and by 1987 half the targets had been achieved.[11] Clearly, establishing and tracking measurable national objectives helped to form a national health agenda and identify explicit health policies. It also identified issues where further attention was needed.[12]

Building on this progress, the Americans have recently published their objectives for the year 2000.[13] Twenty two priorities are presented under three overarching goals—increasing healthy life span, reducing disparities in health, and improving access to services. What is impressive is how these targets have been formulated. Work began in 1987 with the convening of a consortium, which now includes 300 national organisations. Some 10 000 people were consulted, and 750 discrete responses have been received. The American targets therefore do not reflect the views of just one organisation but are rather the product of a national process. Such participation is vital for there to be a real sense of ownership and common purpose.

The quality of their work is also impressive. Figures are not plucked from the sky but are founded on careful analysis of trends, opportunities, and challenges—an approach that Wales has also been following. Nor are targets merely set where information to monitor them already exists: if a subject is important enough for an objective to be proposed then a method of monitoring it must be found.

New Zealand provides another case study. Health goals and targets are being used to reorient the health system systematically "to provide a focus and direction." "Goal and target setting is a basic pre-condition to effective management and is the basis for accountability for both the use of health resources and for achieving health care outcomes."[14] Targets are incorporated into contracts with area health boards.

For health targets to cascade through the NHS, regional and district health authorities will need to draw on a set of new skills and invest in more monitoring of health states. Public health medicine has a unique part to play, and already the faculty has developed an initiative on "United Kingdom levels of health." This will be reported in June and should give guidance on methods and approaches as well as recommending valid indicators of health and suggesting targets. Another important task will be to identify missing information on the health of the nation as the common dataset for public health is patchy.[15]

There has probably never been a better moment for the United Kingdom to develop and implement a comprehensive national health strategy using targets to provide direction and pace. There is all party support, the offer of help from the Faculty of Public Health Medicine, and considerable experience to draw on from within the United Kingdom and overseas. Our NHS, which has so many good things about it, has another opportunity to lead.

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New developments in renin and hypertension

Tissue generation of angiotensin I and II changes the picture

The renin-angiotensin system plays an important part in cardiovascular homoeostasis through the actions of angiotensin II on target organs such as the kidneys, the blood vessels, and the adrenals.[1] Standard teaching is that renin secreted by the kidney acts on circulating angiotensinogen produced by the liver to release angiotensin I; this is converted to the active angiotensin II by angiotensin converting enzyme (ACE), mainly in the pulmonary circulation.[1]

This classic concept has been challenged by several recent observations that suggest that the primary site of generation of both angiotensin I and II may not be in the circulation but in tissues and that the vital step in the cascade may not be the delivery of angiotensin II but the delivery of renin and angiotensinogen to tissues.[2,3] Angiotensin II would then be formed locally. Further recent research has shown the presence of messenger RNA for renin[4,5] and angiotensinogen[6] in a wide variety of tissues—indicating that both may also be locally synthesised. Such locally synthesised components might interact with components derived from the circulation and critically determine the amount of tissue angiotensin II being generated. The overall effect of the system would then result from the sum of local generation of angiotensin II at multiple sites, each of which could be differently regulated.

This revised concept has important implications for our understanding of the role of the renin-angiotensin system in hypertension. In particular, it suggests that the concentrations of circulating renin and angiotensin II may not accurately reflect the activity of the system in this condition. Although there is no evidence to suggest selective uptake of renin or angiotensinogen into tissues in any form of hypertension, angiotensin converting enzyme activity has been found to be raised in vascular tissue in at least one model of renovascular hypertension at a stage when the circulating renin level is falling.[7] This raised activity may play some part in maintaining the hypertension.[7]

Increasing evidence is also accumulating that in various forms of hypertension locally synthesised tissue renin may also be important. Thus concentrations of renin messenger RNA have been found to be raised in several tissues in rats with spontaneous hypertension—a recognised genetic model[8]—and in the adrenal glands of rats with chronic renovascular hypertension.[9] Even more dramatic evidence has recently

come from an experiment by Mullins *et al*, who introduced a mouse gene for renin into very early rat embryos.[10] The resultant transgenic rats with the mouse renin gene incorporated into their genome developed severe hypertension. The expectation that these animals would have raised circulating concentrations of renin turned out not to be the case. In fact renin activity in the plasma and renal renin concentrations were, if anything, low—suggesting suppression by a feedback mechanism. On the other hand, concentrations of renin messenger RNA and renin activity were both found to be appreciably increased. Intense research is now going on to define the role of tissue renin and establish the mechanisms causing raised blood pressure in these rats—in which (for the first time) the genetic defect underlying the hypertension is precisely known: an extra renin gene. The findings may well increase considerably our understanding of hypertension in humans.

Implicit in the revised concept of the renin-angiotensin system outlined above is that the antihypertensive efficacy of inhibitors of the system is likely to depend on their effects not in the circulation but in critical tissue sites.[11] While this remains to be specifically shown, it could provide at least part of the explanation of the effectiveness of ACE inhibitors in lowering blood pressure when circulating concentrations of renin are not raised or indeed low.[12,13] It could also explain the dissociation recently observed between the antihypertensive effects of a renin inhibitor and its effects on circulating renin activity and angiotensin II concentration in patients with essential hypertension.[14]

The implications of generation of angiotensin in local tissue extend beyond the effects on blood pressure. In the kidney such generation of angiotensin may determine blood distribution, especially in conditions in which renal perfusion is impaired, such as renal artery stenosis; and the deleterious effect of ACE inhibitors on renal function sometimes seen in this condition would then also be understandable.[15] Likewise, the beneficial effects of ACE inhibitors in decreasing proteinuria in patients with diabetes may reflect a specific effect on intrarenal formation of angiotensin II and therefore glomerular haemodynamics.[16,17]

Angiotensin II has been shown recently to stimulate the growth in culture of vascular smooth muscle cells—possibly through induction of proto-oncogene expression.[18] Although there is no direct evidence for such an effect in vivo, local generation of angiotensin in the heart and vascular wall might play a part in causing vascular and cardiac hypertrophy.[18] Structural vascular changes may be important in the long term determination of vascular resistance[19] and of large artery compliance[20]—both important factors in hypertension—and left ventricular hypertrophy has been shown to be an independent risk factor for cardiovascular mortality.[21] Some experimental studies have suggested that ACE inhibitors may cause a greater regression of cardiac and vascular hypertrophy[22,23] and a greater increase in arterial compliance[20] than other equipotent antihypertensive agents, and these properties are now being exploited in the marketing of these agents. These are, however, as yet hypothetical advantages of ACE inhibitors and have yet to be translated into evidence of clinical benefits in the form of reduced cardiovascular morbidity and mortality.

The current assessment is that at most sites locally synthesised renin and angiotensinogen probably interact with components derived from the circulation in determining local production of angiotensin. In a few, however, and especially those with no immediate cardiovascular connection, such as the reproductive tract, there may be distinct tissue renin-angiotensin systems subserving autocrine or paracrine functions entirely independent of the circulating system.[24] Speculation about the possible functions of such systems has preceded any evidence of the spatial and functional existence of such independent tissue systems.[25] A further possibility is that in such sites renin or angiotensinogen may actually have functions that are not mediated through generation of angiotensin at all.[24] Angiotensinogen, for instance, shows considerable homology with the serine proteinase inhibitors such as α_1-antitrypsin,[26] and could have other functions.

Clearly, many questions remain to be answered about tissue renin-angiotensin systems; not the least is which factors regulate the local synthesis of components of the cascade. With the molecular methods now available the answers to many of these questions are likely to become much clearer in the next few years. This is occurring at the same time as novel inhibitors of the system (renin inhibitors[14] and angiotensin II antagonists[27]) are being developed for clinical use. We are there entering a most exciting stage in our understanding of the actions of the renin-angiotensin system and in our ability to manipulate it.

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