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Oral Contraceptives

Renin, Aldosterone, and High Blood Pressure

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A relationship was established between the institution of oral contraceptive therapy and the development or enhancement of high blood pressure in eight of 11 patients. In six of eight patients who stopped taking medication, marked improvement or complete correction of hypertension occurred. In two patients, with a second trial of treatment, hypertension again appeared and disappeared. Oral contraceptive therapy produced impressive abnormalities in renin-substrate concentration and in its reactivity to exogenous renin as well as in endogenous renin activity and aldosterone excretion. The relevance of these abnormalities to the development of hypertension is not clear because similar effects occur in treated normotensive women. Further study of a possible connection between excesses of estrogenic and progestogenic substances, renin, aldosterone, and hypertension seems warranted.

This communication stems from clinical observations, made in certain hypertensive patients, which raise the possibility of a cause-and-effect relationship between the use of oral contraceptive therapy and either the development or the enhancement of arterial hypertension. Because of the widespread use of oral contraceptives, it seems likely that, in the large majority of patients, these medications do not induce an increased blood pressure. However, observations in 11 patients suggest the possibility that in exceptional circumstances these medications may be critically involved in the production of hypertensive disease. Five of the patients were regular members of our Nephritis-Hypertension Clinic; six others were referred from outside sources.

Six of the 11 patients observed were known to have been normotensive prior to the institution of an oral contraceptive regimen, and in four of nine patients who have discontinued medication, blood pressures have returned to normal or have improved. Furthermore, in two patients who had preexisting hypertension, withdrawal of the hormonal therapy was followed by a marked improvement in hypertension. Perhaps of special relevance to the proposed relationship are the additional observations that the administration of oral contraceptives produced very striking increases in renin-substrate levels and that these increases were frequently accompanied by abnormalities in aldosterone excretion and serum renin levels.

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Methods and Materials

Eleven women with high blood pressure were observed. Their ages ranged from 30 to 49. Using previously defined criteria,[1] we classified eight women as having uncomplicated benign "essential" hypertension, two as having renal hypertension, and one as having advanced hypertension. In addition to a complete history, physical examination, and routine laboratory work-up, all patients were repeatedly tested for abnormalities in plasma electrolytes. Renal function was evaluated by rapid-sequence pyelography[2] in all 11 and by renal arteriography in four. Three of the patients (No. 2, 6, and 11) were admitted to the metabolism ward and were studied by the use of controlled conditions of electrolyte and metabolism balance. None of the patients included in the study had been taking medications other than the oral contraceptives, except for the use of occasional sedatives. All patients had unrestricted diets, except for carbohydrate restriction in one with diabetes.

Aldosterone secretion or excretion rates were measured by a double-isotope dilution technique previously described.[1,3] Blood samples for estimation of renin were taken at noon, when the patients had been ambulatory for about four hours. Renin activity, renin-substrate concentration, and the rate of angiotensin formation in response to a fixed amount of exogenous renin were all measured by slight modification of the method of Pickens et al.[4] Serum was used rather than heparinized plasma because heparin inhibits the in vitro reaction of renin with its substrate.[5] Blood was drawn into tubes which were chilled immediately after collection. Rapid coagulation was achieved by the addition of 17 units of thrombin per milliliter. Highly purified angiotonase-free renin was prepared from human kidneys according to the eight-step procedure of Haas.[6] Techniques used for measurement of urine and plasma electrolytes have been previously reported.[1]

In normal subjects, both aldosterone secretion or excretion rates and the level of serum renin activity fluctuate as inverse functions of the state of sodium balance. Therefore, to identify abnormalities, all such measurements must be evaluated in relation to the dietary sodium intake or the rate of urinary sodium excretion. In normal subjects, the latter value closely reflects the salt intake. Nomograms of this relationship have been published.[1,7] It may be stated here that the mean aldosterone excretion rate is 19.8μg/day when the daily rate of urinary sodium excretion ranges from 60 to 120