mEq. With sodium excretion rates in excess of 120 mEq/day, mean aldosterone excretion is 14.6μg/day. In ambulatory subjects, the midday serum renin levels range from 2.7 to 10.4 mμg/ml for four hours of incubation (mean: 6.5 mμg/ml) when the sodium excretion rates range from 40 to 120 mEq/day. With salt excretion rates in excess of 120 mEq/day, renin levels range from 2.1 to 4.4 mμg/ml for four hours of incubation (mean: 3.2 mμg/ml). With sodium depletion, as evidenced by a urinary sodium content of less than 40 mEq/day, both aldosterone and renin can increase to much higher levels. The serum renin-substrate concentration normally ranges from 500 to 1,500 mμg/ml with a mean value of 1,000 mμg of angiotensin formed per ml.

Results

The association of oral contraceptive therapy with changes in blood pressure, aldosterone excretion, sodium excretion, renin and renin-substrate levels is summarized in the Table.

Effects on Arterial Blood Pressure.—The first four patients were known to have had hypertension prior to the initiation of oral contraceptives. Withdrawal of medication in patient 1 did not have any apparent effect on the degree of hypertension. In patient 3, slight improvement was observed. Cessation of therapy in patient 4 was associated with a striking return of her arterial blood pressure to normal levels. Patients 5 to 10 were all known to have been normotensive prior to the institution of hormonal therapy. After the medication was stopped in patients 6 to 10, blood pressures returned to normal patients 8 and 10) or improved (patients 6, 7, and 9) in a period of from three weeks to three months. Four months later, blood pressure was again elevated in patient 6. Patients 8 and 9 are of special interest because severe hypertension was first noted after institution of oral contraceptive regimens. The abnormality greatly improved in both after cessation of therapy. Furthermore, in both, resumption of therapy with another contraceptive preparation was associated with the reappearance of impressive hypertension, which again disappeared after terminating the treatment. Patient 11, who was known to be hypertensive for ten years, was given norethynodrel with mestranol (Enovid) 10 mg daily for 19 days while maintained on a constant regimen of the metabolism ward. No symptoms were observed, and blood pressure was not adversely affected, except for a transient slight rise noted on the third day of treatment.

Effects on Aldosterone Secretion or Excretion.—Maintenance therapy with estrogen and progestogen was associated with an abnormally increased aldosterone excretion rate in four out of the eight patients in whom it was studied (patients 1, 2, 6, and 8). In patients 1, 6, and 8, cessation of therapy was associated with the return of aldosterone excretion rates to the normal range. In patient 2, the marked oversecretion of aldosterone observed may well be attributable, at least in part, to severe, preexisting hypertensive disease. Patients 3 and 4 repeatedly exhibited normal aldosterone excretion rates while being maintained on hormonal therapy.

Effect on Renin-Substrate Concentration.—In nine of the ten patients in whom the measurements were made, the administration of birth control pills was associated with very striking and sustained increases in the concentration of renin-substrate in the serum, ranging from 1,980 to 8,650 mμg/ml. Only in patient 3 were no significant changes observed. However, this patient's hypertensive disease was complicated by the concurrent appearance of thyrotoxicosis. This feature may be related to the singular failure of this patient to exhibit any abnormalities in renin or aldosterone metabolism. Observations in patients 4, 6, 7-9, and 11 indicate that the increased renin-substrate levels can develop a few days after treatment is started and can persist for as long as four weeks or more after cessation of the therapy.

Evaluation of Serum Reactivity to Exogenous Renin.—Because of the very high concentrations of renin-substrate observed in these patients, an effort was made to evaluate the relative capacity of serum, containing increased amounts of substrate, to form the pressor substance, angiotensin. This was accomplished by employing an in vitro system in which a fixed amount of purified human renin was added to the serum in question, and its capacity to form angiotensin in a four-hour incubation was determined. The values were compared with results obtained from the study of the same subjects after correction of the renin-substrate abnormalities had occurred following cessation of therapy. The results of these studies (Table) demonstrate that the increased concentration of renin-substrate is uniformly associated with an increased capacity to form the pressor agent, angiotensin, when a standard concentration of exogenous renin is presented to the system. These observations indicate that, in the presence of an increased renin-substrate concentration, less renin would be required to release a given amount of angiotensin.

Effects on Endogenous Serum Renin Activity.—Because practically all methods for evaluating serum renin activity are based on the yield of angiotensin obtained after plasma incubation in which the endogenous substrate is the only source of angiotensin, one might expect that the patients with markedly elevated substrate levels would exhibit, ceteris paribus, relatively higher values for renin activity. In fact, serum renin activity was uniformly normal in four patients (No. 1, 3, 7, and 9) and abnormal in four (No. 2 and 4-6). In two other patients (No. 8 and 11), the values were at times elevated. This latter observation raises the possibility that abnormalities in renin activity might perhaps be more often demonstrable with more frequent sampling. This idea is supported by the serial studies made in patients 8 and 11. In