INTRODUCTION

It is now clear that the pathophysiology of hypertension in man varies from subject to subject. Renin and aldosterone levels, blood pressure response to angiotensin antagonists, converting-enzyme inhibitors and diuretics, and other measures indicate that angiotensin plays a preponderant role in some patients, while volume is more important in others. Laragh [1-3] feels that all naturally occurring human hypertensive diseases can be arranged in a pathophysiologic spectrum that ranges from a preponderant dependence on angiotensin to a preponderant dependence on effective blood volume. Malignant hypertension and primary aldosteronism are the clinical expressions of these polar extremes. Within the spectrum are the intermediate forms of hypertension exhibiting an inappropriate excess of one of these factors relative to the other, unilateral renovascular and high-renin essential hypertension at one end and low-renin essential hypertension at the other end.

Low-renin patients, whose high blood pressure appears to be associated with overfilling of the central circulation, often are hemodiluted relative to the high-renin patients and, in contrast to the latter subjects, fail to respond to antirenin drugs [2]. They do respond to diuretics, however [2].

The mechanism of the elevated pressure in low-renin patients is not clear. It does not appear to be related to the blood volume per se, since sudden increase in volume in normal subjects or animals does not immediately raise pressure (see references in [4]). It does raise pressure with time however, suggesting some indirect effect of the increase in volume.

It is this indirect mechanism that has occupied our research time in recent years. We have reproduced a number of models of low-renin hypertension in animals and examined indices of sodium-pump activity in their blood vessels, because it is known that they contain excess sodium [5] and that normal blood vessels respond to sodium-pump inhibition with constriction (see references in [6]). We have also examined the plasma for sodium-pump inhibiting activity. We here summarize our findings, as well as related findings of others.
EVIDENCE FOR SUPPRESSED SODIUM-PUMP ACTIVITY

We used ouabain-sensitive $^{86}$rubidium uptake by freshly excised blood vessels and Na$^+/K^+$-ATPase activity of cardiac microsomes (mainly sarcolemma) as indices of Na$^+/K^+$ pump activity in four models of low-renin hypertension. These included one-kidney, one-wrapped hypertension in the dog and one-kidney, one-clip; one-kidney, DOCA-saline; and reduced renal mass-saline hypertension in the rat. Both indices were suppressed relative to those in appropriate normotensive control animals.

The $^{86}$Rb-uptake technique was adapted to blood vessels by Pamnani [7]. The technique measures maximum capacity to pump rubidium, which is handled by the pump like potassium. Rubidium is used instead of potassium because its radioactive form has a lower energy emission and longer half-life than the radioactive form of potassium. The vessels were taken from the animal and immediately placed in a cold potassium-free solution to stop the Na$^+/K^+$ pump and load the cells with sodium. They were then placed in a warm solution containing nonradioactive rubidium to start up the pump. The solution also contained $^{86}$Rb, and its uptake was measured 18 minutes later. This was examined both in the absence and presence of ouabain. The difference is the ouabain-sensitive $^{86}$Rb uptake, which reflects active pumping of sodium and potassium. The uptake in the presence of ouabain, i.e., the ouabain-insensitive $^{86}$Rb uptake, reflects distribution of $^{86}$Rb in extracellular space and passive penetration into cells (determined by cell membrane permeability and surface area).

Ouabain-sensitive $^{86}$Rb uptake was significantly reduced in the arteries of all four models after four weeks of hypertension, whereas ouabain-insensitive $^{86}$Rb uptake was unaffected (except in the DOCA model where it was increased [7-11]). In the one-kidney, one-wrapped model, the defect was also present in mesenteric veins [7, 10], indicating that it does not result from elevated pressure. A time-course study in the reduced renal mass-saline model showed that the onset of the hypertension correlated with the onset of reduced pump activity [12].

Na$^+/K^+$-ATPase activity was measured in cardiac rather than vascular smooth muscle microsomes, because the methods for measurement in the latter are still rudimentary. Na$^+/K^+$-ATPase activity in cardiac microsomes of the rats was calculated as the difference between total ATPase activity (measured in the presence of potassium) and Mg$^{++}$-ATPase activity (measured in the absence of potassium and in the presence of ouabain). Na$^+/K^+$-ATPase activity was significantly reduced in all three rat models of low-renin hypertension, whereas Mg$^{++}$-ATPase activity was increased [13-15]. In the case of the one-kidney, one-clip model, the findings were the same in microsomes obtained from the right ventricle [16], again indicating that the defect is not secondary to elevated pressure.

The findings in the one-kidney, DOCA-saline model are of special interest because they suggest both increased permeability (increased ouabain-insensitive $^{86}$Rb uptake) and decreased pump activity (decreased ouabain-sensitive $^{86}$Rb