Combined α-β-Blockade
A Round-Table Discussion


Professor Prichard (University College, London): Professor Lund-Johansen, you have described the normalisation of central haemodynamics and feasible regression of structural abnormalities in the heart and resistance vessels with long term labetalol therapy. What would be the likely implications of such regression as regards improved prognosis in hypertension, and have these effects been noted with other antihypertensive drugs?

Professor Lund-Johansen (University of Bergen): Firstly, I must emphasise that we have no long term clinical studies which could tell us whether labetalol will produce a greater improvement in prognosis than other commonly used antihypertensive agents. However, other factors being equal, it seems that drugs able to normalise central haemodynamics and cause regression of pathological changes should be associated with a better prognosis than those without this potential. Regression of left ventricular hypertrophy, demonstrated by echocardiography, has been shown during long term use with other antihypertensives such as methyldopa.

Professor Louis (University of Melbourne): Professor Molinoff, Professor Prichard comments that the contribution of the α-blocking component of labetalol to its antihypertensive effect becomes relatively less important with prolonged therapy. Could radioligand binding studies be used to confirm this clinical observation by demonstrating 'tolerance' or reduced α-receptor affinity?

Professor Molinoff (University of Pennsylvania): The development of tolerance has been demonstrated following administration of agonists and antagonists. The vast majority of the effects of these agents during prolonged administration are mediated by changes in the density of receptors without a change in receptor properties. In general, the administration of agonists results in a decrease in the density of receptors, while the administration of antagonists results in an increase in receptor density. The clinical observation that the contribution of the α-antagonist component of labetalol to this drug's antihypertensive effect is less important with prolonged therapy could be investigated using radioligand binding techniques. It would be important to select an appropriate tissue source - animal blood vessel preparations or human platelets could be used. In experiments of this kind, it would be very important to use Scatchard analysis routinely since persistence of labetalol or a metabolite could result in an apparent change in the affinity of the receptor for a radioligand due solely to the presence of residual drug.

Professor Louis: How does the apparent normalisation of central haemodynamics during long term labetalol therapy correlate with the suggestion that the α-blocking contribution of labetalol gradually declines and the β-component becomes progressively more important for the antihypertensive action? Also, might not the haemodynamics become
progressively less favourable with the increasing contribution of β-blockade?

Professor Prichard: This is an interesting question. β-Blockade is often associated with a delayed onset of the full hypotensive effect, and thus an agent with a combined effect will, presumably, in this sense, have a greater antihypertensive contribution from β-blocking action with time. It is labetalol's α-blockade which lowers the blood pressure acutely. I do not think that the greater contribution from β-blockade means that the haemodynamics are, or would be expected to be, less favourable with time. Indeed, several workers, including Professor Lund-Johansen, have shown that this is not the case. This is at least partly because although the short term effects of a drug with β-blocking action alone could be considered unfavourable - a fall in cardiac output and a rise in peripheral resistance - with time these changes improve as peripheral resistance declines. Thus, with the added α-activity of labetalol the unfavourable short term haemodynamic effects of β-blockade alone do not occur, whereas it might be that any gradual decline in α-contribution will be offset by the improved adaptation from β-blockade that occurs with time.

Professor Lund-Johansen: I would agree with Professor Prichard that the haemodynamics of labetalol are no less favourable during prolonged therapy. On the contrary, in our 6-year study, central haemodynamics were more normal after 6 years than after 1 year. In our study (Lund-Johansen et al., 1983) there was no indication that the β-blocking contribution of labetalol became more important: heart rate at rest and during exercise remained the same after 6 years as after the first year. In fact, over the 6-year period, the total peripheral resistance showed a marked reduction. This could, of course, be partly due to regression of structural changes in the arterioles, but if the α-blocking effect of labetalol had declined to a marked extent, the fall in total peripheral resistance should have been less pronounced.

Dr Taylor (Leeds General Infirmary): There is some suggestion that labetalol may have preferential activity on β-receptors which mediate chronotropic than on β-receptors which mediate inotropic. What are the possible explanations for this observation?

Professor Molinoff: The β-receptors which mediate chronotropic and inotropic appear to be the same. However, the distribution of these receptors, in at least some species, is markedly different. Thus, in cat and guinea-pig heart, the chronotropic effects of catecholamines appear to be mediated through both β1- and β2-receptors, while the inotropic effects are mediated only through β1-receptors. In human heart, on the other hand, β1- and β2-receptors coexist on both atrial and ventricular muscle. The other factor which must be considered relates to the possibility that β1- and β2-receptors may be differentially regulated in terms of their response to situations leading to receptor desensitisation. Thus, exposure to increased levels of circulating catecholamines may lead to a preferential decrease in the density of β2-adrenergic receptors with relatively little effect on the density of β1-adrenergic receptors. Furthermore, compounds such as pindolol are antagonists with weak intrinsic sympathomimetic activity. It is possible that pindolol has some selectivity for β2-adrenoceptors and it may also be a partial agonist only at β2-receptors. Similar experiments to determine whether labetalol is partially selective and/or has intrinsic sympathomimetic activity at either β1- or β2-adrenoceptors have not been carried out.

Dr Taylor: Professor Lund-Johansen, would your clinical observations of the haemodynamics of labetalol agree with this?

Professor Lund-Johansen: The negative chronotropic effect of labetalol is well documented but it has not been shown to have a strong negative inotropic effect. In our own long term study (Lund-Johansen, 1983) the reduction in heart rate was partly compensated by an increase in stroke volume. If labetalol had a strong inotropic action, the compensatory rise in stroke volume would not have occurred. Thus, our findings seem to be in agreement with the observations of Cohn and his colleagues.

Dr Chamberlain (Royal Sussex County Hospital): What other explanation might there be for the