Report on Round Table on renin suppression and the hypotensive action of beta-adrenergic-blocking drugs


ROBERTSON: We have this morning rather a large Round Table, with ten speakers, all of whom have been promised that they will get at least one chance to speak. Also quite a number of people in the audience have indicated to me that they wish to join in. Unfortunately, we are limited to 1 h. It is my job as Chairman to try to reconcile some of these obviously irreconcilable objectives and we shall therefore start straight away. I ask Dr Bühler to open the Discussion.

Bühler (see also paper by Bühler, Marbet, Patel & Burkart, pp. 61s-64s): In a previous study (Bühler, F.R., Laragh, J.H., Baer, L., Vaughan, E.D. & Brunner, H.R., 1972a: New England Journal of Medicine, 287, 1209), we observed that the anti-hypertensive effectiveness of the beta-adrenergic blocker propranolol correlated with the pretreatment plasma renin activity and with the degree of drug-induced renin suppression. In contrast, monotherapy with propranolol was found to be ineffective in low-renin patients (Bühler, F.R., Laragh, J.H., Vaughan, E.D., Brunner, H.R., Gavras, H. & Baer, L., 1972b: American Journal of Cardiology, 32, 511).

In the present study, renin responses to different types of beta-adrenergic-blocking agents were compared in eight normal volunteers at rest, supine, and during moderate upright exercise. Comparable beta-blockade was achieved with equipotent cardiodeceleratory doses of 100 mg of propranolol, 400 mg of practolol, 100 mg of oxprenolol, 10 mg of timolol, 5 mg of prindolol or 100 mg of ICI 66082. All these beta-blockers were found to reduce plasma renin activity during upright exercise. Renin suppression was found not to be related to either beta 1- or beta 2-type receptor-blocking action. These results should be compared with reports in which beta-blockers other than propranolol, e.g. prindolol (Johnston, C.I., Anavekar, N., Chua, K.G. & Louis, W.J., 1973: Clinical Science and Molecular Medicine, 45, 287s) and ICI 66082 (Aberg, H., 1974: New England Journal of Medicine, 290, 1026) were also found to reduce renin.

The failure of renin to respond to the same drugs observed by other workers remains unexplained (Stokes, G.S., Weber, M.A. & Thornell, J.R., 1974: British Medical Journal, 1, 60; Amery, A., Billiott, I. & Fagard, R., 1974: New England Journal of Medicine, 290, 284). In the present study, renin levels at rest were generally reduced by the beta-blockers but these responses did not reach significance for oxprenolol and prindolol. In the case of both of these drugs, the lesser suppressibility of basal plasma renin activity may be due to inherent sympathomimetic activity. Our data suggest that different types of beta-blockers suppress plasma renin activity and therefore that they all may lower blood pressure through reduction of angiotensin vasoconstriction. It should be noted that there seems to be a dissociation between the cardiodynamic responses to various beta-blocking drugs on the one hand, and the observed consistency in renin suppression, as well as in the known similarity in anti-hypertensive effectiveness, on the other.

The degree of renin suppression in normal subjects found in the study was considerably less than the 80% average reduction in renin observed in high-renin and the 60% average renin reduction found in normal-renin hypertensive patients given propranolol. This greater suppressibility of renin in high-renin and in normal-renin essential hypertensive patients further suggests the presence of relatively increased beta-adrenergic nerve activity. In these patients, elevated plasma renin activity and blood pressure can be normalized by beta-blockade.

ROBERTSON: Thank you very much, Dr Bühler. Since no-one at this stage appears to have any pressing points or objections which require to be dealt with, I will ask Dr George to put his view of the case.

George (see also paper by George, Lewis, Steiner & Doherty, pp. 65s-67s): The effects of propranolol and RO3-4787, a new beta-adrenoreceptor antagonist with a partial agonist activity, have been studied in a blind cross-over comparison with a placebo. In ten patients who completed this study, the two drugs produced a similar reduction in blood pressure whilst the reduction in heart rate on propranolol was significantly greater than that produced by RO3-4787. Plasma renin activity averaged 7.69 ng h-1 ml-1 on placebo, fell to 4.33 ng h-1 ml-1 on propranolol, and rose to 11.53 ng h-1 ml-1 on RO3-4787. The average plasma renin activity fell in patients receiving propranolol and rose when these same patients were taking RO3-4787. This suggests that the hypotensive effect of the latter drug at least is independent of any effect on renin. Furthermore, we have been unable to correlate changes in blood pressure with the degree of suppression of plasma renin activity. This experience conflicts with that of Dr Bühler and his colleagues. In our view the decision to treat hypertensive patients with beta-adrenoreceptor antagonists should not be based on measurements of plasma renin activity alone.

ROBERTSON: Thank you very much, Dr George. I think the two leading speakers have put their respective cases very lucidly. Would you like to express your point of view, Dr Morgan?
Morgan (see also paper by Morgan, Carney & Roberts, pp. 81s-83s): The present study was conducted in untreated hypertensive males aged 38-70. Basal recumbent plasma renin activity was measured after 4 days in hospital on a dietary sodium intake greater than 100 mmol/day. Ambulant plasma renin activity was measured at the outpatient department before treatment was started with a beta-blocking drug. In all, ninety-two patients with essential hypertension and optic fundal changes of grade II or less entered the study. Diastolic blood pressure was greater than 95 mmHg on three occasions. Propranolol was used in forty-eight of these; prindolol in the remainder. It was found that both prindolol and propranolol caused a chronic fall in mean blood pressure and in mean plasma renin activity but there was no correlation between these two variables. Furthermore, the response of blood pressure to prindolol or to propranolol was not predicted by the basal plasma renin activity. Propranolol administered acutely caused the plasma renin activity to fall with no acute change of blood pressure, while prindolol caused the blood pressure to fall with no change in plasma renin activity. Thus the effects of beta-adrenergic-blocking drugs on plasma renin activity and on blood pressure can be dissociated and it appears unlikely that their hypotensive action is mediated through the renin-angiotensin system. Furthermore, basal plasma renin activity does not identify patients who will respond to beta-blocking drugs. These results are obviously in contradiction to the view of Dr Bühler and his colleagues. The reason for this difference is unclear, but the patients in the initial studies of Bühler et al. (1972a, b; see above) were a more heterogeneous group and included patients with renovascular, malignant and accelerated hypertension. The inclusion and treatment of these many have led to the different findings. It appears that beta-adrenergic-blocking drugs are effective anti-hypertensive agents, but their mechanism of action remains to be elucidated.

Robertson: Thank you very much, Dr Morgan. Dr Bühler may be feeling a little exposed at the moment but I can see in the audience a few faces of those sympathetic to his point of view, so that you can take it, Dr Bühler, that you are not entirely on your own. From this point I want to make the discussion a good deal more informal and would like to take comments from the floor of the house. However, I have promised all the ten people sitting around this table that they will get at least one chance to speak before time is up. Any comments?

Bock: I have some objections regarding the arguments of Dr Bühler. One is that there are many other drugs which lower plasma renin very drastically, for example clonidine, and you also find a certain relationship in those circumstances between the drop of blood pressure and the drop of plasma renin activity. This does not necessarily mean, however, that the drop of renin is the cause of the reduction of blood pressure. Furthermore, we have drugs which raise plasma renin activity and lower blood pressure, for instance hydralazine and natriuretics, and this also does not speak strongly in favour of the hypothesis that there is a relationship between the fall in blood pressure and a fall of plasma renin activity. We also know of many studies in which there is no correlation between the height of the blood pressure in essential hypertension and the height of plasma renin activity. All of this should make us cautious in supposing that there is a causal relationship between the fall of renin and the drop of blood pressure.

Robertson: Dr Bühler, would you like to deal with that straight away, please?

Bühler: Just two short comments in reply to Dr Bock. So far as renin-suppressive drugs other than the beta-blockers are concerned, there are some studies from Dr Laragh’s laboratory indicating that indeed the high-renin type hypertensives do appear to respond better than the low-renin patients to such drugs, although the low-renin patients do have some response with clonidine. Also Dr Weidmann, who is on the Round Table here, has some data showing I think, a relationship between the renin-suppressive action of alpha-methyl-dopa and its hypotensive effect. So far as the renin-stimulating drugs are concerned, I do not think that anyone would claim that renin is the only issue to be considered in lowering blood pressure, and with the hydralazine you have just mentioned, of course you can get some renin-independent vasodilator action.

Morgan: I wonder if I can ask Dr Bühler to comment on the use of propranolol in renovascular hypertension? Do you find that you can use beta-blocking drugs to control the blood pressure and hence not worry about surgery?

Bühler: Can I point out that in the studies we have presented today we have focused on patients with essential hypertension, so that it is not quite right, Dr Morgan, that we have included there patients with renovascular hypertension, high-renin, or malignant hypertension. Now as to the point you mentioned just now, I think this is a very problematic issue. In an initial series of eleven patients we found quite a good correlation between the pre-operative response to renin-suppressive anti-hypertensive therapy and the subsequent response to surgery. Later, we encountered patients in whom we did have difficulty in lowering blood pressure with beta-blocking drugs in renovascular hypertension and in two or three of these we could not suppress renin activity. So it might well be that there are some types of high-renin hypertension in which the high renin is the result primarily of factors other than the beta-adrenergic nervous system. In these we are not able to lower renin or to lower blood pressure with beta-blockers.

Robertson: Thank you very much, Dr Bühler. To be fair, I think Dr Morgan was quite clear that in the study you presented today you were not including patients with renovascular hypertension, high-renin or malignant hypertension; the comments he was making there were directed to your 1972 studies (Bühler et al., 1972a, b; see above).

Dr Weidmann, Dr Bühler mentioned your studies on the comparative effects of methyl-dopa and propranolol. Would you like to discuss your findings at this point?

Weidmann: This was work done in collaboration with Dr Hirsch and Dr Maxwell in the Department of Medicine, Cedars-Sinai Medical Center and UCLA School of
Los Angeles. The effects of methyldopa and propranolol on blood pressure, serum renin concentration, plasma renin activity and aldosterone were compared in twenty-two patients with benign essential hypertension of moderate to severe degree. Methyldopa (1 g daily for 2 weeks and then 2 g daily for another 2 weeks) and propranolol (40-640 mg/day for 4-6 weeks) lowered supine mean blood pressure by 60±6.2% and 47±9.4% respectively in nine patients with low-renin hypertension, and caused significantly greater decreases of 14.1±5.6% and 15.6±7.1% in thirteen patients with normal-renin hypertension (P<0.02). The effects of methyldopa and of propranolol on upright blood pressure were comparable. Neither drug had consistent effects on serum renin concentration, plasma renin activity or on plasma aldosterone in low-renin patients, but decreased these variables in normal-renin patients (P<0.005), with a significantly greater renin-lowering effect of propranolol (80%) than of methyldopa (51%; P<0.005). Significant correlations were found between propranolol-induced changes in blood pressure and changes in plasma renin activity (r=0.59; P<0.01), and between methyldopa-induced changes in blood pressure and changes in plasma renin activity (r=0.49; P<0.05).

These data demonstrate comparable anti-hypertensive effects of methyldopa and propranolol in patients with low-renin or normal-renin hypertension. The action of propranolol (Bühler et al., 1972a; see above) and to a lesser degree that of methyldopa (Weidmann, P., Hirsch, D., Maxwell, M.H. & Okun, R., American Journal of Cardiology, 1974; 34, 671) may partly depend on lowered plasma renin and aldosterone levels. However, renin has not been established as a pathogenic factor in benign essential hypertension, and lowered renin levels following propranolol and methyldopa might simply indicate diminished adrenergic activity (Weidmann et al., 1974; see above). Whatever the definite interrelations between blood pressure, renin and adrenergic activity, consideration of control plasma renin levels in patients with essential hypertension may permit a more rational selection of anti-hypertensive drugs.

I should like to add, at this point, that we have also studied renin-blood pressure interrelations in several patients with renovascular hypertension and high plasma renin levels; in these patients, propranolol failed to lower blood pressure significantly, despite a marked decrease in circulating renin activity. This suggests that in renovascular hypertension, control plasma renin levels are not helpful in predicting the blood pressure response to propranolol.

ROBERTSON: Dr Maggiore has some data on that last point, too, I think?

MAGGIORE (see also paper by Maggiore, Biagini, Zoccali & Misefari, pp. 73s-75s): I should like to bring into the Discussion the problem of defining the forms of arterial hypertension most likely to benefit from propranolol treatment. As you know, Dr Bühler's group claimed that patients with high plasma renin activity are those most likely to benefit from propranolol treatment. We have tried propranolol as a hypotensive agent in the treatment of resistant hypertension in patients undergoing regular dialysis treatment. As you know, this form of arterial hypertension is found in a small percentage of patients on regular dialysis treatment, and is characterized primarily by its unresponsiveness to ultrafiltration and dietary sodium restriction and by high levels in plasma renin activity; hence the label of 'renin-dependent' hypertension. This form of hypertension is very difficult to control with traditional anti-hypertensive drugs, although it can be easily controlled after bilateral nephrectomy.

Propranolol was given to eight patients chosen from among fifty-four uremic subjects on regular dialysis treatment. All the eight patients had resistant hypertension with diastolic pressures equal to or above 120 mmHg, severe retinopathy (grade III-IV) and severe hypertensive cardiomegaly.

Propranolol in doses ranging from 160 to 480 mg/day brought about a fall in diastolic blood pressure toward normal values in all of them. When propranolol administration was stopped there was a prompt rebound of arterial pressure to pretreatment values. After drug withdrawal, plasma renin activity rose from a mean treatment value of 5.97±3.52 to 9.64±1.89 ng h⁻¹ ml⁻¹. There was no significant relationship between the change in blood pressure and the change in plasma renin activity. At the present time, the duration of treatment ranges from 6 to 16 months and its beneficial effect on blood pressure remains unchanged. No adverse effects have been noticed so far. All these patients are well and fully rehabilitated. These results show that adequate pharmacological control of the so-called renin-dependent hypertension can be achieved with propranolol. However, no relationship was found between the hypotensive and the renin-lowering effects.

ROBERTSON: Thank you, Dr Maggiore. Any comments? Dr Mulrow would like to speak, I think.

MULROW: I want to ask the last speaker, and maybe the other members of the panel as well, what was the relationship between the measurements of renin activity and the last dose of propranolol? Obviously, if you take blood for renin assay shortly after you have given a dose of propranolol you might well see plasma renin activity slightly depressed, but if you take the blood some time later plasma renin activity might have returned to its higher levels. We observed this phenomenon in rabbits and there is a correlation between the plasma levels of propranolol and plasma renin activity (Forman, B.H. & Mulrow, P.J., 1974: Proceedings of the Society for Experimental Biology and Medicine, 146, 530). This, of course, is dependent on the time after the last dose, so I wonder if anyone has studied in a uniform manner the relationship of plasma renin activity to the time of taking the last dose of propranolol?

MAGGIORE: Yes, the last dose of propranolol before the collection of blood for plasma renin activity was at 08.00 hours, and blood was taken off for renin assay between 08.00 hours and 11.00 hours after 1 h of recumbency.

GEORGE: Could I add that man is rather different from rabbit; in that species the plasma half-life following a single dose of propranolol is less than 4 h (Black, J.W.,
Renin suppression and beta-adrenergic-blocking drugs

Duncan, W.A.N. & Shanks, R.G., 1965: British Journal of Pharmacology, 25, 571). In man, the half-life after a single dose is just over 3 h (Shand, D.G., Neckolls, E.M. & Oates, J.A., 1970: Clinical Pharmacology and Therapeutics, 11, 112), while on chronic doses the half-life is at least 4 h and possibly considerably longer.

Zanchetti: In answer to Dr Mulrow’s question, in our studies which Dr Leonetti is going to present later in this Discussion, we have always measured plasma levels of propranolol and, if propranolol is given in four doses a day for several days, you get stable levels of plasma propranolol throughout the day, since the half-time is, on chronic administration, about 4 h. It is not a problem, therefore, in studies of this kind, although it is a problem which needs to be carefully watched during the acute administration of propranolol.

Amery: I wish to report a study in which we compared plasma renin concentration first in the presence of a placebo and then with propranolol at increasing doses of 60, 120, 240 and 400 mg/day. These were always received for 1 week. On propranolol, the plasma renin concentration came down. The patients were then switched to the beta-blocker, ICI 66082, and at that point the plasma renin concentration went up again. Blood pressure, however, remained controlled at the same level and the degree of beta-blockade was similar between the first period of ICI 66082 and that during propranolol therapy.

Vernorhy: I would like to report some results with the beta-blocking drug sotalol, which is reputed to have a pure beta-blocking effect. We obtained a variable effect on blood pressure, generally a hypotensive action, together with a lowering of plasma renin concentration, although there was no significant correlation between these two decreases. We also measured angiotensin II plasma levels in this study and again there was no correlation between the decrease of angiotensin II and the decrease in blood pressure.

Salvetti: We have studied the effect of oxprenolol on about 100 patients with essential hypertension and thirty patients with renovascular hypertension as well as in twenty normal subjects. We were interested in the acute effects of the drug. Following the acute administration of oxprenolol, the lowering of plasma renin activity lasted for 3-4 h and then disappeared (Salvetti, A., Arzilli, F., Russo, G. & Zucchini, G.C., 1971: Journal of Nuclear Biology and Medicine, 15, 140). Reverting to an earlier point in the Discussion, I feel that in renovascular hypertension the response of plasma renin activity to a beta-blocker is a good prognostic index of the likely outcome of surgery (Salvetti, A., Arzilli, F. & Bacchi, G., 1973: Journal of Nuclear Biology and Medicine, 17, 142; Salvetti, A., Arzilli, F., Quarta-Colosso, M. & Zucchini, G.C., 1974: European Journal of Clinical Investigation, 4, 333).

Doyle: One of the problems which is encountered in treating hypertensive patients with propranolol is the very large amounts of drug that are often needed to produce a fall in blood pressure. If one looks at the doses needed to treat patients with thyrotoxicosis or angina, they are really very much smaller and I would like to ask the panel: Do they believe, or are there people who still believe, that propranolol and renin are related? Do they either believe or do they have evidence that if you give a small dose of propranolol, say 20 mg, the renin falls, the pulse rate falls, but the blood pressure stays the same? Do any of you have data on that? And in low-renin patients, for example, do any of you have evidence that their pulse rate falls with that kind of dose?

Bühler: Dr Doyle, I think there are several problems to be answered there and one of these is the dose level. It is certainly true that the effective doses of propranolol vary quite a bit in individual patients. We have observed the blood pressure response and the renin response with very small doses in some individuals but, generally, you need somewhat more propranolol to keep blood pressure down than you need for the renin response, so this may be a problem.

Geyskes (see also paper by Geyskes, Boer, Leenen & Dorhout Mees, pp. 69s–71s): I would like to say something in favour of the renin-depressive hypotensive action. We thought that body fluid volumes should also be taken into account when studying the hypotensive action of propranolol. In nineteen patients, five with unilateral renal artery stenosis and fourteen with essential hypertension, blood pressure, plasma and extracellular fluid volumes and plasma renin activity were studied at the end of three sequential periods: first, after 3 days on a 60 mmol sodium diet; secondly, after 3 days of salt depletion induced with a diuretic and sustained by means of a 20 mmol sodium diet; and, thirdly, after 3 days during which the 20 mmol sodium diet was continued and beta-blockade was induced by increasing doses of propranolol up to 320 mg daily. After sodium depletion, extracellular fluid volume and plasma volume decreased and plasma renin activity increased; blood pressure did not change significantly. After adding propranolol, both plasma volume and extracellular fluid volume remained low and there was a significant decrease in plasma renin activity and in blood pressure in all patients, irrespective of their initial plasma renin activity.

Tarazi: In considering the relationship between the initial level of renin and its response to propranolol, it might be important to consider the possible reasons for the increase in renin activity. Whereas propranolol may very well reduce an increased renin activity when this increase is due to some adrenergic mechanism, I wonder whether it would have the same effect if the reason for the rise in renin was a volume contraction or a salt depletion. For this reason we (Bravo, E.L., Tarazi, R. & Dustan, H.P., 1975: New England Journal of Medicine, 292, 66) studied the effect of adding propranolol to patients who were being treated with diuretics and who therefore had a chronically elevated plasma renin activity. Their blood pressure came down very rapidly, almost to normal, in response to the added propranolol; but we did not see any reduction in plasma renin activity. Propranolol will inhibit the increase in plasma renin activity that follows an adrenergic stimulus such as tilting; it may also blunt the increase in renin following acute diuresis and volume
depletion which activate neural compensating mechanisms. But treatment with propranolol did not prevent the increase of plasma renin activity or of aldosterone consequent to 4 days of a low-sodium diet (Bravo, E.L., Tarazi, R. & Duslan, H.P., 1974: *Journal of Laboratory and Clinical Medicine, 83, 119*).

**ROBERTSON:** Time is running out and comments from here on must be brief and to the point. Dr Weber, would you like to speak, please?

**WEBER** (see also paper by Weber, Oates & Stokes, pp. 89s-91s): I should briefly like to change the model that we have been discussing from the hypertensive patient to the normotensive laboratory animal. We have been interested in certain aspects of the physiology of renin secretion and have been using beta-adrenoceptor antagonists as an investigative tool. However, some of the data we have obtained may cast some light on the area under dispute in this Discussion.

Plasma renin activity and blood pressure were studied in groups of conscious unstimulated rabbits receiving infusions of different beta-blockers (Weber, M.A., Stokes, G.S. & Gain, J.M., 1974: *Journal of Clinical Investigation, 54, 1413*). Propranolol and oxprenolol each significantly reduced both plasma renin activity and blood pressure, but prindolol, which had a strong blood pressure-lowering effect, increased plasma renin activity. When prindolol was given to animals in which plasma renin activity and blood pressure had been reduced by propranolol, plasma renin activity returned to control levels although blood pressure remained low. Thus the increase in renin levels caused by prindolol is not mediated by changes in blood pressure, but is probably due to the intrinsic sympathomimetic properties of this agent. These findings, together with the observation that another beta-adrenergic antagonist, H35/25, reduced plasma renin activity without altering blood pressure, suggest that the effects of beta-blockers on blood pressure are unrelated to their effects on renin release.

Similar findings have been obtained in hypertensive human subjects (Stokes, G.S., Weber, M.A., Thornell, I.R., Stoker, G. & Sebel, S., 1974: *Progress in Biochemistry and Pharmacology, 9, 29*). Following in-hospital control studies, patients were treated with propranolol (160–400 mg/day) for 2–24 months and were then readmitted to hospital for further study. Plasma renin activity and blood pressure had each fallen, but the correlations between the change in blood pressure and either the initial plasma renin activity or the fall in plasma renin activity were not significant. With the patients still in hospital, there was a cross-over in treatment from propranolol to prindolol. Blood pressure remained low, but plasma renin activity rose significantly (Stokes *et al.*, 1974; see above). Thus we have concluded that there is probably no direct association between the effects of the beta-blocking drugs on blood pressure and plasma renin activity.

**BIANCHI:** I would like to mention some studies performed in our laboratory in Milan on spontaneously hypertensive rats. We treated a group of these rats with low doses of propranolol, starting the treatment when the animals were in the pre-hypertensive stage, and we observed that this low dose of propranolol did not prevent the development of high blood pressure, although it did reduce the plasma renin activity to about 50% of the values in untreated controls.

**LIEBAU:** I would like to add something concerning prindolol. We have treated fourteen patients, aged from 20 to 49 years, with essential hypertension with prindolol. Any previous anti-hypertensive therapy was discontinued at least 4 weeks before the study. These patients were treated with placebo and with increasing doses of prindolol, each therapeutic period lasting for 2 weeks. With prindolol, although the systolic and diastolic blood pressures decreased very significantly, plasma renin activity both resting and after stimulation with frusemide decreased only a little and this decrease on prindolol was not statistically significant. On prindolol we found a highly significant increase in the urinary excretion of noradrenaline from 30 to 50 µg/day. On prindolol, aldosterone excretion decreased but only to a slight extent. When we plotted the correlations between the decrease of diastolic blood pressure and the decrease of plasma renin activity during treatment, no close relationship was found. These data do not confirm the concept that there is a causal connection between the renin decrease and the blood pressure decrease on beta-blocking therapy.

**MUIESAN** (see also paper by Muiesan, Alicantri, Rosei, Motolese & Valori, pp. 85s–88s): I should like to present some data, although I am very sceptical about the possibility of throwing more light on this argument. We have been interested in the relationship between sympathetic nervous system behaviour and plasma renin activity during beta-blockade. We have studied ten hypertensive patients and five normal control subjects. The urinary excretion and the plasma levels of catecholamines, together with plasma renin activity, were measured before and after the administration of frusemide. The same procedure was repeated in the same subjects 3–4 days later after treatment with oxprenolol. The urinary excretion of noradrenaline and the noradrenaline plasma level increased significantly after frusemide in all cases, normal values being regained within an hour. The plasma levels and the urinary excretion rate of adrenaline were unchanged. Similarly, frusemide caused a significant increase of plasma renin activity in seven patients with hypertension and normal basal renin values, while remaining unchanged in three hypertensive subjects who had low basal renin values. Treatment with oxprenolol suppressed the response of noradrenaline and plasma renin activity to frusemide in all instances.

**ROBERTSON:** Thank you very much, Dr Muiesan. Dr Leonetti?

**LEONETTI** (see also paper by Leonetti, Mayer, Morganti, Terzoli, Zanchetti, Morselli, Di Salle & Chisdey, pp. 77s–79s): It is of interest perhaps that in most of the previous studies concerning the relationship between the hypotensive and renin-suppressive effects of propranolol, a fixed dose has been given to patients and an attempt has been made to correlate the hypotensive effect with the suppressive effect on plasma renin activity. We thought that this most interesting subject could be better studied
by progressively increasing the doses of propranolol, starting from very low doses such as Dr Doyle suggested a few moments ago. In sixteen patients with mild or moderate normal-renin essential hypertension, we began with 40 mg/day divided into four doses and then increased propranolol at intervals of 5–7 days. In this group of patients, the hypotensive and the renin-suppressive actions of propranolol were related to plasma propranolol concentrations in different ways. At the lowest plasma propranolol concentrations (15–40 nmol/l), there was almost no decrease in blood pressure, whereas recumbent plasma renin activity and its responsiveness to various stimuli (standing, or intravenous frusemide) were already strongly depressed. Thus in a large number of normal-renin hypertensive patients taking small doses of propranolol, the renin-suppressive action of the drug can be dissociated from its hypotensive effect. Dissociation of these two effects, though in a contrasting fashion, was also observed in three out of four hypertensive patients with low renin levels, whose blood pressure was decreased by propranolol without detectable further reduction of the already suppressed levels of plasma renin activity. Our data seem to provide clear evidence for the lack of any important relationship between the hypotensive and the renin-suppressive actions of propranolol. While no doubt some blood pressure decrease may be due to suppression of renin, this seems to be a minor factor in the hypotensive effect of the drug. I have to say again that these conclusions are drawn from patients with mild to moderate hypertension, and with low or normal levels of plasma renin activity. It is quite possible that in patients with more markedly elevated plasma renin activity the hypotensive action of propranolol may be mediated by way of renin suppression.

ROBERTSON: Thank you very much, Dr Leonetti, for speaking so clearly and so briefly. I think we just have time for Dr Prichard to make some comments before I ask Dr Bühler to reply to the various criticisms.

PRICHARD: We have been using beta-blockers for some 12 years in about 250 patients with hypertension, and we have not seen large numbers of non-responders, which clearly we ought to have done according to some of the results presented here today. I regret that we have never been able to measure renin. Of course we have always been prepared to adjust the dose and from an early stage to push the dose up to very high levels. I think, looking at the world literature, this is one of the reasons for large numbers of non-responders being reported. I think the proportion of non-responders is getting less as time goes by but I must emphasize that the effective dose of propranolol in hypertension may be up to 2 or 4 g/day. I believe that Dr Zacharias, who has also used beta-blockers in a very large series of patients, would agree with that observation. I would be particularly interested in what Dr Morgan’s observations with prindolol are in this respect.

I would like to disagree with Dr Doyle about the dosage of propranolol and other beta-blockers in the treatment of angina and in hypertension; the maximal effect in these two conditions is achieved in the same dose range. There is no significant difference (Prichard, B.N.C. & Gillam, P.M.S., 1969; British Medical Journal, 1, 7; Prichard, B.N.C., 1974: Drugs, 7, 55).

I am interested in the studies where investigators have changed treatment from one beta-receptor-blocking drug to another and have shown then that plasma renin rises while the blood pressure stays down. These workers may indeed be correct in concluding that the anti-hypertensive action of beta-receptor-blocking drugs is not related to suppression of renin, but I would like to see them make their plasma renin measurements more than a week after changing treatment, because we have observed with a number of beta-blockers, particularly with propranolol (Prichard, B.N.C. & Gillam, P.M.S., 1969: above) and sotalol (Prichard, B.N.C. & Boakes, B., 1974: Advances in beta-Adrenergic Blocking Therapy: Sotalol, Excerpta Medica IV, 7), a delay in the change of blood pressure after treatment has been commenced or stopped.

ROBERTSON: Thank you very much, Dr Prichard. I see that still a large number of people would like to speak, but unfortunately we are already over time. I must ask Dr Bühler to reply to the various points for and against him that have been raised and must also ask him, with regret, to keep this brief.

BÜHLER: Thank you very much, Dr Robertson, for giving me the opportunity to reply to this really luxurious meal. First of all, I am, of course, glad that the list of my supporters does seem to have grown a little during the course of this Discussion. I now have people like Dr Weidmann, Dr Salvetti, and to some extent Dr Geyskes also, on my side. I would also mention that Dr Castenfors in Sweden has found a nice correlation between the anti-renin effect and the hypotensive effect of alprenolol.

To Dr George I must apologize; the drug RO3-4787 is probably the only beta-blocker we have not yet studied, so I do not know whether it would suppress renin in our model or not. However, I do not think that renin suppression per se necessarily touches on the concept that the pretreatment level of renin secretion could be a predictor of the anti-hypertensive response.

Dr Morgan does seem to have some quite important differences in methodology from us, particularly regarding the definition of low-renin patients, so I am not surprised that he finds different responses in his population.

Dr Amery’s results are certainly intriguing, too, since at certain points in the experiment the drug ICI 66082 appears to lower both renin and blood pressure; whilst at other stages in other experiments there is no correlation.

Dr Verniory’s data with angiotensin II are very important; of course one would like to have angiotensin II measured more routinely. It is nice that he has shown a correlation between the renin suppression and the angiotensin II suppression under beta-blockade.

If we consider the problems of thiazides and low renin, clearly, when you have introduced another compound, a renin stimulator, then it is quite possible, Dr Geyskes and Dr Tarazi, that you might lower blood pressure in low-renin patients. Then you are getting probably at the renin mechanisms as well as at volume depletion.

One of the last problems perhaps is the question of prindolol, the drug which has the most positive intrinsic sympathomimetic activity. In our studies, this was the
only drug we really encountered problems with in lowering renin. It could be that the agonist effect of prindolol might cause vasodilatation, so that with prindolol one might have a double effect—on renin and possibly also on the peripheral vascular muscle.

To summarize, I do not think that we would claim that there is a moment-to-moment correlation between renin suppression and anti-hypertensive effect, but there might be a correlation between the long-term effects. I also believe that the pretreatment level of renin is a good indicator of the anti-hypertensive response to beta-adrenergic-blocking agents. Of course, the different beta-blockers do have, or appear to have, different potency in suppressing renin. We have found that with the blockers so far tested at least, upright renin appears to be lowered generally.

ROBERTSON: Thank you very much, Dr Bühler, for that very crisp final speech for the defence. It is sad we did not allow more discussion time for this topic, which obviously is of great interest to many workers. I should like to thank all the participants for so nobly enduring the constraints imposed by shortage of time, and for presenting their data so clearly nevertheless. Perhaps it is no bad thing that we can reflect on the various contrasting viewpoints at our leisure later.

Summary of Discussion

J. I. S. ROBERTSON

Dr Bühler restated the thesis that the anti-hypertensive effectiveness of the beta-blocking drug propranolol correlated with the pretreatment level of plasma renin activity and with the degree of drug-induced renin-suppression. He presented new data indicating that a variety of beta-blockers suppress renin and may all reduce blood pressure in this way.

Dr Weidmann's findings generally supported those of Dr Bühler, and Dr Maggiore reported a consistent beneficial effect of propranolol in lowering renin and blood pressure in 'renin-dependent' hypertension in patients on regular dialysis therapy. Dr Salvetti felt that the response to a beta-blocker was a good guide to the likely outcome of renal artery surgery in renovascular hypertension; on the other hand, Dr Weidmann had found that in similar patients propranolol failed to lower blood pressure, despite reducing plasma renin.

In contrast to Dr Bühler, Dr George, Dr Morgan, Dr Weber, Dr Leonetti, Dr Liebau, Dr Amery and Dr Verniory, with varying emphasis, had failed to confirm a significant relationship between the renin-suppressant and blood pressure-lowering effects of beta-blockers. Much of the Discussion was concerned with the reasons for the disagreement. Dr Geyskes had found a consistent blood pressure-lowering effect, in parallel with a fall in renin, after sodium depletion; the findings of Dr Tarazi did not entirely agree with these results of Dr Geyskes.

Dr Prichard, while presenting no renin measurements, emphasized that in his experience hypertension rarely failed to respond to propranolol, provided the dose was increased sufficiently.

The majority view was that beta-blocking agents can reduce blood pressure by other mechanisms than by reducing renin; moreover, the effect on renin release is very different with different drugs. Dr Bühler nevertheless held to his view that the initial level of plasma renin activity is a good guide to the anti-hypertensive response with most beta-blocking agents.

When hypertension is renin-dependent, and a beta-blocker effectively suppresses renin release, blood pressure must surely fall. A point some of the investigators may have neglected is that the plasma renin level as such is not a good guide to the renin-dependence of the hypertension. A more certain approach would be to evaluate plasma renin (or, better, angiotensin II) in relation to the concurrent sodium status. Dr Bühler was careful to emphasize that, in his work, plasma renin activity estimations were always considered in relation to urinary sodium excretion. However, urinary sodium output might not always reflect the state of sodium balance and this might explain some of the discrepancies.