

However, the complete reversal of documented hypertension after drug withdrawal in 3 of 9 and the improvement of hypertension in another 3 of the 9 raise the possibility of a more specific relationship. In Fig. 1 the time course for blood pressure improvement and for correction of associated abnormalities in the renin-angiotensin system is presented for 4 of these patients.

In 2 patients, in each of whom correction or considerable improvement in blood pressure was observed after drug withdrawal, the oral contraceptives were readministered. In both, hypertension returned and, concurrently, characteristic abnormalities in the renin-angiotensin-aldosterone system reappeared. Such sequential observations (Fig. 2), demonstrating reappearance and disappearance of hypertension, perhaps provide the most convincing evidence, suggesting a specific connection between the administration of oral estrogen-progestogen and the development of high blood pressure.

One patient (Table II) who had hypertension prior to the use of contraceptives also seems to have been cured of the condi-

tion by drug withdrawal.¹ She first developed hypertension during pregnancy and subsequently underwent nephrectomy for unilateral renal infection. Pre-existing hypertension in the region of 180/110 persisted during 20 months of oral contraceptive therapy. However, she has now been normotensive for over a year since stopping medication.

Effects on renin substrate. The most consistent attendant biochemical abnormality was the appearance of marked and persistent increases in the concentration of plasma angiotensinogen, observed in all but one of the hypertensive women studied (Figs. 1 to 4). The elevated values ranged from 1,980 to 8,650 ng. of angiotensin generated per milliliter of plasma or to as much as eight-fold the normal concentration. In 2 normal male subjects and in one male hypertensive patient (Figs. 5 and 6), entirely similar changes were produced by treatment with these agents.

The maximum effect on renin substrate with the use of a combined estrogen-progestogen was observed to develop from as soon as 4 days to as long as 2 weeks after starting

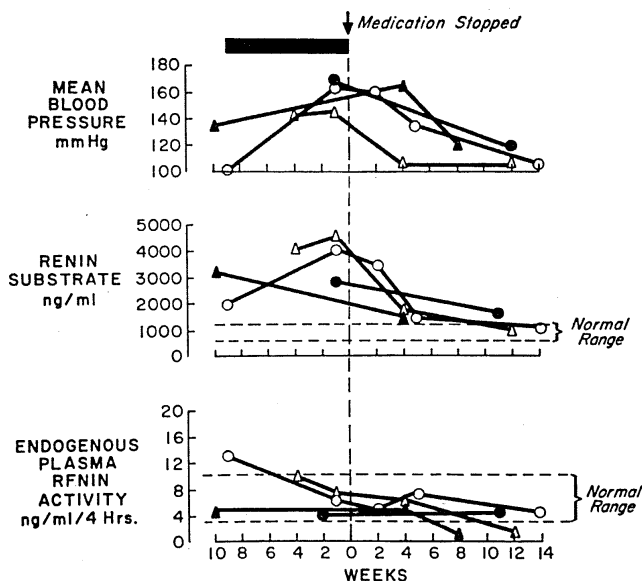


Fig. 1. Effects of withdrawal of oral contraceptives in 4 patients. After withdrawal of medication elevated blood pressure was improved in 2 and completely corrected in 2 others. At the same time elevated renin substrate levels returned to normal and plasma renin levels, though not abnormal, tended to decline. It is of note that plasma renin levels were at times elevated earlier in treatment but tended to decline as therapy was continued.