this effect appeared to be largely due to the presence of the progestogen, norethynodrel, in the preparation.[9,10] It has also been shown that the administration of Enovid can produce significant increases in a plasma aldosterone-binding protein, an effect which seemed to be due to the estrogenic component of the medication.[11]

The most impressive and consistent abnormality observed in the present study was the striking increase in the concentration of serum renin-substrate. This observation confirms the original report of Helmer and Griffith[12] which demonstrated a marked increase in renin-substrate in rats given diethylstibestrol. Helmer and Griffith also found that the effect did not occur with progesterone, could be neutralized by the administration of androgen, and was not modified by removal of the pituitary or adrenal glands.

In every instance studied, it was possible to demonstrate that the 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 serum. These observed increases in reactivity to renin suggest that increases in the concentration of substrate above normal can exert an important accelerating influence on the rate of production of angiotensin. The finding is somewhat surprising since it has been thought that substrate is normally present in amounts which are sufficient to provide nearly maximum enzyme velocity.[4,13] The possibility of a qualitative alteration in the substrate molecule or of a role for an activator or inhibitor of the renin-substrate reaction remains to be investigated. Despite the presence of increased substrate and increased substrate reactivity, persistent increases in net endogenous renin "activity" were only observed in about half of the patients. These data indicate that the true renin concentration, when corrected for the augmenting effect of the increased substrate, must at times have been actually reduced as a consequence of oral contraceptive administration. Recently, Crane et al[14] have reported increases in plasma renin activity in seven normal subjects who were given doses of ethinyl estradiol. The dosage employed was much larger than that contained in oral contraceptive medications. An effect on renin-substrate levels was not considered, although this may have been a major factor in the observed increases.

The relevance of these observed biochemical abnormalities to the production or augmentation of hypertension remains obscure because we have repeatedly observed the same abnormalities in patients exhibiting no change whatever in their blood pressure. One can only speculate about the possibility that in certain susceptible individuals the induced increases in substrate concentration lead to an increased reactivity towards endogenous renin which cannot be adequately compensated for by appropriate adjustments in the complex homeostatic systems which normally operate to regulate blood pressure and salt balance.

Because the renin-substrate is made in the liver,[15] and because estrogens appear to increase[11] or decrease[16] the synthesis of various other proteins, it seems possible that the estrogens raise the serum renin-substrate by stimulating hepatic biosynthesis. An alternate possibility would be an effect of estrogens on the kidney, since renal insufficiency and nephrectomy often produce sharp rises in renin-substrate concentration.

The possible relevance of the effect of steroids with estrogenic and progestogenic activity on the pathogenesis of hypertensive disease, and especially on the hypertensive states occurring during pregnancy, will require much more study. This preliminary report is submitted to alert clinicians to a possible relationship.

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Generic and Trade Names of Drugs

Norethindrone with mestranol—*Ortho-Novum, Norinyl, Norinyl-1.*
Norethynodrel with mestranol—*Enovid, Enovid E.*
Dimethisterone with ethinyl estradiol—*Oracon.*
Ethynodiol diacetate with mestranol—*Ovulen, Metrulen.*

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