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GENERAL DISCUSSION

Crabbé. I would like to ask Dr. Fraser and Dr. Liddle whether the elements available at the moment lead to an interpretation for the hypertension in patients suffering from Cushings disease. It has been said, hasn't it, that these patients do not behave exactly like those with a mineralocorticoid induced hypertension. It has even been reported that this hypertension fails to react favourably to spirolactone, for instance.

Liddle. I think this is another matter separate from mineralocorticoid hypertension. Dr. Krakoff in New York has done some interesting studies recently on what he calls 'glucocorticoid hypertension', and if I am correct he believes that a major factor in the evolution of this hypertension is the stimulation of renin substrate and a general lack of suppression of the renin-angiotensin system in the presence of some excess of sodium retaining steroids. Maybe it's a combination of abnormalities. It is a fact that most patients with Cushing's disease do not have low plasma renin activity, which surprised us at first, but we've come to live with it if not to understand it. I should say that in many patients with Cushing's Syndrome there is a mild excess of quite a variety of steroids. Corticosterone is elevated in the more severe cases. Desoxycorticosterone is elevated in some. Cortisol itself when given as a single treatment can occasionally cause hypertension. So I think perhaps the mixture of steroids that are produced excessively might do more than any single steroid in the mixture.

Crabbé. Am I correct in understanding that spirolactone fails to help these patients as to high blood pressure anyway.

Liddle. In general, our limited experience with spironolactone in Cushing's disease has not been very satisfactory. I did do one experiment years ago (when working on the mechanism of action of spironolactone) in which I gave to an adrenalectomized subject 100 milligram daily of cortisol and then superimposed spironolactone; no sodium-losing effect of spironolactone was observed under those circumstances.

Hökfelt. To Dr. Liddle a question related to his discussion of the relation between steroids and sodium retention in the studies with the WIN-compound. I would like to know whether the effect on blood pressure in low renin hypertension was related to an increased excretion of sodium and if so, reflected in an increase in plasma renin activity and perhaps also in aldosterone production. Then I would like to ask Dr. Fraser if he thinks that sodium retention is an important aspect in the type of hypertension discussed by him. When cortisone in large doses, ACTH or DOC is given to a patient, he will retain sodium up to a certain point and then escape around the 10th day. I noticed that in your studies with 9-alpha-fluorohydrocortisone you gave 2 mg for about 10 days during which hypertension developed. I wonder whether you saw an escape phenomenon with respect to sodium but still continuing increase in blood pressure.

Liddle. Dr. John Hollifield has found plasma renin activity to rise during treatment with WIN 24,540.

Fraser. Treatment with 9α-fluorocortisol caused a rise in blood pressure in the six subjects studied although the rise was minimal in one of these. Escape occurred between 3 and 10 days in five of the six subjects.

Adlercreutz. I just wanted to say for the records that my intention was to present more data on our new steroid, which we have called 'hypersterone' and which was described in a letter to the editor of British Medical Journal. However, a computer disaster, destroying all reference spectra, put the work off for many months. I just wanted to tell you that we are still trying to work on the problem, but very slowly, due to lack of money. We have some new observations suggesting that it has something to do with the electrolyte balance as we found the highest values in hypokalemic subjects without hyperaldosteronism and there seems also to be a negative correlation between the urinary output of hypersterone and plasma level of potassium. However, we are not yet absolutely sure that it is a new compound, it may still be an artifact or a conversion product from some known steroid.