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*Review Articles*

# Diabetes and Arterial Hypertension

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**Summary.** The epidemiology, pathogenesis, significance and management of hypertension in diabetic subjects are discussed. In Type 1 diabetes the presence of diastolic hypertension is closely related to the presence of diabetic nephropathy, from the stage of persistent proteinuria onwards. There may also be some elevation of systolic pressure. The apparent increased prevalence of hypertension in Type 2 diabetes is largely explicable, directly or indirectly, by obesity but there may be an excess of systolic hypertension among elderly patients. Hypertension in the diabetic population is associated with an increased incidence of both microvascular and macrovascular complications, but whether the high blood pressure is causal is not clear. The possible roles of sodium and insulin, the renin-angiotensin system, catecholamines and physical factors are explored. All current antihypertensive agents have additional limitations and disadvantages when used in diabetic patients: diuretics and beta-blockers are probably the initial drugs of choice. Only in the case of diabetic nephropathy is there yet reasonable evidence of antihypertensive treatment reducing the rate of progression of the disease.

**Key words:** Type 1 diabetes, Type 2 diabetes, hypertension, epidemiology, obesity, diabetic complications, nephropathy, retinopathy, sodium, renin, catecholamines, peripheral vascular disease, antihypertensive drugs.

Arterial hypertension is a common problem in patients with either Type 1 (insulin-dependent) or Type 2 (non-insulin-dependent) diabetes. This review will attempt to clarify some aspects of the epidemiology, aetiology, clinical importance and treatment of hypertension in diabetic subjects. It will be apparent that in many areas adequate data are not yet available for definite conclusions to be possible. Other recent reviews have been published by Christlieb [1, 2] and Sowers and Tuck [3].

## Epidemiology

The prevalence of hypertension among diabetic patients has been a controversial subject for 70 years, estimates ranging from less than 10% to 80% in different populations. As early as 1929, Major [4] was able to review more than 12 such reports, most of which suggested that there was an increased prevalence. Numerous other workers have since addressed the problem [5–13]. Many of these reports are, in retrospect, open to significant criticism on the grounds of unsatisfactory control populations, the definitions of both diabetes and hypertension employed, conditions and techniques of blood pressure measurement, and methods of statistical analysis. Among early studies historical controls were often used and, when simultaneous controls were first employed, they were frequently not matched for body weight which has since been shown to have an independent effect on blood pressure [14, 15]. Inadequate cuff sizes for obese patients [16, 17] and varying postures during measurement have further compounded the problem, both in terms of absolute values and comparability between studies: even where 'correction' for body weight has been applied, recent studies suggest that the methods used may not be adequate [16]. Further problems arise from the variable criteria for recording of blood pressure (e.g. Korotkoff phases IV or V for diastolic) [17] and the many 'definitions' of hypertension. Recently this has usually involved pressures of about $>160$ mmHg systolic and/or $>95$ mmHg diastolic [18]: such fixed limits will inevitably give an increasing prevalence of hypertension with age in any Western population. It is also difficult to interpret from many reports whether there may be a sub-population with definite hypertension or an overall upward shift in the pressure distribution. Almost all these studies have been performed among predominantly Caucasoid populations.

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Major concluded that the majority of elderly diabetic patients had significantly greater systolic blood pressures than normal or hospital based control subjects [4]; John also showed a significant rise in systolic pressure after the age of 50 years but noted that only 9% of diabetic patients below 30 years had hypertension by his criteria [5]. Adams reported a sixfold excess of systolic hypertension in both sexes above the age of 40 years but, when corrected for obesity, the difference was not significant [6]. Of more recent reports Freedman and colleagues studying a hospital diabetic clinic population [8] showed an increased prevalence of diastolic hypertension only in those patients over 60 years. In another large study of 662 diabetic patients with carefully matched controls, Pell and D'Alonzo [9] found a prevalence of hypertension (>150/94 mmHg) 54% greater among the diabetic than the control subjects: this was independent of obesity. They also noted that those diabetics requiring 50 or more units of insulin daily had a lower prevalence of hypertension than others. In the Framingham study, mean systolic pressures were slightly higher in diabetic subjects than in age- and sex-matched controls, the difference being greater in women [10]. Jarrett et al., in the Whitehall and Bedford studies, also showed a correlation in men aged over 40 years of both systolic and diastolic pressure with blood glucose, independent of body mass [11]. A recent study in a community of subjects aged 50–80 years has again demonstrated a consistent association between diabetes and hypertension in both sexes and at all ages; adjustment for obesity reduced the extent but not the presence of the relationship [12]. The presence of the association in undiagnosed patients but not in some series of established diabetes [19] may reflect weight changes following diagnosis.

Few of these studies have differentiated between Type 1 (insulin-dependent) and Type 2 (non-insulin-dependent) diabetes [20]. Christlieb et al., studying juvenile-onset insulin-dependent patients only, but using retrospective control subjects, showed a significant excess of hypertension among the diabetic patients [13]. The prevalence was however only 15%–20% in the age group 35–44 years, but rose sharply above 54 years, especially in women. In contrast Moss, using matched controls, showed that children with diabetes may have slightly elevated systolic pressures from adolescence onwards [21]; this does not necessarily conflict with the former study as the use of such criteria as > 160/95 mmHg is clearly inappropriate in young people. It is noteworthy that at ages 20–45 years there are similar prevalences of significant hypertension and diabetic nephropathy and a close temporal relationship between them [7, 13, 21]; this will be discussed later. Perhaps surprisingly hypertension was commoner in women among Christlieb's patients [13], while nephropathy occurs with a male excess [22, 23].

Thus it appears that, in both Type 1 and Type 2 diabetes, there is an excess of systolic hypertension. In Type 2 disease much of this is clearly related to the obesity seen in many of these patients but, even when this factor is taken into account as far as possible, a significant increase in prevalence is observed, at least above age 50–60 years. Evidence of any increased frequency of diastolic hypertension, at least before old age, is not totally convincing. With Type 1 disease there may be a small increase in systolic pressure from early in the disease. Definite diastolic hypertension (>95 mmHg) in this group is generally closely associated with the presence of renal involvement (see below) while there appears to be a marked increase in systolic hypertension above the age of 45–50 years.

## Classification of Hypertension

Several classifications of hypertension in diabetes have been proposed [1, 2] but in the absence of clear understanding of the pathophysiology involved any such attempt must clearly be tentative and speculative (Table 1).

The secondary causes of diabetes and hypertension, such as thyrotoxicosis, phaeochromocytoma, Cushing's syndrome and acromegaly, are occasionally seen [3, 24–28]. Some oral contraceptive preparations may also induce the combination. Though it is commonly stated that these conditions occur with no greater frequency than in the general population, this was not so in the only systematically investigated hospital series to date [24]. There are usually clinical clues to the presence of each of these and, as each has been well documented [22–25], they will not be discussed further. Apart from a single

**Table 1.** A tentative classification of hypertension in diabetes mellitus

| | |
|---|---|
| Type 1 diabetes: | Hypertension of diabetic nephropathy (systolic + diastolic)<br>Essential hypertension (systolic + diastolic)<br>Predominant systolic hypertension (increasing with age) |
| Type 2 diabetes: | Essential hypertension<br>Hypertension of simple obesity (systolic + diastolic)<br>Predominant systolic hypertension (increasing with age) |
| Endocrine causes: | Thyrotoxicosis<br>Phaeochromocytoma<br>Cushing's Syndrome<br>Acromegaly<br>Renovascular disease and other angiotensin-dependent causes<br>Primary hyperaldosteronism (diabetes very uncommon)<br>Some synthetic oestrogen/progestogen combinations |
| Other secondary causes: | Other renal disease<br>Coarctation, etc.<br>Neurogenic causes |

report [29], there does not seem to be any increase in the prevalence of renal artery stenosis [30].

Essential hypertension may presumably occur by chance in patients with diabetes but, in the absence of a 'marker' for this disease, it is not possible to differentiate it from 'diabetic' hypertension. In patients with Type 1 diabetes below the age of 50 years, diabetic nephropathy appears to be the most common cause of hypertension. Among those with Type 2 disease, some will have hypertension associated simply with obesity while others may have essential hypertension. Systolic hypertension occurs in both groups, especially in Type 2 disease. While it is commonly associated with peripheral vascular disease [31], the relationship between the two is obscure.

All observers are agreed that, anecdotally, accelerated (malignant) hypertension is extremely rare among diabetic patients, unless a secondary cause is present.

## Pathogenesis of Hypertension in Diabetes

The aetiology of hypertension in diabetes, like that of essential hypertension, remains unknown. Some of the many theories of the cause(s) of essential hypertension are summarized in Table 2; this review will concentrate on areas where specific abnormalities have been shown in diabetic subjects with hypertension. Many investigations of the subject have not discriminated between Type 1 and Type 2 disease; it may well be that the pathogenesis of hypertension in the two groups is not the same.

### *Role of the Central Nervous System*

The association between mild degrees of impaired glucose tolerance and hypertension [11] suggests that diabetes may not be the cause of hypertension, but that both might be manifestations of a single defect, perhaps of central nervous origin. Recent suggestions have included a possible role for endogenous opiates which may have profound effects on both blood pressure regulation and glucose homeostasis [34–36]. Similar claims can be made for abnormalities of central catecholamine control [37]. Such proposals are not necessarily exclusive [38].

### *Sodium, Insulin and Blood Pressure*

In Type 2 diabetes there are considerable experimental data and major theoretical considerations why abnormalities of body sodium may be involved. DeFronzo [39] has elegantly studied the role of insulin in sodium reabsorption by the kidney and shown significant sodium retention with only small increases in plasma insulin (30 mU/l); it is thus possible that the basal hyperinsulinism seen in Type 2 diabetes (especially with obesity) may lead to increased exchangeable sodium, as reported by some in essential hypertension. To support this there is evidence that exchangeable sodium is increased by about 10% in diabetic subjects, normotensive and hypertensive, compared with normal age and weight-matched controls [40–42]. This increase could be reversed by diuretic agents which also reduced blood pressure very significantly [41]. This 'obligatory' retention of sodium by insulin should not be confused with the possible role of dietary sodium in hypertension. From a carefully controlled trial by MacGregor et al. [43], it appears that reduction of dietary salt intake to 80 mmol/day will produce a small but significant fall in blood pressure; such data are not available for diabetic subjects but the mechanism may clearly be relevant.

**Table 2.** Some theories of the pathogenesis of essential hypertension

| Theory | Proponent or discussant |
|---|---|
| Mosaic (multifactorial) | Page |
| Excessive sodium ingestion or inability to excrete (with genetic predisposition) | Dahl, Freis<br>Lever |
| Imbalance between salt and water retention and renin-angiotensin system | Laragh |
| Membrane sodium transport defect | Garay, Canessa |
| Cryptic mineralocorticoid excess | Genest, Melby |
| Catecholamine abnormality | de Champlain, Brown |
| Haemodynamic theory | Ledingham, Cohen |
| Baroreceptor resetting | Kezdi |
| Failure of renal autoregulation | Guyton |
| Primary neurogenic origin | Dickinson |
| Natriuretic hormone | Ledingham, MacGregor |
| Intra-renal blood flow redistribution | Britten |

These theories are not necessarily mutually exclusive. References to most may be found in Genest et al. [32] and Mendlowitz [33]

### *The Renin-Angiotensin System*

The renin-angiotensin system has received considerable attention, particularly from Christlieb and his collaborators [44, 45]. Plasma renin activity has been variously reported as normal [40, 44] or high [46] in non-ketotic patients with uncomplicated diabetes mellitus, whether normotensive or hypertensive. When nephropathy or autonomic neuropathy are present, most studies show suppression of renin activity [45, 47]. One recent report of patients with Type 1 disease alone showed higher renin activity (and higher mean blood pressures) in patients with proliferative retinopathy than in matched patients without complications [48]. Several workers have shown an increased vascular sensitivity to angiotensin II in both diabetic patients and animals [41, 49]. Sullivan et al. have shown a fall in plasma angioten-

sin II levels with improved glycaemic control of Type 2 diabetes [50], while falls in plasma renin activity and aldosterone paralleled the drop in blood pressure seen with weight loss in the obese [15]. It may thus be that plasma renin activity, and therefore angiotensin II, are partially suppressed by volume expansion (sodium excess) but still remain inappropriately high.

### *Catecholamines*

Increased vascular sensitivity to plasma catecholamines has been described in diabetic patients with hypertension [41, 49] although plasma catecholamine levels themselves are normal, except with autonomic neuropathy, ketoacidosis, and perhaps during poor control [42, 49, 51, 52]. It is not clear whether they can be reduced by improvement of glycaemic and metabolic control, though they are known to fall with dieting [53].

### *Physical and Other Factors*

Raised blood viscosity and arterial stiffness are among the many physical abnormalities reported in diabetic subjects [54], though their relationship to hypertension is unclear. Recent reports also describe decreased distensibility of the vascular bed in diabetic subjects [55], and abnormal reactivity to stimuli. Increased platelet aggregation is also seen in subjects with diabetes and hypertension, and may be important in the pathogenesis of complications [56].

### *Cause or Effect?*

Many, if not all, of the hormonal and physical findings mentioned above have been derived from studies of patients on conventional diet, oral or insulin therapy who were imperfectly controlled. It remains to be shown whether many of these abnormalities persist with optimal glycaemic control, or whether they are simply secondary changes and thus mechanisms by which poor diabetic control may lead to vascular damage. A further possibility is that initial damage by any such mechanism may eventually lead to irreversible physical changes.

### *The Hypertension of Nephropathy*

No precise mechanism has yet been elucidated although, as described above, there is indirect evidence of increased exchangeable sodium in these patients [45].

## Hypertension and Diabetic Complications

### *Diabetic Retinopathy*

Anecdotal reports have long suggested an association between hypertension and the development of diabetic retinopathy. Several studies have shown an association of hypertension with hard exudates, haemorrhages and other severe retinopathy, but probably not with microaneurysms [57–59]. In the best controlled study yet performed, Knowler et al. [60] examined Pima Indians with predominantly Type 2 diabetes. They demonstrated a twofold excess of exudates developing over a period of 6 years in those with systolic pressures of $> 145$ mmHg compared with those $< 125$ mmHg; this difference persisted when all other known associations were removed. Such prospective reports are not available for Type 1 diabetes but there are retrospective indications of excess hypertension among patients with Type 1 diabetes and retinopathy when compared with matched patients free of eye complications [22, 48]. Postulated mechanisms include increased platelet aggregation [56], increased angiotensin II levels [48], and physical factors [54]. It must however be stated that no controlled study has yet been performed to establish whether effective antihypertensive treatment may prevent the development or progression of retinopathy. Such evidence is urgently required, as it is possible that hypertension and retinopathy are both markers of an underlying severe microangiopathy, rather than hypertension leading to retinopathy.

### *Diabetic Nephropathy*

Renal failure is the cause of death of 20%–35% of patients with Type 1 diabetes [7, 61, 62]. Recent work from Denmark has thrown considerable light on the natural history of this problem. Though it appears that preceding hypertension does not usually contribute to the development of nephropathy [63], nor does it antedate persistent proteinuria, there is now good evidence that it is an early accompaniment of established proteinuria. Parving et al. have shown markedly higher blood pressures in Type 1 diabetic patients with persistent proteinuria than in matched diabetic subjects without proteinuria or in control subjects [23]. Christiansen and colleagues have clearly demonstrated that, in 14 young Type 1 diabetic patients with persistent proteinuria, blood pressure rose from 132/88 to 153/101 mmHg ($p < 0.001$) over a period of 26 months; over the same time glomerular filtration rate decreased from 107 to 87 ml/min per 1.73 $m^2$ [64]. Though one study suggested that the rate of progression of nephropathy was directly proportional to initial blood pressure [65], others have been unable to reproduce this prospectively. Except for a single report [66], it does not appear that even immaculate glycaemic control will reduce the progressive fall in glomerular filtration rate [67, 68], although albuminuria may be decreased both by this and antihypertensive therapy.

However, Mogensen has described significant slowing of the deterioration in glomerular filtration rate in six patients placed on antihypertensive medication [69]. All patients showed a reduction in the rate of deteriora-

tion, while taking triple therapy (beta-blocker, diuretic and vasodilator), though the extent of response was very variable. Further studies are urgently required to confirm this observation and to clarify the optimal mode of treatment and ideal time for intervention.

## Macrovascular Disease

There is little doubt that the incidence of arterial disease is markedly increased in both Types 1 and 2 diabetes, and that this is now the major cause of premature death [7, 61, 62, 70–73]. The risks of hypertension for arterial disease in the non-diabetic population have recently been reviewed [74], though its importance as a risk factor when diabetes is present remains controversial.

### *Coronary Artery Disease*

The relative contribution of hypertension to the risk of coronary artery disease in diabetic patients is uncertain [70, 72, 73]. It also remains unknown whether control of hypertension in the non-diabetic will reduce rates of coronary artery disease. Although the incidence of myocardial infarction in diabetes is further increased by hypertension, the effect is probably only additive. In the Framingham study in particular, diabetic patients did not seem to have an altered ability to contend with other risk factors [72]. In a series of 21 patients with severe nephropathy and hypertension, abnormalities on angiography were present in only 54% [75]. Similarly it remains unclear whether control of hypertension will reduce the incidence of myocardial infarction in essential hypertension; this may relate to the drug regimens used in early trials before beta-blockers were widely available.

### *Cerebrovascular Disease*

Two recent investigations have clarified the extent of this problem. Palumbo et al. have shown a 1.7-fold excess of stroke and a threefold excess of transient ischaemic attacks in diabetic patients [76]. Asplund et al. have confirmed the former observation and shown a close relationship with pre-existing hypertension [77]. Although the prognosis for survival was worse in diabetic subjects with stroke, it was relatively better in those with hypertension as well.

### *Peripheral Vascular Disease*

At least in the older diabetic patient, there is a close correlation between the presence of systolic hypertension and peripheral vascular disease [31, 78]. However, it is not clear whether the former may cause the latter or merely reflect the altered physical properties of the vasculature [54]. Even if the latter is true, high pressure may nevertheless hold its usual risks [79].

## Investigation and Management of Hypertension in Diabetes

The extent of necessary investigation in these patients will depend upon many clinical circumstances: little may be felt justified in the elderly patient with mild systolic hypertension. Four aims of investigation may be defined: (1) determination of any underlying cause, and in particular the exclusion of secondary hypertension; (2) detection of contributory factors, such as poor diabetic control or high salt intake; and assessment of other risk factors (e.g. smoking and lipids); (3) determination of the extent of damage to eyes, kidneys, heart and peripheral vasculature; (4) assistance in the choice of treatment, both for the hypertension itself and for other risk factors [80].

There are usually clinical clues to the presence of thyrotoxicosis, phaeochromocytoma, Cushing's syndrome or acromegaly [24–28]. Renal hypertension, other than that due to diabetic nephropathy, is more difficult to exclude but an intravenous urogram is indicated only where there are unequal renal sizes on plain abdominal radiography, abnormal cells in urine specimens or specific reasons to expect other renal pathology. Patients with Type 1 diabetes or an abnormal serum creatinine require a complete assessment of renal function with estimation of creatinine clearance or glomerular filtration rate, together with urinary protein excretion measurements – Viberti et al. have recently shown that albumin excretion rate may predict subsequent deterioration in renal function, and hence might allow early intervention [81].

## General Measures

Assessment of the patient should include an evaluation of diabetic control and of other risk factors for complications which may be amenable to intervention. There is no clear evidence whether or not poor glycaemic control per se affects blood pressure, but the increasing evidence linking quality of control with occurrence of complications [82] is itself sufficient justification. Other risk factors should, as far as possible, be removed or reduced [80]: smoking for example has been shown to increase blood pressure acutely [83].

Obesity is a major factor in the hypertension associated with Type 2 diabetes; weight loss should be actively encouraged [14, 15]. Sodium intake should be assessed and reduced to reasonable levels (perhaps 80 mmol/day) wherever possible. There is now adequate evidence in non-diabetic subjects that such a restriction will cause a small but significant reduction in pressure [43]. Unfortunately long-term compliance with either of these dietary recommendations is usually poor, although adequate response may avoid the need for drug therapy.

**Table 3.** Specific advantages, disadvantages and limitations of anti-hypertensive agents when used in diabetic subjects

| Drug | Advantages | Disadvantages or limitations |
|---|---|---|
| Beta-blockers | ? Reduction in deaths from ischaemic heart disease | ? Impair recovery from hypoglycaemia<br>? Deleterious effect on lipid profile |
| Diuretics | Restore excess body sodium to normal | May precipitate ketoacidosis or hyperosmolar coma<br>Deterioration of diabetic control (Type 2)<br>? Deleterious effect on lipid profile<br>Can cause orthostatic hypotension |
| Hydrallazine | – | Orthostatic hypotension<br>Tachycardia |
| Prazosin | – | Orthostatic hypotension |
| Spironolactone<br>Amiloride<br>Triamterene | – | Danger of hyperkalaemia, especially if renal function impaired |
| Methyldopa | – | Orthostatic hypotension<br>Deterioration in lipid profile<br>Impotence |
| Clonidine | – | Orthostatic hypotension<br>Impotence |
| Minoxidil | – | Further sodium retention, often severe |

Fuller discussions and references may be found in Passa [84], Husserl and Messerli [85], Christlieb [2], Waal-Manning [92] and Bengstøn [90]

## Drug Therapy

It is salutary to realize how few controlled trials between different antihypertensive medications in diabetic subjects have yet been performed. No firm conclusions about an optimum regimen can thus be drawn, still less any about the long-term efficacy in prevention of complications. Nearly all antihypertensive drugs have significant disadvantages or limitations when used in diabetic subjects (Table 3). Choice of an agent will depend upon the presumed pathophysiology of the hypertension, the type of diabetes and presence of complications, and the potential side-effects of the drug concerned [1–3, 84, 85].

The level of pressure justifying intervention is unknown. A patient with Type 1 diabetes and any evidence of nephropathy should probably be treated aggressively, aiming for below the 50th centile for control subjects of that age: in this situation pressures of 155/90 mmHg cannot be regarded as either normal or acceptable. No firm recommendations can be made for most other situations, even by comparison with the situation in essential hypertension, where the overall benefit for diastolic pressures below 105 mmHg remains incompletely proven [74, 86]. Opinions vary yet more widely regarding systolic hypertension: some authorities would not treat levels of 220 mmHg [87], and there is a little evidence in the elderly non-diabetic that hypotensive agents may indeed be harmful [88]. It is however clear that cerebrovascular, and overall, morbidity and mortality relate more closely to systolic than to diastolic pressure [79]; while firm evidence is awaited [89] treatment of diabetic subjects with systolic pressures (taken with an adequate cuff [16]) above perhaps the 80th to 90th centile for age would seem advisable.

### *Diuretics*

Thiazide diuretics are commonly employed and are rational therapy if sodium excess is accepted as a significant factor in much of the hypertension in diabetes. Weidmann et al. demonstrated a 10% fall in total body sodium, back to normal levels, on diuretics with an improvement in mean blood pressure from 165/93 to 145/82 mmHg [41]. There are, however, a number of disadvantages (Table 3): thiazides have been shown to worsen glucose tolerance in non-insulin-requiring patients, probably because of both hypokalaemia and a further separate action [90, 91]. Apart from their considerable side-effects in any subject, recent evidence from the Medical Research Council trial of mild hypertension suggests that they are also associated with a significant incidence of impotence [86], rendering them less than ideal for many male patients. 'Loop' diuretics have similar limitations. Potassium-sparing drugs should be used with caution, and rarely with renal impairment as deaths from hyperkalaemia have been reported. These and other problems have been extensively and well reviewed [84, 85].

### *Beta-Blockade*

The use of beta-blockers in diabetic subjects remains controversial: comprehensive reviews are available [84, 92]. There is conflicting evidence that some at least may reduce the rate of recovery from hypoglycaemia [92, 93], but their effect on overall diabetic control in Type 2 diabetes appears small [94], and in practice they do not seem to induce an increase in number or severity of hypoglycaemic reactions in insulin-treated patients [95]. Some aspects of awareness of hypoglycaemia may be

affected but, with the increasing use of home glucose monitoring, this may in future be less of a concern. The dangers attaching to their use have probably been overemphasized, although there remain problems when peripheral vascular disease is present. Evidence on their hypotensive efficacy in diabetes is variable, reductions of as much as 29/14 or as little as 12/4 mmHg being reported [94–97]. A possible theoretical benefit of beta-blockade, unrelated to blood pressure control alone, is the postulated reduction in myocardial infarction in this high-risk group, though this is totally unproven. The advantages of cardio-selectivity are often extolled, though at clinically relevant dosage much of this may be lost. On balance, however, cardio-selective drugs such as acebutolol, atenolol and metoprolol are to be preferred as they probably cause less metabolic disturbance and possibly fewer peripheral vascular symptoms [84, 92].

### *Other Drugs (Table 3)*

The usage of antihypertensive drugs varies considerably between Europe and the USA [1–3, 84]. Most European physicians with an interest in hypertension no longer use either reserpine or the ganglion blockers, both being especially unsuitable in diabetes because of their postural and potency effects [84, 85]. Passa [84] provides a full review of the advantages, disadvantages and limitations of the various agents when used in diabetic subjects. The main problems relate to orthostatic hypotension, high incidences of impotence and allegedly deleterious changes in plasma lipid patterns [84, 97]. Apart from methyldopa [97] few studies of more than a handful of diabetic patients have been performed; this is even more true of recently introduced drugs such as labetolol, indapamide, minoxidil and captopril.

Failure to control hypertension with two or three drugs warrants serious reconsideration of the possibility of an endocrine or other secondary cause. The multiple drug therapy usually employed in such 'refractory' patients [98] is often associated with a high incidence of toxicity, perhaps especially so in diabetic subjects. We have recently found the combination of captopril, an angiotensin converting enzyme inhibitor [99], with diuretic to be effective and well-tolerated in three patients with Type 2 diabetes and 'refractory' hypertension. Mean blood pressure while on beta-blocker, diuretic and vasodilator was 183/114 mmHg; after 6 months on captopril and diuretic it was 152/95 mmHg [Drury PL, unpublished observations]. Controlled studies are required.

### *Selection of Therapy*

The choice of therapy in the diabetic is a difficult decision and must be tailored for each individual patient. In general, thiazide diuretics and beta-blockers, despite their major limitations, remain the initial agents [1–3, 84], usually being combined where one is inadequate. Which of the two is preferable is not clear even in the non-diabetic population [100]. Good blood pressure control must be balanced against side-effects and problems of patient compliance: the physician must be especially alert for insidious side-effects, such as tiredness, breathlessness and drug-related impotence [86]. It is to be hoped that adequate studies enabling a more rational selection of therapy will soon be available.

## Conclusion

The balance of evidence suggests that hypertension is increased in frequency among the diabetic population as a whole, with major components associated with nephropathy (Type 1 disease) and obesity (Type 2 disease); predominant systolic hypertension occurs in older patients with both types of disease. Pathogenetic mechanisms are unclear, although obesity itself is a significant, and potentially reversible, factor. There is extensive evidence that both microvascular and macrovascular disease are more common when hypertension is present, although only in the case of nephropathy is there yet reasonable proof of benefit from effective antihypertensive treatment. If results obtained in the non-diabetic are taken as a guide while further studies are awaited [89], adequate control of blood pressure may significantly reduce the excess mortality and morbidity associated with both Types 1 and 2 diabetes, certainly from cerebrovascular and renal disease, though not clearly so from coronary artery disease. Whilst all antihypertensive drugs have particular limitations in the diabetic patient [84], they do appear to reduce blood pressure; choice of an effective but well-tolerated regime is a matter of considerable skill for the physician. If intervention can indeed be shown to prevent or slow the development of nephropathy, retinopathy and large vessel disease, then the frequency of hypertension among the diabetic population suggests that adequate detection and treatment of high blood pressure may be among the most important fields of preventive care available to the diabetologist.

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