Recent Advances in CARDIOLOGY

EDITED BY

JOHN HAMER
and
DEREK JOHN ROWLANDS

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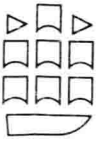

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Preface

It is four years since the last volume of *Recent Advances in Cardiology* was published. In that period few areas of cardiology have remained static. The editorial policy of dealing with important clinical problems, with recent advances in investigative techniques and in therapeutics and with aspects providing new scientific insight remains unchanged, though the publication itself is now under joint editorship. Sloman et al (myocardial infarction), Hamer (treatment of hypertension), Julian and Campbell (sudden death), Pluth (valve replacement), Balcon and Cattell (coronary artery surgery) and Rose (primary prevention programmes) deal with 'main-line' problems of continuing clinical importance but of shifting emphasis. There have been developments in the management of heart failure but this was covered extensively in the previous volume. The place of digitalis and new stimulatory drugs together with the indications for vasodilator therapy are still under discussion. It therefore seemed reasonable to defer this topic to the next volume in the hope that a more settled consensus will have emerged. In the late 1960s cardiac transplantation was being undertaken at more than 60 centres throughout the world. Most centres soon became disillusioned with the results but the transplantation programme at Stanford University Medical Centre continued and Reitz and Stinson describe the results of 183 transplant procedures. Unusual aspects of common problems are presented by Cade and Pain (respiratory aspects of cardiac disease) and by Greenbaum and Gibson (left ventricular structure in health and disease). Kent and Shand discuss the scientific basis of adrenergic receptor regulation and Anderson and Tynan propose a personal viewpoint of sequential chamber localisation in cardiac embryology. A timely reminder of the extent and limitations of our knowledge of the pathology of myocardial infarction is given by Becker and recently evolving investigative techniques are covered by Rowlands et al (nuclear cardiology) and by Pullan and Best (computed tomography of the heart). No work on recent advances in cardiology would be complete without a section of myocardial performance and this is extensively covered by Strobeck and Sonnenblick.

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Contents

1. Modern treatment of hypertension

John Hamer

Indications for treatment

The justification for regarding hypertension as a disease needing treatment in spite of the normal distribution of blood pressures in the population is the association of dangerous complications and a reduced survival with higher levels of blood pressure. The search for an arbitrary level of blood pressure which will separate hypertension is illusory, for complication and mortality increase progressively as pressure rises, but the alternative is to wait for target organ damage, to the heart, kidney or brain. Cardiac involvement is usually seen early in the electrocardiogram, but as damage to the kidney is often occult and damage to the retina often difficult to interpret, this alternative policy is unsatisfactory. Severe damage, such as cerebral vascular accident, may appear without warning and the early detection and treatment of hypertension is necessary to obtain the best results. A compromise is best achieved by taking a diastolic blood pressure (BP) at 105 mmHg (by the fifth phase) as marking hypertension in need of treatment, as this level marks a knee in the mortality curve which increases more rapidly at higher pressures. A diastolic BP of 115 (fifth phase) is usually taken as marking 'severe' hypertension as opposed to 'moderate' from 105–114. The accelerated phase of 'malignant hypertension', characterised pathologically by fibrinoid necrosis in renal arterioles is generally marked clinically by the presence of papillodema. The use of fifth phase diastolic BP measurements (disappearance of the Korotkoff sounds) is usual in hypertension, as it favours reproducibility and uniformity of results. It is customary to take the average of three separate measurements before making a decision to eliminate transient effects of anxiety. Although a great advance in our understanding and management of hypertension, the measurement of BP in the conventional way, from the Korotkoff sounds produced as the cuff is deflated, is relatively inaccurate and has as yet been little compared to invasive measurement. Spence et al (1978) report as pseudohypertension patients with cuff readings greatly above intra-arterial measurements: these discrepancies were suspected because of unexpectedly high pressures in the elderly, or from the presence of high BP without target organ damage in younger patients, but it is possible that they represent only the extreme form of a more widespread phenomenon. The more recent application of continuous recorders of intra-arterial pressure, as reported by Goldberg & Raftery (1976) and Watson et al (1979), is beginning to bring useful results, but there are formidable problems of data handling and analysis. In fact, it may be more accurate to compare cuff BP to subclavian or more central arterial pressure as this is the pressure acting on the cuff as it is deflated to produce the Korotkoff sounds. Recommendations for standardisation of the sphygmomanometric technique of BP recording (Thulin et al, 1975, British Medical Journal, 1975; Kirkendall et al, 1967) are often disregarded.

The problem of the diastolic BP measurement is well reviewed by Short (1976). Many physicians in Great Britain were trained to take the diastolic BP at the fourth phase (muffling) of the Korotkoff sounds. Although in most normals and hypertensives this is less accurate than the fifth phase (disappearance), the latter is grossly misleading when sounds continue down to zero, as in severe aortic regurgitation, and may be similarly too low in vasodilated states, such as after exercise. In most normal subjects and patients with hypertension the difference between fourth and fifth phase is only 5 mmHg and makes little practical difference to assessment of the individual patient as the difference is within the range of natural variation, but it may make a difference to the interpretation of clinical trials. American studies of 'mild' hypertension are not a mild as expected (by this difference) to a British reader accustomed to fourth phase measurement (Short, 1974). The argument shows the folly of separating different groups on the basis of indirect measurement of a physiological variable.

The improvement in survival from treatment of malignant hypertension is unquestioned (Smirk et al, 1958) and there is good evidence of benefit in severe and moderate hypertension (Hamilton et al, 1964; Marshall, 1964; Wilhelmsen et al, 1979). The improvements in outlook is mainly related to the removal of the direct effects of high arterial pressure, which caused death in untreated patients in roughly equal proportions from cerebral haemorrhage, left ventricular failure and progressive renal damage. Extension of these arguments to 'mild' hypertension, with diastolic BP between 90 and 104 mmHg, is more problematical as many of the deaths in this group are due to the complicating effcts of the accelerated atherosclerosis which accompanies hypertension (Freis, 1969). It seems unlikely that these changes will be reversed more than very slowly if blood pressure is reduced and there is a continued mortality from cardiac infarction and thromboembolic stroke after treatment. There is also concern that inappropriate reductions in blood pressure might precipitate infarction in critically ischaemic regions (Goldberg & Raftery, 1976; Stewart, 1979). Not surprisingly, it has been difficult to detect any advantage in terms of reduced mortality from treatment of this mild hypertension, and current policy is to treat selectively if there is evidence of target organ involvement (e.g., retina or e.c.g.) or in well known 'high-risk' groups such as young negro men or patients with a strong family history, but otherwise to continue observation to detect the usual increase of BP over the years into the range treatable with advantage. The proposed MRC trial of therapy in this group (Peart et al, 1977) is unlikely to provide any definitive answers, but will be helpful in determining the problems of long-term side effects of treatment. There may be benefit in these patients from reducing other risk factors for atherosclerosis, such as cigarette smoking and hypercholesterolaemia as the risks are compounded by multiple coincident factors.

The target of treatment

Some stress the importance of aiming to bring the BP down to normal levels, while emphasising that this target is often not achieved (Taguchi & Freis, 1974) especially in more severe hypertension. Coexistent atherosclerosis as described above may be a limiting factor, but not as often as might be thought without full consideration. In coronary artery disease the reduction in left ventricular work as BP falls usually outweighs the disadvantages of a lower coronary perfusion pressure and angina is consistently improved by treatment of hypertension; beta-blockers may be particular-

ly useful in these patients. In cerebral vascular disease, caution is needed in the rapidity of BP adjustment, but cerebral autoregulation of blood flow can generally adapt to the fall in BP (Lancet, 1979c), as described by Griffith et al (1979) with beta-blockers, so that a suitable response can be obtained. The precipitation of incidents by inappropriate falls in BP described by Goldberg & Raftery (1976) refers to the effect of drugs with a large postural action, which are certainly unsuitable for this group of patients. The occasional patient with failure of autoregulation (Woolner et al, 1979) may show symptoms with BP control and be at risk of cerebral infarction if the BP is reduced quickly. With the advance of non-invasive measurement of cerebral blood flow, preliminary screening may be a practical policy for suspect patients in the future.

Stewart (1979) makes a case against too rigorous control of hypertension. He found a greater risk of myocardial infarction in patients with a final diastolic BP below 90, than in those between 100 and 109, i.e., with relative failure of treatment. Risk factors were no greater in those infarcting, but the reduction in BP was greater than usual. He suggests that the vogue for 'normalisation' of BP may precipitate infarction in susceptibles. His data are strongly criticised by Kaplan (1979), who points out that the treatment diastolic BP was unduly low in terms of U.S. studies using the fifth phase, which he assumes to be 10 mmHg below 'fourth phase'. A possible further factor is the effect of anxiety and a visit to the doctor on BP readings, so that normal values at the time of examination may be associated with too low a pressure during sleep and at other times Boyd (1979). This problem may be overcome by less reliance on a casual BP measurement, the use of home readings (Moser, 1978; Lancet, 1979a) or assessment by continuous intra-arterial measurements. The lesson may be to use drugs with a smooth action on BP, i.e., without large postural effects and to reduce pressure gradually. It will have been raised for some time and any fall will reduce the risks.

Taguchi & Freis (1974) looked at this problem in the patients with moderate hypertension in the Veterans Administration studies. They analysed their patients at four months as those with BP well-controlled (diastolic BP 80 or less) and those with poor control (diastolic BP 90 or more); they could detect no difference in compliance between the groups at this time. Over a three year period cardiovascular complications occurred in 9.7 per cent of those with good control and in 14.9 per cent of those with poor control, compared with 25.9 per cent in a comparable untreated group. Although this shows some benefit from partial control, the response is even better when the BP is brought to normal. Contrary to the expectation of Stewart (1979) stroke was confined to the poorly controlled group. In a study of hypertensive stroke survivors, Beevers et al (1978) found fewer recurrences, over an average period of four years, with good control of blood pressure (diastolic BP below 100), with intermediate benefit with fair control (diastolic BP below 110). Recurrence rates were 16 per cent and 32 per cent, compared to 55 per cent for poor control. The reassuring thought that inadequate treatment does some good should not discourage attempts to improve compliance, as good control is better, but we should try to avoid the problems described by Boyd (1979), and the profound swings of BP described by Goldberg & Raftery (1976) with adrenergic neurone blockers. The main concern of Kaplan (1979) is that the polemic of Stewart (1979) will be used as an excuse for inadequate therapy. It seems reasonable to control casual BP to the level of mild hypertension, at which we

cannot demonstrate benefit of treatment. Kaplan (1979) suggests that a fifth phase diastolic BP of 90 mmHg is a widely-accepted goal, and this seems an excellent target which will sometimes be difficult to achieve.

High-renin versus low-renin hypertension

The distinction of renin sub-groups of hypertension proposed by Laragh and his colleagues in 1972–1973 seemed to offer the prospect of a rational approach to treatment on the basis that a high-renin group, with augmented sympathetic activity, would respond to beta-blockers and a low-renin group, represented in the extreme by primary hyperaldosteronism, had fluid retention with consequent suppression of renin and would respond preferentially to diuretic therapy (Buhler et al, 1972; Laragh, 1973). This optimistic expectation is supported by the studies of Karlberg et al (1976), using propranolol and spironolactone, although there was evidence of a better combined effect of the two treatments together. However, the suggestion has not generally been fulfilled, as might be expected from the evidence reviewed elsewhere (Hamer, 1976) that, as suggested by Hollifield et al (1976), block of renin release is only one component of the action of beta-blockers in hypertension and the appreciation that the hypotensive effect of diuretics represented a non-specific adjustment by auto-regulation to a reduction in circulating blood volume (Shah et al, 1978).

In a recent review of the Laragh hypothesis, Thurston et al (1978) concluded that measurement of renin in a group without accelerated or reno-vascular hypotension did not significantly assist prediction of the blood pressure response to diuretic therapy alone or in combination with beta-blockers. These findings are in keeping with the postulation (Padfield et al, 1975) of the low-renin state as a late stage of essential hypertension, although age in itself seems to be a minor factor, and Thurston et al (1978) indicate that the distinction of high-renin and low-renin hypertensives is spurious. Esler et al (1976) suggest that the low-renin state is part of a general depression of sympathetic action in long-standing hypertension. The more recent suggestion of Laragh (1976) that the high and low-renin groups are not sharply demarcated from the therapeutic point of view and that some low-renin patients might respond to beta-blockers and the uniform response to combined treatment found by Karlberg et al (1976) are in keeping with this view. The failure of primary hyperaldosteronism to respond to thiazides, effective in low-renin essential hypertension (Adlin et al, 1972), suggests that a different mechanism, responsive to non-specific diuresis, is responsible for low-renin essential hypertension. The corollary of the Laragh hypothesis that high renin levels are particularly associated with hypertensive vascular damage (Brunner et al, 1972; Brunner et al, 1975) is weakened by the analysis of Kaplan (1975) and could not be confirmed by Doyle et al (1973) or Mroczek et al (1973), as might be expected on the basis of the views of Thurston et al (1978) on the homogeneity of essential hypertension; the findings probably arose through patient selection (Lancet, 1972; Kaplan, 1975). It seems likely that the vascular damage is primarily related, as long supposed, to the level of arterial pressure and the high plasma renin in some patients, such as malignant phase hypertensives, is an index of reflex or vascular effects on the kidney rather than a causative mechanism needing specific treatment. Attention should be directed to treating the blood pressure rather than the plasma renin!

Non-specific methods of treatment

Although behavioural modification has been shown to reduce BP (Patel, 1975; Shapiro et al, 1977) and transcendental meditation will lower BP (Wallace, 1970), it is doubtful how long the effect is maintained and whether it is effective enough in the long-term to prevent hypertensive complications (Blackwell et al, 1976). It seems likely that such approaches will be quickly abandoned by the patient when they become inconvenient or if there is a change in life-style, and may act as a cover for inaction by the patient or physician in terms of effective therapy. To many non-medical people, 'hypertension' means a tendency to nervousness, and the use of sedatives to treat high BP is a reflection of this view. Sedatives are ineffective in hypertension (Cooper & Cranston, 1957), and if the BP falls with sedatives it is an indication of a falsely high initial reading which might have become lower with greater familiarisation.

Obesity has long been linked with hypertension (Chiang et al, 1969), but the situation is complicated by the 'fat arm error' which gives erroneously high readings for the BP when a conventional cuff is used on a fat arm. Some obese people do not have fat arms, but the tight correlation quoted by Chiang et al (1969) suggests that this is unusual. They suggest correction of BP measurements for 'fat arm error' on the basis of arm circumference or body weight if a standard cuff is used, and they report that even with this correction, there is still a relationship between obesity and hypertension. However, the prescription of a reducing diet for hypertension is often a cloak for therapeutic inactivity, giving both the physicians and the patients the impression that matters have been taken in hand. This attitude is reinforced by the continued reporting of studies such as that of Ramsey et al (1978), in which the 'fat arm error' is ignored. Ramsey et al (1978) state that a standard cuff was used and make no mention of any correction of BP for body weight or arm size. They describe an average BP fall of 2.5/1.5 mmHg per kg of weight loss, consistent with reduction in the 'fat arm error', with an average fall of 16.7/6.4 in their more successful group with the enormous weight loss of about just over 6 kg, suggesting that Glasgow provided some very large patients initially. Experience with treatment of obesity suggests that such results cannot be widely achieved or long maintained. Nevertheless weight reduction is worthwhile and has the advantage of requiring the continued observation and encouragement needed to ensure the effective pharmacological control of BP, which will be needed if the BP does not fall to normal levels on weight reduction.

Other dietary changes may be considered. Modest salt restriction, such as avoiding salty foods and not adding salt at the table, may aid the action of diuretics, but the strict salt restriction of the Kempner (1948) rice diet, one of the few treatments available at that time, is not needed since the introduction of modern diuretics. A prudent diet to limit animal fat intake might be thought advisable if there is hypercholesterolaemia, since combined reduction of all risk factors may be expected to have synergistic effect in delaying atherosclerosis. For similar reasons patients should give up smoking. For the majority of patients with moderate or severe hypertension (i.e., a diastolic BP consistently 105 or more) drug therapy will be needed for effective control.

The pharmacological approach

The prescription of an antihypertensive drug does not in itself ensure correction of

hypertension. A process of continued assessment is needed to ensure satisfactory results and is very demanding on the physician's time and patience. All drugs have side effects and the maximum co-operation between patient and doctor is needed to make sure that these are anticipated and explained, and the treatment adjusted to keep side-effects to a minimum.

If patients do not take their tablets, they will not benefit and many patients vote against their treatment in this way. Patient as well as physician must be convinced of the need for treatment, which must be made as easy as possible. Patients are only human and may forget to take their tablets at times. Patient compliance may be enhanced by clear instructions, reinforced by the pharmacist. Once-daily dosage has been shown to improve compliance and is being achieved with many drugs by the use of slow-release formulations. Combination tablets, generally subject to disapproval as they limit the relationship between the doses of the drugs involved, find a place in hypertension as more likely to be taken than a complicated regimes of many tablets a day. Calendar packs, as used for oral contraceptives, may also be helpful in the less obsessional patients (Forrest, 1977), but there is a temptation for the patient to take two tablets today, if he missed a dose yesterday. The great investment in time needed for management of hypertension suggests that it is a useful field for paramedical control, such as the use of nurse-physicians, which could be facilitated by the setting-up of mini-clinics on housing estates or in factories with the support of interested physicians, or perhaps by a group practice in the domestic environment.

The pharmacological approach to treatment of hypertension involves titration of the blood pressure by the gradual introduction of drugs in combination until effective control is obtained. The stepped-care approach recommended in the U.S.A. (Report of the Joint Committee, 1977), is a useful basis to consider the different agents. Although there is some debate as to which should be used first, diuretics are usually considered step 1, beta-blockers are added as step 2. If this combination is inadequate, step 3 involves the introduction of a vasodilator or other more potent drug. The uniform tendency of vasodilators to produce fluid retention and reflex tachycardia is countered by the simultaneous use of diuretics and beta-blockers of steps 1 and 2 (Koch-Weser, 1976), and without this combination therapy the vasodilators would more often give rise to intolerable side-effects. The ideal anti-hypertensive has not yet been discovered and my colleagues in the pharmaceutical industry will not be surprised to find problems with all drugs described under step 3, which are uniformly 'weighed in the balance and found wanting'!

Step 1: diuretics

Diuretics seem to be effective in hypertension in relation to a prolonged action in producing sodium and water loss to give a chronic depletion of extracellular fluid (e.c.f.). The thiazide diuretics and the related drug chlorthalidone are generally effective, but a similar response is difficult to produce with the short-acting high potency loop diuretics, which are so effective in reducing the expanded e.c.f. of heart failure and cirrhosis (Anderson et al, 1971; Healy et al, 1970), perhaps because of restoration of normal e.c.f. volume in hypertension in the antidiuretic phase between doses. Where these drugs are employed, as in renal failure (which makes the patient unresponsive to thiazides), or to control the powerful fluid retention of diazoxide treatment, frequent, large doses are needed. The work of Shah et al (1978) has

outmoded all previous speculation on the action of diuretics in hypertension; they found an initial rise in systemic resistance as plasma volume and cardiac output fell, with a fall in resistance and BP after six to eight weeks which they attribute to an autoregulatory vasodilator response to the lower cardiac output; van Brummelen et al (1979) noted similar effects on renal blood flow, which rose above placebo levels after nine months. Differences between the various thiazide analogues and chlorthalidone are trivial. Duration of action varies with protein binding and renal tubular reabsorption. Doses producing equivalent sodium loss have similar antihypertensive effect (Cranston et al, 1963); the potency in terms of the size of the dose of each drug is irrelevant. It is not certain that sustained diuretic effect throughout the whole day is necessary to a hypotensive response, although the longer-acting drugs such as cyclopenthiazide (Navidrex) and chlorthalidone have the advantage of a less dramatic diuresis to disturb the patient. The side-effects of diuretic therapy are generally trivial (Brest, 1969; McLeod et al, 1970). There has been concern about hypokalaemia which is generally unimpressive (Ramsay et al, 1977). Unless other factors contribute, there is only slight (Healy et al, 1979; Edmonds & Jasoni, 1972) or no significant fall in total body potassium (Anderson et al, 1971), so potassium supplements are generally inappropriate and may carry the hazard of hyperkalaemia in patients with impaired renal function. The amount of potassium in combined tablets such as Navidrex K is generally trivial from the point of view of correcting serious potassium depletion. The situation differs from the treatment of congestive heart failure where secondary hyperaldosteronism potentiates potassium loss and hypokalaemia accentuates digitalis toxicity. Digitalis may be needed to control atrial fibrillation in hypertensive heart disease, but is probably better avoided in hypertensive heart failure in sinus rhythm (Hamer, 1979a).

There has been concern about the possible long-term adverse effects of thiazide diuretics in terms of hyperuricaemia and impaired glucose tolerance, as these drugs may be needed for many years in the treatment of hypertension. Hyperuricaemia is associated with hypertension (Breckenridge, 1966) and is accentuated by thiazide diuretics which compete with uric acid for renal tubular excretion (Bryant et al, 1962). Frank gout is unusual but indicates the need for specific treatment with allopurinol. The new uricosuric diuretic, tienilic acid (Bolli et al, 1978), could be used in combination with thiazide to reduce this effect, but is now withdrawn as too toxic.

Impaired glucose tolerance is not infrequent on thiazide diuretics (Lewis et al, 1976) and is usually reversible; precipitation of diabetes may indicate a pre-diabetic state. Control of pre-existing diabetes may be impaired, but suitable therapeutic adjustment can usually be made. The effect seems to be a peripheral antagonism to insulin as plasm insulin levels are raised; in this situation plasma triglyceride levels may also be raised (Johnson et al, 1974). Ames & Hill (1978) report an increasé in plasma cholesterol, but not triglyceride on thiazides and suggest that these changes may counteract any beneficial effect on the atherosclerosis risk from the modest reduction in BP. In spite of those drawbacks, thiazides are the main basis of treatment of hypertension and are effective alone in about two-thirds of patients; otherwise they form a suitable background to other drugs (Finnerty, 1979). The thiazide diuretics generally produce only a modest fall in blood pressure and have a flat dose-response curve (Cranston et al, 1963) so there is little advantage in doses above the equivalent of 150 mg hydrochlorothiazide a day (McLeod et al, 1970). If this dose is inadequate to

control the BP, we proceed to step 2, adding a beta-blocker (Finnerty, 1979). Bing et al (1979) studied long-term thiazide therapy over a period of two years. They found no change in salt excretion, so there is no compensatory change in diet, but plasma renin rose progressively, even in low-renin hypertension, although some had no early effect. A rising renin may limit diuretic action and adds point to the use of beta-blockers, which inhibit renin, as step 2.

The new diuretic, metolazone, has a similar site of action to the thiazides (Michelis et al, 1970) with some proximal tubular activity, but seems to offer little advantage over the thiazides in the treatment of uncomplicated hypertension (Pilewski et al, 1971). A possible advantage of metolazone is that it continues to be effective in renal failure (Bennett & Porter, 1973), but the full implication of this property in hypertension does not seem to have been fully explored. Another new diuretic, xipamide, with similar renal effects to metolazone seems particularly potent and long-acting (Weber et al, 1977), and may be more effective than thiazides in hypertension.

The use of aldosterone antagonists in hypertension carries the overtones of the renin controversy, discussed previously. Although a useful long-acting diuretic, spironolactone seems to carry no specific effect by virtue of its action as an aldosterone antagonist (Hoffbrand et al, 1976) to favour its use in preference to the thiazide diuretics (Adlin et al, 1972; Thurston et al, 1978). The spectrum of side-effects differs from that of the thiazides as spironolactone is also an androgen-antagonist and there is an added risk of hyperkalaemia if renal function deteriorates. Spironolactone might be useful in the presence of gout or diabetes. In contrast to thiazides the main effect on lipids was to increase plasma triglyceride rather than cholesterol (Ames & Hill, 1978). It may have an advantage in the treatment of patients with secondary hyperaldosteronism, common in malignant hypertension. Although the thiazides are ineffective Adlin et al (1972), the non-competitive aldosterone-antagonists such as amiloride seem as effective as spironolactone in the medical management (Kremer et al, 1977) of primary hyperaldosteronism (Conn's syndrome). The potent vasodilator effect of the non-diuretic thiazide, diazoxide which is used in severe hypertension had led to search for vasodilator properties in related diuretic compounds and the thiazide analogue, indapamide, may have such properties (Moore et al, 1977), with a prolonged diuretic effect and low toxicity and has been shown to be useful in hypertension (Turner et al, 1977). This combination of properties could be very useful in giving step 1 (diuretic) action with some of the step 3 (vasodilator) effect in one drug.

Step 2: beta-blockers

The original step 2 drug was *reserpine*, acting mainly by central suppression of sympathetic activity. It had the advantage of a simple dose regime and prolonged action and is generally moderately effective, but even a low incidence of suicidal depression, probably related to depletion of brain monoamines, seems too high a price to pay when other suitable drugs are available. The almost accidental discovery of the antihypertensive action of the beta-blockers (Prichard & Gillan, 1964) caused some surprise (Frohlich et al, 1968), as on theoretical grounds a vasoconstrictor effect might be expected.

The mechanism of action has been reviewed extensively elsewhere (Turner, 1978; Hamer, 1979b). In summary, an initial effect by suppression of plasma renin is seen

acutely (Hamer, 1976), and gave rise to hope of a specific effect in high-renin hypertension, not realised in practice (Thurston et al, 1978; Hamer, 1979b). Block of renin release and haemodynamic effects can be produced by very small doses (Davies et al, 1979). Hollfield et al (1976) suggested that a second, later effect unrelated to renin status would explain the observation of a general delayed response. The *central* hypothesis has been revived by Turner (1978). The central beta-sympathetic is vasoconstrictor, and blockade in the central nervous system (c.n.s.) might be expected to cause vasodilation. Turner (1978) suggests that the receptor sites on the c.n.s. synapses are influenced by drugs in the brain water in equilibrium with the cerebrospinal fluid (c.s.f.) which behaves as a protein-free filtrate of plasma. The relatively high free plasma levels of the more polar beta-blockers such as practolol and atenolol might compensate for the low free levels of the less polar drugs, such as propranolol which are highly protein-bound in plasma. The physical requirements for entry to the c.s.f. (high lipid-solubility) are similar to those for entry to the brain cells, through the blood–brain barrier, and the low brain levels observed for practolol and atenolol which are effective anti-hypertensives seem to make the central hypothesis unlikely. A possible explanation is an *autoregulatory adjustment* (Hansen & Werko, 1977), to the adaptive haemodynamic response of the heart described by Brundin et al (1976). The description of the haemodynamic response as 'resetting the baroreceptors' (Prichard & Gillam, 1964) neatly illustrates the haemodynamic situation on treatment with a reduction in blood pressure and retention of alpha-adrenergic peripheral vascular control which is such an advantage in treatment with these drugs, in that there is no postural hypotension. The cardiac output tends to remain low when the blood pressure falls (Frohlich et al, 1968). There is no evidence of a sub-group of high-output hypertensives, particularly sensitive to beta-blockers; when such patients are found, the acute effects of beta-blockers reduce the high output and tachycardia, but the blood pressure may remain raised (Ibrahim et al, 1975). However, Stumpe & Overlack (1979) suggest, from the acute renin response, that young borderline hypertensives might be better treated with beta-blockers than diuretics as step 1.

The relative freedom from side effects with beta-blockers in most patients and the fear of long-term adverse effects on diuretics have suggested that these drugs might replace the diuretics and be considered step 1 rather than step 2, in the approach to treatment of hypertension. In more severe hypertensives, not responding to one drug, the net effect of step 1 and step 2 (diuretics and beta-blockers) would be identical.

Many beta-blockers suffer from the pharmacokinetic disadvantage of extensive and variable first-pass metabolism, i.e., metabolism during absorption, so that it is not possible to predict a standard oral dose and repeated visits to the physician may be needed while the dose is adjusted. The more polar compounds, such as atenolol, which is generally excreted by the kidney with little metabolism avoid this disadvantage. The subsidiary properties of the various beta-blockers (Hamer, 1979b) have little influence on their effectiveness in hypertension (Prichard et al, 1976), in spite of differences in their effect on plasma renin (Hamer, 1976), suggesting again that adaption to cardiovascular beta-blockade is the essential mechanism.

The standard beta-blocker, propranolol, suffers extensive first-pass metabolism, but it is usual to begin with very small doses such as 10 mg, six hourly; as occasional patients with sinus node disease may be hypersensitive to the bradycardiac effect