SHOULD THE COSTS OF DEVELOPMENT INHIBIT RESEARCH INTO NEW ANTIHYPERTENSIVE DRUGS?

SUMMARY. Although hypertensive therapy has had spectacular successes, there is now an important trend away from mere control of blood pressure to the attempt to normalize the cardiac and vascular accompaniments of the disease, such as left ventricular hypertrophy and medial hypertrophy of resistance arterioles. New agents may need to be developed to cope with these specific aims. The costs of development should not inhibit these important goals.

KEY WORDS. hypertension, cost effectiveness, antihypertensive drugs, research

The therapeutic and preventive achievements of antihypertensive drug use are substantial and undeniable. The malignant phase and hypertensive heart failure can be cured or prevented, and prophylactic antihypertensive drugs have been shown to diminish the attack rate of stroke and to retard the speed of progression of hypertension-related renal functional impairment [1–3].

Indeed the magnitude of the attainments of antihypertensive treatment is probably greater than often claimed. The much-quoted but indiscreet concluding statement of the Medical Research Council trial of mild hypertension [4], namely, that 850 persons with mild hypertension need to be treated for 1 year in order to prevent one stroke, almost certainly underestimates the extent of benefit. In that trial, 1011 patients considered to be most at risk were transferred from placebo to active therapy, although they were subsequently evaluated as though they had remained on placebo. These were the very patients in whom morbid events were most likely to occur. It was against these events that the benefits of antihypertensive therapy should most readily have been measured. In that trial, 1011 patients considered to be most at risk were transferred from placebo to active therapy, although they were subsequently evaluated as though they had remained on placebo. These were the very patients in whom morbid events were most likely to occur. It was against these events that the benefits of antihypertensive therapy should most readily have been measured. In that trial, 1011 patients considered to be most at risk were transferred from placebo to active therapy, although they were subsequently evaluated as though they had remained on placebo. These were the very patients in whom morbid events were most likely to occur. It was against these events that the benefits of antihypertensive therapy should most readily have been measured. In that trial, 1011 patients considered to be most at risk were transferred from placebo to active therapy, although they were subsequently evaluated as though they had remained on placebo. These were the very patients in whom morbid events were most likely to occur. It was against these events that the benefits of antihypertensive therapy should most readily have been measured.
controversial affair of the so-called J-shaped curve [11-17]. Clearly, there must be a level of arterial pressure below which blood pressure reduction enhances, rather than diminishes, risk. It has been suggested that this level lies, at any rate in subjects with coronary artery stenosis, rather higher than had often been supposed, possibly as high as a fifth-phase diastolic pressure of 85 mmHg. This important issue urgently requires resolution.

Fifth, potentially adverse biochemical accompaniments of some drug classes, for example, potassium and magnesium depletion or glucose intolerance induced by diuretic therapy, or distortions of plasma lipid patterns caused by diuretics or beta-adrenoceptor blocking agents, may in part have offset the benefits to be obtained from blood pressure reduction [8, 9].

Sixth, and potentially of greatest future exploitation, is that antihypertensive drug treatment hitherto has focused on blood pressure reduction per se, to the relative neglect of important vascular accompaniments of hypertension such as left ventricular hypertrophy, loss of compliance and distensibility in large arteries, and medial hypertrophy in resistance arteries [16, 17]. There is now compelling evidence that hypertensive left ventricular hypertrophy as such predisposes individuals to subendocardial ischemia and to impaired diastolic filling of the coronary arteries. Reduced compliance in larger arteries leads to a disproportionate elevation of systolic pressure, while also causing blood flow turbulence, endothelial lesions, and thus atheromatous plaque formation. Because medial hypertrophy in resistance arteries reinforces, via simple geometric principles, blood pressure elevation, only partial regression of such hypertrophy with treatment must necessarily also constrain the extent of therapeutic blood pressure reduction.

There are therefore adequate reasons for the limited, however spectacular, success of antihypertensive therapy. The achievements have been particularly related to those complications that derive most directly from high arterial pressure, namely, the malignant phase, hypertensive heart failure, hemorrhagic stroke from rupture of microaneurisms, and lacunar infarcts from fibrinoid necrotic arteriolar damage. Coronary artery disease and atheromatous cerebral arterial lesions, consequences of arterial blood flow disturbances, have, by contrast, been improved modestly, if at all [8, 16].

Therefore, there should now, for the reasons given, be increasing attention paid to newer antihypertensive agents that, while lowering arterial pressure, can also facilitate regression of hypertensive left ventricular hypertrophy and medial hypertrophy in resistance vessels, while improving distensibility and compliance in larger arteries. Avoidance of biochemical, electrophysiologic, and symptomatic drug side effects is obviously also highly desirable.

These goals do not exclude the possibility of ancillary benefits that are less obviously related to hypertension. For example, the incidence of serious adverse vascular events has been found to be reduced by 25% in patients at risk of occlusive vascular disease by treatment with drugs that can broadly be described as “antiplatelet agents” [18]. Provided that the risks of hemorrhage are not correspondingly increased, an antihypertensive drug that also has such properties could be especially useful in obviating hypertension-associated vascular disease.

In my opinion, therefore, muted but appropriate satisfaction with the achievements of antihypertensive therapy should not yield to complacency. Complacency nonetheless exists; indeed appears widespread, with confident assertions being made that we now possess a sufficient repertoire of drugs, with some, notably the thiazide diuretics, having the added attraction of low cost [19-21]. The adequacy and safety of diuretics, in particular, is not rarely held to be substantiated by their evident superiority over placebo in preventing cardiovascular complications of hypertension [20, 21]. Such claims miss the point. The concern is not simply whether diuretics are beneficial; clearly they are, but it is whether they might be a great deal more beneficial if they did not have the disadvantages of causing potassium and magnesium losses and cardiac ventricular ectopy, impairing glucose tolerance, and distorting the plasma lipid pattern in a potentially adverse fashion [2, 3, 8, 16].

My case is based therefore on the dual premise that we need antihypertensive agents that carry fewer unwanted effects, while addressing and correcting cardiac and vascular abnormalities, apart from high blood pressure as such, and already described in detail—abnormalities that accompany arterial hypertension and give rise to a range of its complications.

The foregoing outlines the medical and scientific case to be considered in addressing the question, “Should the costs of drug development inhibit research on new antihypertensive agents?” The answer in my view is unequivocal: They should not. The concern of the medical profession is to ensure that the issues are clearly and dispassionately presented and that the benefits and demerits of drugs are critically evaluated. This involves scrupulous clinical pharmacologic and therapeutic trial assessment. These