addison's disease, low cortisol production results in high plasma ACTH concentrations; circadian rhythmicity in ACTH levels is maintained. ACTH levels are normal or high in Cushing's disease, but this occurs in spite of increased cortisol production indicating an abnormality in feed-back control of pituitary ACTH; in addition, normal circadian rhythmicity in plasma ACTH is lost. Plasma ACTH concentrations are decreased in Cushing's syndrome due to adrenal neoplasms as a result of feed-back inhibition of pituitary ACTH; circadian rhythmicity in plasma cortisol is not present, but this results from autonomous cortisol production by the tumour. When an adrenal neoplasm is removed, plasma ACTH and cortisol initially are decreased. After several months, plasma ACTH increases to supranormal values and demonstrates circadian rhythmicity. However, adrenal responsiveness is subnormal, resulting in low plasma cortisol values, thus resembling the physiological abnormalities in Addison's disease. After plasma ACTH concentrations have remained elevated for several months, adrenal responsiveness is restored to normal, leading finally to normal plasma cortisol and ACTH levels with normal circadian rhythmicity of each.