now supported by findings from other clinics.[9, 16, 17]

The most impressive and consistent abnormality observed in the present investigation was the striking increase in the concentration of plasma angiotensinogen. In every instance it was possible to demonstrate that this observed increase in renin substrate concentration was associated with a marked enhancement in the rate of angiotensin formation upon addition of a fixed amount of endogenous renin to the plasma. These increased responses suggest that increases in the concentration of substrate above normal levels can exert an important accelerating influence on the rate of production of angiotensin, so that the rate of angiotensin formation can be increased by as much as the factor of two. The finding is somewhat surprising, since it has previously been thought that substrate is normally present in amounts which are sufficient to provide nearly maximum enzyme velocity.[12, 14, 15] However, while the findings in this study demonstrate that normal concentrations of renin substrate are insufficient to produce a maximum rate of reaction with renin, they also suggest that, from a physiologic standpoint, the suboptimum substrate concentrations of normal subjects are probably not rate limiting for angiotensin production. This is strongly suggested by the observation that when substrate concentrations are elevated by this drug, there is often a tendency for the renin concentration to fall so that the rate of formation of angiotensin tends to remain unchanged. Thus, there is a tendency to autoregulate the formation of the final product, angiotensin.

In addition to their effects on substrate concentration, these hormonal substances appear to act by another means to produce true increases in levels of plasma renin. Thus, in some patients increased endogenous plasma renin activity could be accounted for by increases in the plasma angiotensinogen concentration. However, in others, either transient or sustained increases in renin activity were of greater magnitude than could be accounted for by the aforementioned mechanism. It therefore seems likely that these female hormonal substances can act by other, possibly more direct, means to increase plasma renin concentration. It is clear that the increases in plasma renin were not consequent to induced sodium depletion, since oral contraceptives or their components generally tend to promote fluid retention.

The relevance of the observed derangements in the renin-angiotensin-aldosterone system to the associated production or augmentation of hypertensive disease remains obscure. This is because we have repeatedly observed the same abnormalities in patients receiving the same medications, who at the same time exhibited no change whatever in their blood pressure. However, one may speculate about the possibility that in certain susceptible individuals the induced increased reactivity toward endogenous renin may reduce the buffer capacity of this hormonal interaction. In this way the increased responsiveness to renin, perhaps aided by the second direct stimulating effect on renin secretion, might create a situation leading to an exaggerated pressor response to the usual physiologic stimuli for renin release. This idea that, in certain subjects, feedback compensation for the angiotensinogenemia produced by these drugs may be incomplete, is perhaps supported by our observations illustrating that only some patients fully compenated for the induced increases in renin substrate levels by suppressing their renin secretion.

One can only speculate about the factors which might act to sensitize certain individuals to the pressor action of these contraceptive agents. Pre-existing occult renal disease with reduced buffer capacity of the renin angiotensin system may be one factor as evidenced in 2 such patients included in our series and in one other now under study. Another sensitizing factor may be related to the tendency for sodium and water retention produced by these drugs in certain individuals. In future studies serial measurements of sodium balance or of sodium spaces or weight fluctuations[18] in outpatients may be especially illuminating. The oft repeated pro-