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THE ADRENAL CORTEX AND HYPERTENSION: SOME OBSERVATIONS ON A POSSIBLE ROLE FOR MINERALOCORTICOIDS OTHER THAN ALDOSTERONE

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SUMMARY

Mineralocorticoids such as 11-deoxycorticosterone, corticosterone and their 18-hydroxy derivatives affect electrolyte metabolism but, unlike aldosterone, their plasma concentrations respond mainly to ACTH secretion and, with the exception of 18-hydroxycorticosterone, are insensitive to changes in electrolyte balance. ACTH, by stimulating secretion of these and possibly other adrenocortical hormones, may cause sodium retention and potassium loss inappropriate to the prevailing body electrolyte status and thus affect blood pressure. The possibility that this mechanism may be important in human hypertension is examined.

INTRODUCTION

Although the adrenal cortex has been implicated in hypertension, it can be identified as a cause in only a small fraction of the hypertensive population. These cases are usually associated with sodium retention and potassium loss occurring as a result of excessive secretion of corticosteroids with mineralocorticoid activity. The most potent of these is aldosterone and its importance in electrolyte metabolism and in determining blood pressure in health and disease has been fully discussed [1–4]. However, the adrenal cortex secretes a variety of other steroids, notably 11-deoxycorticosterone (DOC) and corticosterone, which although considerably less potent weight for weight than aldosterone, also cause sodium retention and loss of potassium. The 18-hydroxylated derivatives of these compounds have mild mineralocorticoid activity [5, 6]. Although less potent than aldosterone, the importance of these minor mineralocorticoids may lie in the fact that their secretion rates are controlled by different influences from that of aldosterone. While aldosterone secretion rate depends largely on sodium status, probably mediated by changes in the renin-angiotensin system, those of the minor mineralocorticoids, like other corticosteroids originating mainly from the zana fasciculata, are controlled by ACTH secretion from the anterior pituitary. Thus, although these compounds may have a profound effect on the electrolyte status of the subject their secretion rates are largely unresponsive to the prevailing electrolyte status. It is theoretically possible, therefore, for such compounds to exert an inappropriate mineralocorticoid effect and this type of effect may predispose to hypertension. Whether such a hypothesis is tenable is briefly discussed below.

Mineralocorticoids and hypertension

In considering the role of mineralocorticoids, it is necessary to show that they are capable of increasing blood pressure and maintaining hypertension. The dose rates required and the duration of exposure necessary must also be examined.

Study 1—hypertensive effect of mineralocorticoids in animals

Administration of DOCA to unilaterally nephrectomised rats, particularly when these animals are given saline to drink, causes rapid increases in blood pressure and malignant hypertension eventually occurs [7]. Such was the case when a group of rats given 12.5 mg of DOC pivalate (i.m.) three times per week was compared with a control sham-injected group [8]. Blood pressure was significantly higher in the experimental group at two weeks and malignant changes were apparent when the animals were killed after eight weeks. Plasma DOC concentrations were measured in the injected and control rats at intervals between consecutive injections. No change was seen in the control group but in the experimental animals plasma DOC levels rose to a maximum 200–300% above basal between 4–6 h after injection and had fallen to normal control levels by 12 h at the latest (Fig. 1). Thus, plasma DOC levels remained abnormal for not more than 25% of the total time of the experiment but blood pressure continued to rise steadily. It would appear that mineralocorticoid secretion need only be mildly and intermittently raised to cause hypertension.

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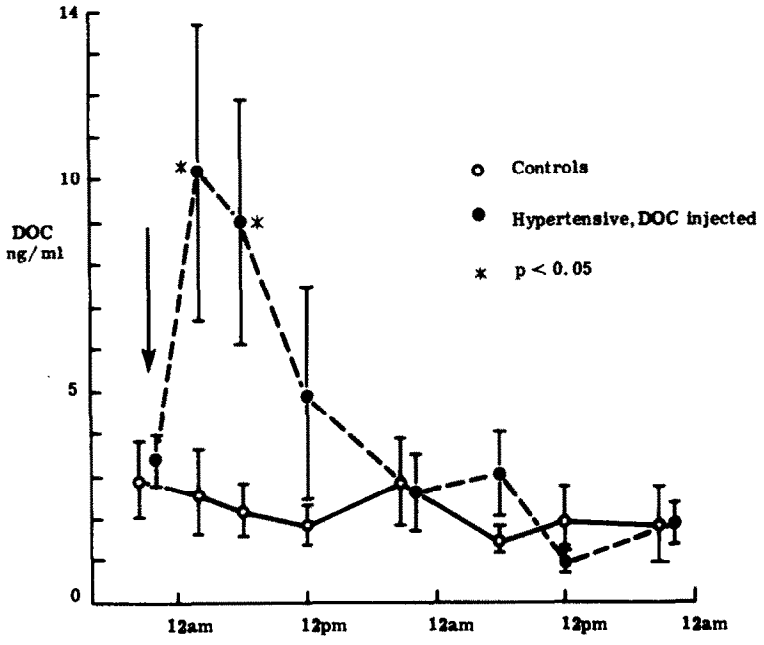

Fig. 1. Changes in plasma DOC concentration after a single injection of DOC pivalate [8].

Study 2—hypertensive effect of mineralocorticoids in man

Exogenous mineralocorticoid can also cause hypertension in man. Six normal male subjects were given 9α fluorocortisol (1 mg/day) for a period of 14 days and blood pressure was measured daily under carefully standardised conditions [9]. The mean of both systolic and diastolic blood pressure for the group was significantly elevated after 10 days of treatment (Fig. 2). In one subject in whom the effects of the mineralocorticoid were counteracted with the diuretic frusemide, blood pressure fell to basal, pretreatment levels within 24 h during which time 100 m-equiv of sodium were excreted.

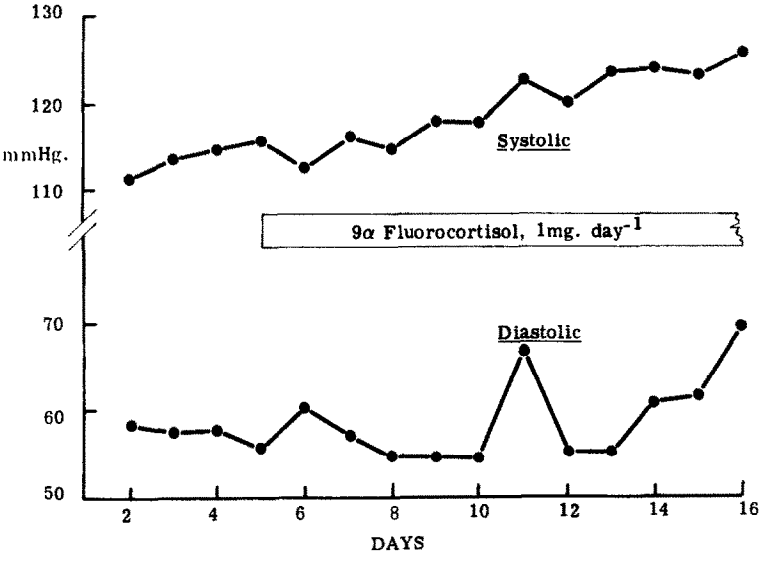

Fig. 2. The effect of 9α fluorocortisol on blood pressure in a group of normal subjects [9].

Study 3—mineralocorticoids in hypertensive man

There are a number of rare conditions in which the causative role of mineralocorticoids in hypertension is indisputable. For example, in primary hyperaldosteronism, caused by excessive aldosterone secretion from a benign adrenocortical adenoma [10], blood pressure levels can be reduced either by surgically removing the source of the steroid or by antagonising its effects at the target organ by spironolactone therapy [11–14]. It should be emphasised that the symptoms of this disease, although probably entirely due to abnormal adrenocortical activity, may only partly be attributable to aldosterone because the affected gland also secretes abnormally large quantities of corticosterone, 18-hydroxy DOC and possibly other corticosteroids also. Similar symptoms can occur in the presence of normal or low aldosterone levels in plasma as a result of excessive secretion of DOC or corticosterone from adrenal carcinomata [15, 16], in a series of subjects without proven adrenal abnormality [17] and in a number of other situations [18, 19]. In these cases, complete removal of the source of the steroid is not possible although in the case of corticosterone secreting carcinoma [16] radiotherapy temporarily reduced blood pressure.

High circulating levels of DOC and corticosterone also occur in subjects with defective 11β and 17α hydroxylase activity [20–22]. In both situations, the concentrations of the minor mineralocorticoids are high and hypertension is also a feature.

It is thus clear that mineralocorticoids such as DOC and corticosterone, like aldosterone, are capable of acutely and chronically raising blood pressure. While experimental studies in the rat show that mineralocorticoid levels need only be intermittently raised, and while cases of primary hyperaldosteronism exist in which plasma aldosterone concentrations may be normal for a large proportion of the time [4, 23] in most of the conditions described the steroid levels are raised continuously and, when the source is removed or inhibited, symptoms remit.

Low renin hypertension and mineralocorticoids

Aldosterone secretion in normal man is mainly controlled by the renin-angiotensin system [3, 4]. Loss of sodium or reduced sodium intake results in an increase in the renal release of the proteolytic enzyme renin which in turn catalyses the release of the decapeptide angiotensin I from a plasma-borne protein substrate. The decapaptide is further converted to the pressor octapeptide, angiotensin II, in the circulation and this peptide stimulates aldosterone secretion to promote sodium reabsorption in the kidney. Conversely, a sodium load suppresses renin release and therefore aldosterone secretion. In any situation in which mineralocorticoid secretion is high for reasons other than high renin secretion, the renin and angiotensin II levels will be suppresssed. For example in primary hyperaldosteronism where aldosterone secretion from the tumour is maintained autonomously at a high rate, plasma renin concentration or activity is low [24–27].

In the search for primary hyperaldosteronism in the hypertensive population it was revealed that a considerable proportion of the subjects had low plasma renin levels in the presence of normal or low levels of aldosterone. Moreover, plasma renin failed to respond to manoeuvres which normally raise its levels such as assuming an upright posture or restricting sodium intake [28]. Since factors such as aminoglutethimide [29], partial adrenalectomy [30] or spironolactone [31–34] which reduce the quantities or the effects of corticosteroids in the body, tend to lower blood pressure in some cases it has been assumed that hypersecretion of a mineralocorticoid other than aldosterone must be responsible. Unfortunately, no single compound has been discovered. Although small series of subjects in whom DOC [17], 18-hydroxy DOC [53], 16α,18-dihydroxy DOC [54] or 16β-hydroxy DHA [55] levels or excretion were higher than normal have been described, in none of these has cause and effect been established. More seriously, the state of excess body sodium and probably also deficient potassium which should be the hallmark of mineralocorticoid excess is by no means obvious in most cases of low renin hypertension and, while the search for non-aldosterone mineralocorticoids continues, other explanations of suppression of renin in these subjects are also available [33–37]. This subject has recently been reviewed by Gunnells and McGuffin [28].

ACTH and mineralocorticoid secretion in normal subjects

The importance of ACTH in the control of electrolyte metabolism through its effect on aldosterone secretion or plasma concentration is equivocal. While in sodium deplete subjects plasma aldosterone levels may be sensitive to ACTH [38, 39] and while recent evidence reveals certain similarities between the diurnal rhythms of plasma levels of aldosterone and ACTH dependent corticosteroids such as cortisol [40, 41] the fact remains that in subjects replete of sodium, whose plasma aldosterone levels readily respond to infusions of angiotensin II, aldosterone is singularly unresponsive to ACTH. In contrast, the secretion of the minor mineralocorticoids, particularly DOC and corticosterone, is very sensitive to the anterior pituitary hormone.

In a group of normal male subjects whose endogenous ACTH secretion had been suppressed by means of the synthetic glucocorticoid dexamethasone, α^{1-24} ACTH was infused at a series of rates ranging from 0.25 to 10 $\mu g\ h^{-1}$ designed to cover the normal ACTH range and above [42]. Plasma concentrations of DOC, 18-hydroxy DOC, corticosterone, 18-hydroxycorticosterone, cortisol, 11-deoxycortisol and aldosterone were measured by gas-liquid chromatography [43, 44] and the responses were calculated for

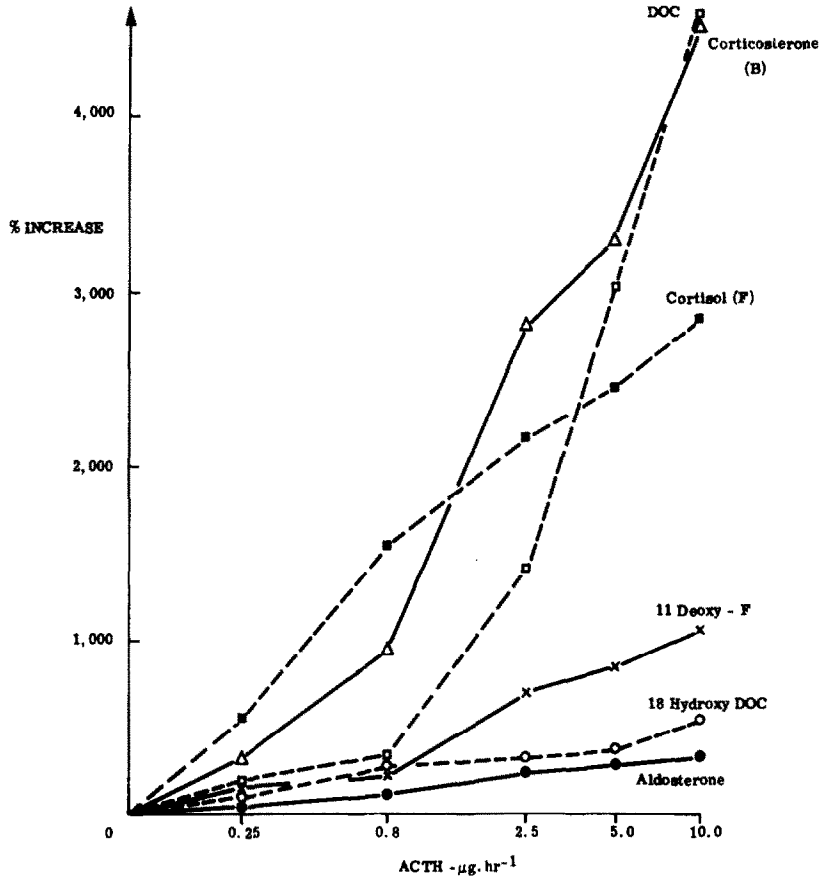

Fig. 3. The effect of ACTH infusion on the relative response of individual plasma corticosteroid concentrations in normal subjects [45]. Each rate of α^{1-24} ACTH infusion was continued for one hour and subjects were pretreated with dexamethasone.

each compound as per cent increase above basal levels. While the rate of increase in cortisol concentration at the lower rates of ACTH infusion were steeper than other corticosteroids, at rates higher than 0.8 μg h^{-1}, plasma DOC and corticosterone levels accelerated markedly while that of plasma cortisol became less steep (Fig. 3). There was a small response in plasma aldosterone concentration. It would appear therefore that in normal subjects ACTH, at high rates of infusion, increases the proportion of mineralocorticoid activity in the adrenocortical secretion. Such a situation is potentially hypertensive. Stress, such as hypoglycaemia, can also raise plasma DOC and corticosterone levels. These studies have been fully reported elsewhere [45].

Excess ACTH secretion and hypertension

ACTH raises the secretion rate and plasma concentration of the minor mineralocorticoids but has only a small effect on aldosterone levels. Abnormally high levels of ACTH should therefore result in the onset of the symptoms of hypermineralocorticoidism, but as a consequence of accumulation of sodium, plasma concentrations of renin, angiotensin II and aldosterone should be low. Situations of ACTH excess are as follows:

(a) Blood pressure in patients receiving ACTH for rheumatoid arthritis

Pharmacological quantities of α^{1-24} ACTH in a long-acting form used in the treatment of arthritis frequently cause marked rises in blood pressure [46]. A group of 14 such patients treated with 1 mg of ACTH (i.m.) twice a week were compared with a group of similar patients treated with Indomethacin [47]. While blood pressure in the control group remained unchanged that of the ACTH-treated subjects was significantly higher at 2 months and remained high after 5 months of treatment (Fig. 4). Plasma corticosteroid levels are not yet available for this study but levels in response to such high doses of ACTH are likely to have been high. From experiments in the rat (see above) it is possible however that plasma steroid concentrations will have been normal for at least part of the time. Recent work has suggested that known mineralocorticoids such as DOC or corticosterone are incapable of sustaining hypertension if administered in quantities resembling

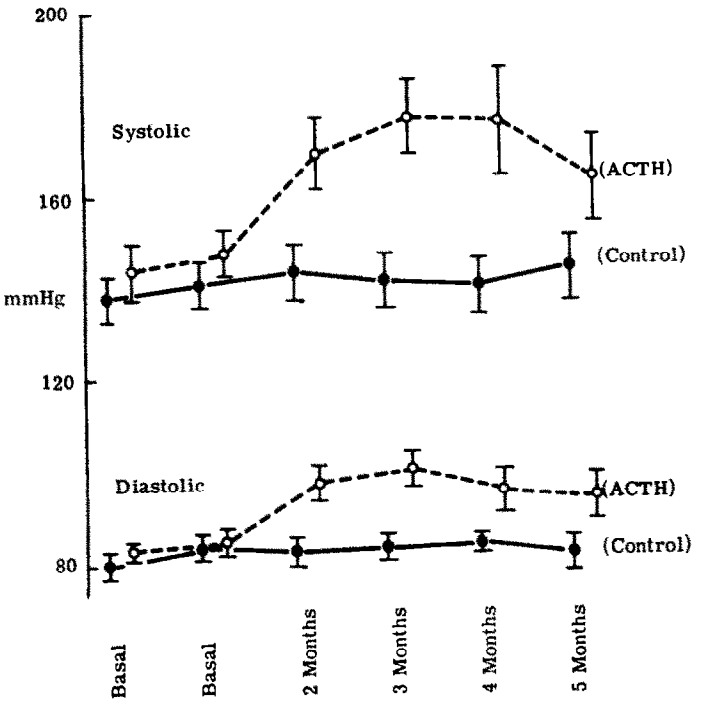

Fig. 4. The effect of ACTH administration on blood pressure in subjects with rheumatoid arthritis [47].

those achieved by ACTH stimulation but that 17α hydroxy progesterone and particularly 17α 20 dihydroxy-progesterone are more effective in this respect. The levels of both compounds respond to ACTH [48].

(b) Bronchial carcinoma

ACTH can be secreted in large quantities ectopically from carcinomata of the bronchus and in patients with this condition the symptoms of hypermineralocorticoidism and hypertension are frequently present [49, 50]. Two such cases were studied. Both had severe hypokalaemia but, probably due to their moribund condition, blood pressure was normal to low. Plasma concentrations of cortisol and ACTH were high. Plasma aldosterone levels were either normal or suppressed but plasma corticosterone was high in one subject and plasma DOC in both. Again, it seems possible that the minor mineralocoids such as DOC and corticosterone at least contributed to the disturbance of electrolyte metabolism.

(c) Inborn errors of steroid biosynthesis—17α-hydroxylation defect

Subjects who lack the ability to hydroxylate adrenal steroid precursors in the 17α position are unable to synthesise cortisol. ACTH, unsuppressed by cortisol, therefore rises to very high levels stimulating excessively the secretion of 17 deoxycorticosteroids.

Such a case recently reported by Brown *et al.*[51] had severe hypertension and clear evidence of hypermineralocorticoidism as judged by total body and plasma levels of sodium and potassium. Plasma amalyses revealed high plasma ACTH concentrations and, with the exception of cortisol and 11 deoxycortisol, the concentrations of the ACTH-dependent steroids, DOC, corticosterone and their 18 hydroxy derivatives, were well above the upper limit of their normal ranges. Conversely, plasma concentrations of aldosterone, renin and angiotensin II were low presumably because non-aldosterone mineralocorticoid activity was high. Dexamethasone therapy suppressed the plasma levels of ACTH and 17 deoxycorticosteroids to normal or low values. These changes were accompanied by a rise of plasma aldosterone, renin and angiotensin II to normal presumably as a result of correction of the patient's electrolyte status. Blood pressure fell to normal.

Again, it seems probable that the excessive secretion of ACTH, by causing hypersecretion of mineralocorticoids other than aldosterone was responsible for hypertension. In this type of case, the hypertension cannot have been due to the hydroxy derivatives of progesterone mentioned above. Another important observation is that, although the ACTH-induced hypertension in this subject was probably considerably long-standing, suppression of ACTH caused a rapid remission.

ACTH and low-resin essential hypertension

Evidence has been presented that mineralocorticoids other than aldosterone can be associated with

hypertension in man and animals and that in animals, at least, levels of these compounds need only be mildly and intermittently raised. ACTH, albeit in rather large quantities is also capable of raising blood pressure presumably by increasing the circulating levels of the minor mineralocorticoids whose secretion rates, especially those of DOC and corticosterone, are particularly sensitive to the anterior pituitary hormone. In all these situations, aldosterone concentration and probably also those of renin and angiotensin II are likely to be low and unresponsive to standard stimuli. However, the proportion of hypertensive subjects falling into these categories is small, disturbance of electrolyte metabolism is readily demonstrable and, where ACTH secretion can be suppressed, symptoms seem readily reversible. This contrasts with low renin hypertension where changes in electrolyte metabolism are much less clear cut and where suppression of ACTH with dexamethasone administration is usually without effect on blood pressure [14]. To implicate ACTH in the aetiology of this disease it would be necessary to make the following postulations: (i) intermittent increases in ACTH secretion, for example as a result frequent stress, results in rises in mineralocorticoid activity sufficient over a long period to cause mild hypertension and to suppress renin levels in plasma; (ii) that hypertension eventually becomes self-sustaining.

No direct evidence for such assumptions exists although it has been proposed in another context that small changes in blood pressure may produce renal changes which then sustain the rise [52]. It is also known that certain variants of the syndrome of mineralocorticoid excess, particularly those associated with bilateral adrenocortical hyperplasia, respond relatively poorly both to antimineralocorticoid therapy and to adrenalectomy suggesting [13] that hypertension has become refractory. Thus, although the case is not strong, a role for ACTH in low renin hypertension may be worth investigating further.

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DISCUSSION

Ulick. What is your experiences as far as the reproducibility of the effect of ACTH on blood pressure. My impression was that it was an occasional phenomen, do you see it quite regularly?

Fraser. It seems to be a common phenomenon. The 16 patients studied all raised their blood pressure.

Ulick. I would like to comment about the significance of the elevated levels of 18-hydroxycorticosterone relative to aldosterone in the 17α-hydroxylase defect. Ordinarily this finding would indicate a defect in the terminal portion of the aldosterone biosynthetic pathway, but as you have mentioned the elevated levels of 18-hydroxycorticosterone are readily suppressible by dexamethasone. While 18-hydroxycorticosterone is normally largely of glomerulosa zone origin, the 17α-hydroxylase defect appears to represent a unique circumstance in which the steroid arises largely from the fasciculata zone in association with oversecretion of two potential precursors, corticosterone and 18-hydroxy-DOC.

Fraser. In that particular subject, plasma aldosterone concentration became normal when the electrolyte status was corrected probably indicating that no defect in aldosterone biosynthesis existed. I agree that it is probable that the source of the high, ACTH dependent levels of 18-hydroxycorticosterone was the zona fasciculata.

Taylor. It is some time since I have worked in this field, but am I right in thinking that some types of the adrenogenital syndrome in children are due to deficiency of the C-21 hydroxylating enzyme? It was said that children with this condition had hypertension. Is more known about this now?

Fraser. We have had no opportunity to study this defect.

Taylor. But on the basis of your scheme a dificiency of C-21 hydroxylation would be difficult to explain, wouldn't it?

Fraser. One possible explanation might be the excessive production of hydroxylated progesterone derivatives. The secretion of these compounds is said to be ACTH dependent and recent work in the sheep shows them to be capable of affecting blood pressure.

Crabbé. Dr. Taylor, is it not so that those patients suffering from the hypertension form of congenital adrenogenital syndrome are those with a deficient 11-hydroxylation process? Your case was one with the 21-hydroxylation defect wasn't it?

Taylor. Yes, I was thinking of the C-21 hydroxylation deficiency.

James. I refer to the possible effect of ACTH on blood pressure. I believe you said these patients received 2 mg of corticotrophin every other day. This is a very big dose and I wondered what plasma levels of cortisol and DOC you found in these subjects.

Fraser. In the human experiments, plasma corticosteroid levels had returned to normal, or almost so, at the time of the first sample 24 h. Previous studies of the effect of intravenous ACTH showed that plasma cortisol, 11-deoxycorticosterone, corticosterone and 18-hydroxy-11-deoxycorticosterone levels rose rapidly. Thus it would seem that the peak response to implanted ACTH occurred earlier than 24 h and earlier, more frequent sampling will be required to establish the maximum level of steroid response.

James. With the dose of corticotrophin which you used, I would guess that the plasma steroid levels would be elevated for at least 24 h and possibly longer. I think you should bear that in mind, since it is quite a different situation from your postulate of intermittent increases in plasma steroid levels.

Fraser. The dose of ACTH was dictated by therapeutic needs but we would certainly like to follow more closely the changing pattern of steroids in plasma and, if technically possible, the time course of ACTH release also.

Adlercreutz. Have you studied other patients except for that case you showed with or without hypertension with regard to these steroids?

Fraser. The only hypokalaemic situation we have studied is primary hyperaldosteronism and in this situation circulating levels and adrenal vein concentrations of corticosterone and 18-hydroxycorticosterone may be raised in addition to those of aldosterone.

Adlercreutz. But if you have no hyperaldosteronism; I mean hypokalemia without increased aldosterone?

Fraser. Excessive secretion of corticosterone for example from an adrenal carcinoma causes hypertension associated with hypokalaemia.

Birmingham. We have compared synthetic synactin ACTH with natural (Parke–Davis) ACTH in rats and we found a very funny thing. With the synthetic ACTH we got a tremendous increase in plasma corticosterone and then a rebound. We actually got a subnormally low level

so the time course was quite different compared to that obtained with the natural ACTH preparation. In our dogs implanted with steroids we also measured plasma steroids and were surprised to find that the peak hypertensive effect occurred at a time when plasma levels of DOC and aldosterone were quite low, I think what one should also probably consider is a central effect and the conversion to active steroid metabolites.

Liddle. When you have an indisputable case of DOC-induced hypertension, removal of the DOC is usually followed by disappearance of the hypertension. You showed an example, as a matter of fact. If you are postulating that ACTH-dependent steroids are responsible for essential hypertension, then it would be reasonable to treat several of these patients with small doses of dexamethasone, suppress all of these ACTH-dependent steroids and see if the blood pressure does indeed fall to normal.

Fraser. These have been preliminary experiments and the results do not lend themselves to this type of speculation. There is information suggesting that rats become hypertensive under conditions of chronic stress and it would be of interest to follow the mineralocorticoid activity and ACTH secretion in this situation. Perhaps the important point is that, in the rats studied here, hypertension developed in circumstances where mineralocorticoid levels were only intermittently raised. Possibly this may be an analogous situation to the development of hypertension in rats with a clipped renal artery. If the treatment is maintained for long enough, removal of the stimulus, the arterial clip, does not lead to a return of blood pressure to normal.

Liddle. I think I can add a comment which will supplement what you presented here with regard to the ectopic ACTH syndrome. In our experience it is common for such patients to have hypertension. I wonder if you care to generalize as the frequency with which ACTH-dependent steroids are responsible for hypertension in our general hypertensive population? I think we would all agree that in certain unusual circumstances (such as 17-hydroxylase deficiency and DOC-producing tumours and ectopic ACTH syndrome) there are ACTH-dependent steroids that are responsible for hypertension, but do you really believe that ACTH-dependent steroids are also frequently responsible for essential hypertension?

Fraser. This would only be true if the continued presence of an ACTH-dependent mineralocorticoid excess was necessary to maintain hypertension. I agree however that the ready fall in blood pressure in the subject with the 17α hydroxylase defect and also in many subjects with Conn's syndrome after treatment argues against the hypothesis. However, removal of adrenal lesions in hyperaldosteronism does not always correct blood pressure and in these, if mineralocorticoids were indeed the primary cause, hypertension appears to have become refractory. We have tried dexamethasone therapy in a number of cases of primary hyperaldosteronism without success.

Grant. In relation to this, is it not possible there are what one might call psychosomatic features? I think you know Dr. Fraser, of Dr. Rao's work in Glasgow. It's all very well to study patients by deliberately suppressing them or stimulating them, but in addition to this, do we not have to consider the type of existence they normally lead. Some people who are very stoical, can put up with all kinds of stresses with presumably their ACTH remaining fairly level, but there are others who several times a day "blow their tops" and may produce sudden rises in the plasma concentration of the injurious steroids. The people who don't "blow their tops" don't raise concentrations of these steroids enough to do any damage.

Fraser. It would certainly be of interest to compare the effect of stress on the secretion of minor mineralocorticoids in the different personality groups.