(5) Iproniazid, like ACTH, inhibits the adrenocortical response to only selected stimuli. The stimuli largely differ from the ones inhibited by ACTH. The corticosteroid sensitivity of a stimulus is not relevant to its sensitivity to either ACTH or iproniazid.
(6) The adrenocortical system is profoundly affected by its own recent past history. Some but not all stimuli that provoke corticosteroid-sensitive responses, when applied alone, become either less sensitive or completely refractory to corticosteroids within two hours after a prior response of the adrenocortical system to stimuli arriving over a corticosteroid-sensitive pathway.

Dr J R Hodges
(*Department of Pharmacology, Royal Free Hospital Medical School, London*)

The Influence of Corticosteroids on the Stress-induced Release of Corticotrophin

It is still widely believed that a negative feed-back mechanism involving the blood corticosteroid concentration is of major importance in regulating the release of corticotrophin from the adenohypophysis. Experiments were performed in which blood and pituitary ACTH and plasma corticosterone changes in adrenalectomized rats were studied before and after stress with and without replacement therapy with corticosteroids. The results provide evidence that the corticoids influence the rate at which ACTH is synthesized and stored in the pituitary gland. They appear to exclude the possibility that the release of corticotrophin in response to stress is initiated either by a fall in the corticosteroid concentration in the blood or by resetting at a higher level of the blood corticosteroid concentration necessary to inhibit the release of the trophic hormone. Nevertheless the corticosteroids appear to play some part in regulating corticotrophin secretion but their mode and site of action remain obscure.

Dr H S Lipscomb and Dr B V Critchlow
(*Baylor University College of Medicine, Houston, Texas, USA*)

A Study of Compensatory Adrenal Hypertrophy and Hyperfunction

To test whether compensatory adrenal responses depend on increased ACTH secretion, 80 male rats were hypophysectomized, subjected to removal or sham-removal of left adrenals, and treated daily for nine days with 1 or 2 units of ACTH (ACTHar-Gel). On day 10, fifteen minutes following an intravenous challenge dose of 1 mU of ACTH (USP Ref Std), plasma was collected for corticosterone determination and adrenals weighed. In 3 of 4 experiments, right adrenals of rats with one adrenal were significantly heavier than those of rats with two adrenals. In all 4 experiments, rats with one adrenal showed steroid responses to the challenge dose of ACTH that were 65-100% of those observed in rats with two adrenals. This compensation in secretory response is not dependent upon the ten days following removal of one adrenal: in recent experiments it occurred five hours after left adrenalectomy in rats that were hypophysectomized and treated with ACTH for nine days, as well as in rats that were hypophysectomized and left adrenalectomized five hours prior to the challenge dose of ACTH.

In more recent experiments, hypophysectomized rats were given acute infusions of maximal and submaximal doses of ACTH with measurement of peripheral plasma corticosterone at ten-minute intervals. Maximal or submaximal levels of plasma corticosterone so obtained were sustained by continuing infusion, and the animals were then subjected to acute removal of one adrenal. As predicted, animals with both adrenals maximally stimulated showed an (approximate) 50% decrease in peripheral plasma steroid levels, while animals submaximally stimulated showed no decrease in steroid levels in peripheral plasma. Finally, we have observed in the same system, when the left adrenal vein is cannulated and steroids measured directly, that abrupt removal of the right adrenal from an animal submaximally stimulated leads to an immediate (approximate) doubling of steroid output from the remaining adrenal. These data suggest that the amount of adrenal cortical tissue available conditions the response per unit of cortical tissue to ACTH, that the adrenal cortical cell is capable of recognizing and binding and/or inactivating the ACTH molecule, and that compensatory responses may thus occur in the absence of a reflex increase in secretion of ACTH.

Dr Ivor H Mills
(*Department of Investigative Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge*)

Control of Adrenal Precursors of Urinary 17-Oxosteroids

It has been shown that the urinary 17-oxosteroid response to ACTH depends upon the age of the patient who is studied. In children more than 3 weeks old there is a very poor 17-oxosteroid response. As puberty approaches this response to a standard dose of ACTH steadily rises until the

adult pattern is established. If in the adult the pituitary is removed the 17-oxosteroid response to ACTH returns to that characteristic of the prepubertal child. In women with hirsutism which is not due to a tumour of the adrenal or ovary the 17-oxosteroid response to ACTH is usually greater than normal. The same applies to some men who have lost their Leydig cell function. The reverse is true in patients with delayed puberty and women with testosterone-secreting tumours. These facts suggest that the adrenal precursors of urinary 17-oxosteroids are controlled by a hormone other than ACTH and that there is integration in the overall production of some precursors from both adrenal and gonad. There is suggestive evidence that the human pituitary contains a factor which potentiates adrenal 17-oxosteroid synthesis.

Dr J W Dobbie, Dr A M Mackay and Professor T Symington
(*University Department of Pathology, Glasgow Royal Infirmary*)

The Structure and Functional Zonation of the Human Adrenal Cortex

Adrenal morphology and vasculature were studied by reconstruction models, microangiography and electron microscopy. The adrenal can be divided into head, body and tail regions. In each region the characteristic longitudinal muscle bundles of the venous system have distinct arrangements. Emissary veins linking the central and capsular venous system provide an alternative route for the venous effluent. Electron microscopy reveals variations in mitochondria, lipid (which may be free or membrane-bound), endoplasmic reticulum and lysosome-like particles. The complex cortical vasculature may be of significance in controlling the rate of ACTH presentation in the interface zone to certain cells which show special ultrastructural features.

Dr J K Grant, Dr K Griffiths and Miss Margaret Lowe
(*Department of Steroid Biochemistry, University of Glasgow*)

Biochemical Investigations of the Actions of Corticotrophins on the Adrenal Cortex

Results of our early experiments with adrenal glands from human subjects suggested that natural corticotrophin of bovine origin, *in vitro*, influences the amount of secretion of steroids from the cells of the zona fasciculata to a greater extent than that from other cells. Further investigations suggested that cells lying in the border between the fascicular and reticular zones are particularly sensitive to this corticotrophin administered *in vivo*. Of four NADP-linked dehydrogenases in the adrenal cortex studied *in vitro*, only glucose-6-phosphate dehydrogenase showed a marked increase in amount or activity after corticotrophin administration *in vivo*. The increase does not parallel the concomitant increase in weight of the gland. The enzyme activity is distributed uniformly in the 'resting' gland but, after corticotrophin administration, shows a marked increase in the same 'border zone'. By application of the more refined microchemical techniques of Glick, we have further shown a similar regional distribution of increased steroid 11β-hydroxylation in response to corticotrophin in the adrenal cortex of the rat. It is an open question whether increases in RNA which follow corticotrophin administration are associated with steroid production *per se* or tissue hyperplasia or both. Our results offer some evidence that at some stage at least the two processes may not be associated.

In recent experiments, the effect on the adrenal cortex of the synthetic β^{1-24} ACTH (Synacthen) has been studied. Synacthen was administered prior to the second stage of bilateral adrenalectomy. The patients, women with carcinoma of the breast, had previously had pituitary function destroyed by yttrium implants. Satisfactory adrenal gland growth observed with the synthetic corticotrophin suggests that postulation of a separate adrenal growth factor is unnecessary.

Steroid biosynthesis has been investigated *in vitro* in greater detail than formerly, using the severely atrophic and Synacthen-stimulated adrenal glands from the hypophysectomized patients. The results confirm and extend our earlier findings.

Dr P A Desaulles and Dr W Rittel
(*Ciba Limited, Basle, Switzerland*)

Adrenocorticotrophic Activity of Synthetic Peptide Sequences Related to ACTH

The steroidogenic properties of two derivatives of β-corticotrophin-(1–24)-tetracosa peptide (tetracosactide), namely D-Ser^1, β^{1-24}-corticotrophin and D-Ser^1, 17, 18-di-orn-β^{1-24}-corticotrophin, have been investigated in comparison with tetracosactide. The melanophore-expanding properties of the three substances have also been studied *in*