THE METABOLIC EFFECTS OF PROGESTERONE IN MAN*†

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INTRODUCTION

INTEREST in the metabolic effects of progesterone has heretofore centered primarily about its role in the reproductive functions of the female organism, where its restricted growth-promoting influence on the uterus and breast have been well documented (1, 2). Its more general metabolic properties have not been so extensively explored. In this category progesterone has been shown to be life-preserving and salt-retaining in adrenalectomized rats, ferrets and dogs (3–6) and salt-retaining in normal dogs when administered in 10–20 mg. doses per day (5, 6). It failed, however, to support the work capacity of adrenalectomized rats (7), and in a man with Addison's disease who was maintained with added salt, 30 mg. of progesterone per day had no influence on urinary chloride excretion (8). Recently it has been demonstrated that progesterone induces growth in the sebaceous glands of rats (9). In contrast to this report of an anabolic effect and similar influence on the uterus and breast is the report of Abels and Dobriner (10) that 100 mg. daily of progesterone is catabolic in a normal man. This brief description of a single metabolic experiment seems to have been overlooked, or perhaps discounted as the record of a freak or toxic reaction. Prior to the present study (11), Abels and Dobriner's results had not been confirmed.

It was the intent of this investigation to determine the metabolic consequences of approximately physiologic amounts of progesterone in man. As the amount of pregnanediol excreted daily during the luteal phase of the menstrual cycle is from 2–7 mg. (12), and there are several estimates to the effect that as a rule 10–20 per cent of parenterally administered progesterone is excreted as urinary pregnanediol (13), it may be estimated

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that the amount of progesterone secreted during the luteal phase of the menstrual cycle in from 10–70 mg. per day. In early pregnancy, during which the excretion of pregnanediol ranges from 5 to 40 mg. per day (14), 50 to 400 mg. of progesterone may be delivered to the organism daily. We accordingly selected 50 and 100 mg. of progesterone per day as dosages which might approximate the maximum rate of secretion during the normal menstrual cycle and would be well within the range of secretion during pregnancy.

The response to progesterone was determined in several patients with intact and presumably normal adrenal glands. Progesterone was also given to 1 woman and 2 men with Addison's disease who were receiving replacement quantities of desoxycorticosterone and cortisone, and to a third man with Addison's disease both before and during hormone replacement. Thus it was possible to obtain information concerning the influence of adrenal hormones and of adrenal secretory activity on the metabolic effects of progesterone.

METHODS

These investigations were carried out in the Metabolic Unit, where patients were maintained on constant regimens in the usual manner. Changes induced in the metabolic status of the subjects were defined by significant shifts from a control series of determinations of various urinary constituents. Thus, when values rose above such a control baseline a loss was recorded; and when they dropped below the control baselines, retention was said to have occurred. Determinations were always perfomed on 24-hour or 48-hour pools. By comparison with 4-day or 6-day collections, these relatively short collections are felt to enhance the sensitivity and the precision of such studies. Complete balances were not carried out but, on occasion, estimates of the total nitrogen balance were made by assuming a constant fecal nitrogen of about 1 gram daily (15). Completeness of urine collections was ascertained by creatinine determinations.

All of the progesterone[1] used in these studies fulfilled U.S.P. specifications for purity. Melting-point specifications were met. The trace of contaminants to be found in such a preparation would not be expected to be metabolically active. The progesterone was dissolved in sesame oil and 20 per cent benzyl benzoate and administered by intramuscular injection. The 50-mg. daily dose was given in a single 1-ml. injection; the 100-mg. daily dose was administered in two injections of 50 mg. each, given about ten hours apart. In the patients with Addison's disease the cortisone acetate in aqueous suspension was given in one intramuscular injection each

[1] Progesterone generously supplied by Dr. Edward Henderson of Schering Corporation, Bloomfield, N. J.

day, and the desoxycorticosterone acetate dissolved in sesame oil in one daily intramuscular injection.

Methods for the determinations of total urinary nitrogen, inorganic phosphorus, creatine, creatinine, uric acid, alpha amino acids, sodium, potassium, chloride and 17-ketosteroids have been previously detailed (16). Pregnanediol was determined according to the procedure of Stimmel (17). The technique of Randolph (18) was followed for eosinophil counts. Urinary urea was estimated by means of the Conway micro-diffusion technique (19); and blood urea by the same Conway procedure and by means of a modification of Ormsby's method (20). The same method for blood urea was employed throughout each study.

PROTOCOLS

M.K. (Fig. 1) was a 23-year-old girl with no apparent organic disease. Her basal metabolic rate was −17 per cent[2]; basal calories were 1,250 per twenty-four hours.

J.S. (Fig. 2) was a 47-year-old man with a chronic, mild to moderately severe rheumatoid arthritis. His metabolic rate was −12 per cent, with basal calories of 1,600 per twenty-four hours.

M.P. (Fig. 3) was a 36-year-old woman who was moderately obese and had experienced menstrual irregularities for twelve years. She had been amenorrheic for eighteen months. Her metabolic rate was −19 per cent; her basal calories were 1,160 per twenty-four hours. She menstruated on withdrawal of the progesterone.

X.C. (Fig. 4) was a 41-year-old woman with rather inactive rheumatoid spondylitis. Her metabolic rate was −15 per cent, with basal calories of 1,120 per twenty-four hours.

V.W. (Fig. 5) was a 36-year-old woman with Addison's disease. She was treated throughout with 50 mg. of cortisone acetate and 3 mg. of desoxycorticosterone acetate per day. Her metabolic rate was ±0; basal calories were 1,500 per twenty-four hours. She felt sick toward the end of the period of progesterone administration, and on the last day of treatment an adrenal crisis was diagnosed. The serum sodium concentration had dropped from 137 to 132 mEq. per liter.

V.V. (Fig. 6) was a 42-year-old laborer with Addison's disease. He received 2 mg. of desoxycorticosterone acetate and 25 mg. of cortisone acetate every day. His metabolic rate was −10 per cent; basal calories were 1,370 per twenty-four hours. The serum sodium concentration declined from 138 to 128 mEq. per liter as a result of the progesterone treatment.

J.B. (Fig. 7) was a 26-year-old man with newly discovered Addison's disease. He had recently lost 20 pounds and was emaciated. His metabolic rate was −20 per cent, with a basal caloric requirement of 1,420 per twenty-four hours.

H.C. (Fig. 8) was a 40-year-old Chinese plant foreman. The diagnosis of Addison's disease had been made about two weeks before this investigation was begun. He was just well enough to get along for a limited time in the hospital with only 8 grams of added salt per day as treatment. The effects of progesterone were accordingly studied while he was maintained on the salt alone and again while he was receiving, in addition, 25 mg. of cortisone acetate and 1 mg. of desoxycorticosterone acetate daily. His ultimate replacement requirement on leaving the hospital was 37.5 mg. of cortisone per day and

[2] Basal metabolic rates were calculated on the basis of Mayo Foundation standards.

2 mg. of desoxycorticosterone (buccal). The sodium intake as calculated from the known consumption of salt and the published estimates of the sodium content of foods was 241 milliequivalents per day. The baseline of 231 milliequivalents thus suggested that there was a slightly negative sodium balance before replacement therapy was started. The serum sodium concentration did not decrease from 135 mEq. per liter during the first course of progesterone, but dropped to 129 mEq. per liter just before cortisone and desoxycorticosterone were begun. The concentration then rose to 138–140 mEq. and subsequently fell to 135 mEq. per liter during the second progesterone course. His metabolic rate was −17 per cent, with basal calories of 1,170 per twenty-four hours.

RESULTS

The metabolic effects of progesterone in subjects with apparently normally functioning adrenal glands were sufficiently uniform to permit a description of the results as a group. In every instance 50 mg. of progesterone per day induced a rise in urinary nitrogen excretion which began during the first or second 48-hour pool and reached peak values 1.7–2.4 Gm. per day higher than control levels. In the representative studies detailed here the nitrogen elevations as measured from pretreatment baselines averaged 1.6 Gm. in M.K. (Fig. 1), 1.0 Gm. in J.S. (Fig. 2), 1.1 Gm. in M.P. (Fig. 3) and 1.1 Gm. during the first six days in X.C. (Fig. 4). In all subjects urinary nitrogen fell to the baseline level or below within four days after treatment was discontinued.

In J.S. the enhanced nitrogen excretion was maintained for the thirty days of treatment; and no abatement was noted during the sixteen and fourteen days of administration of progesterone in M.P. and M.K., respectively. In contrast, the urinary nitrogen elevation waned after six days in X.C. (Fig. 4) and equilibrium was restored during treatment with 50 mg. of progesterone daily. Doubling the dosage at this point did not increase the nitrogen excretion. After treatment was stopped, however, urinary nitrogen dropped to a level about 1.0 Gm. below the control average. Thus the influence of progesterone was sustained for thirty-two days, although a degree of counteraction may well have been exhibited. A similar counteracting influence was illustrated in 2 other subjects (data not shown here).

In M.K. (Fig. 1) the rise in urinary urea closely paralleled the rise in total nitrogen, in this instance accounting for virtually all of the increased nitrogen excretion. In all of the studies, fasting blood urea nitrogen concentrations were either uninfluenced or were elevated 1–3 mg. per 100 ml. during the period of enhanced nitrogen excretion. Accordingly the induced losses of urea could not be explained as a strictly renal effect and must indicate a net acceleration of protein catabolism.

Of the other nitrogenous constituents of urine determined, only uric acid excretion seemed to be increased (Figs. 1 and 3), and the increases

were very slight. Alpha amino-acid excretion did not rise, and endogenous creatinuria was depressed during progesterone treatment in X.C. (Fig. 4), during the first course in M.P. (Fig. 3), and in 2 other women (detailed data not presented). Creatine excretion was not affected in J.S. (Fig. 2), or during the second course in M.P. (Fig. 3).

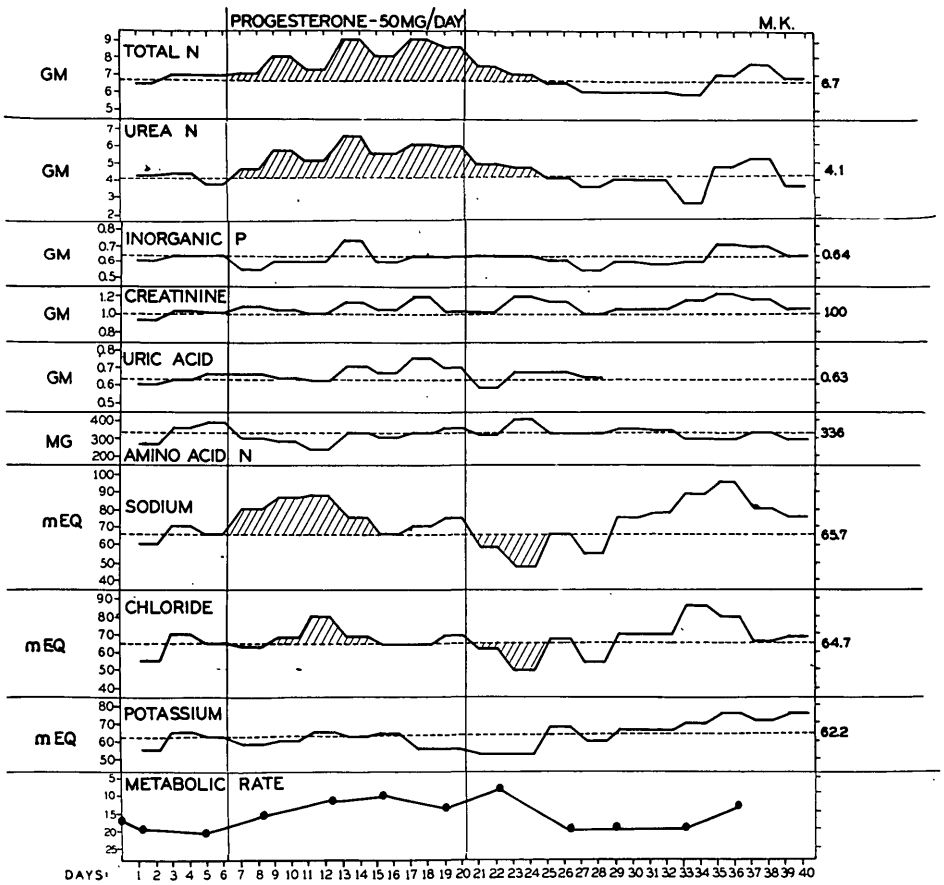

FIG. 1. The effect of progesterone administration in a young woman **M.K.**, on the excretion of several urinary constituents and on the basal metabolic rate. Horizontal broken lines indicate the averages of control values. The diet was 185 Gm. carbohydrate; 50 Gm. protein (nitrogen, 8.0); 120 Gm. fat; calories, 2,020.

The mildness of this catabolic response to progesterone is attested to, not only by the limited nitrogen losses, but also by the absence of parallel elevations in the urinary inorganic phosphorus and potassium during either 50-mg. or 100-mg. daily dosages. In M.P. (Fig. 3), increasing the progesterone to 100 mg. per day seemed to evoke a greater nitrogen loss, the elevation averaging 1.7 Gm. in comparison with the daily loss of 1.1 Gm.

induced by a dosage of 50 mg. In the 2 other subjects for whom data are not given, the same increase in dosage also led, at least temporarily, to an additional rise in nitrogen excretion. More detailed dose-response relationships have not been studied.

Uniformity also prevailed with respect to the influence of progesterone

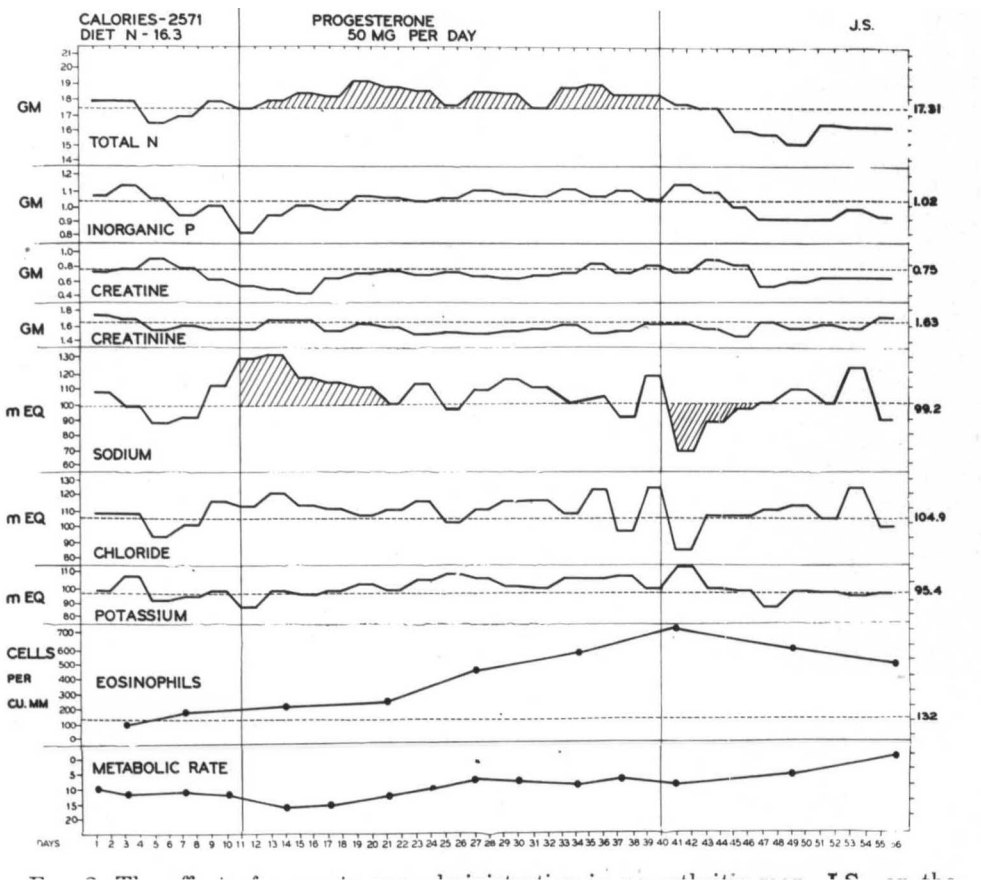

FIG. 2. The effect of progesterone administration in an arthritic man, **J.S.**, on the excretion of several urinary constituents, circulating eosinophils, and the basal metabolic rate. Broken horizontal lines indicate the averages of control values. The diet was 237 Gm. carbohydrate; 102 Gm. protein (nitrogen, 16.3); 135 Gm. fat; calories, 2,571.

on urinary sodium and chloride excretion in the subjects with functioning adrenals. The rather wide control variations which are not unusual in such experiments were observed in several subjects, but the consistent effects of progesterone were never masked by baseline irregularities. Sodium excretion always rose during the first two days of progesterone administration and then declined over several days, reaching the baseline before progesterone was discontinued. In J.S. (Fig. 2) this required ten days, and

in M.K. (Fig. 1) eight days. In M.P. (Fig. 3) the baseline excretion was resumed after the first two-day pool on the 50-mg. dose, and after four days when a 100 mg. per day was given. The increase in urinary sodium was also greater as a result of the larger amount of progesterone in the latter patient. In each case prompt compensatory sodium retention developed immediately after progesterone was discontinued, the quantity of sodium re-

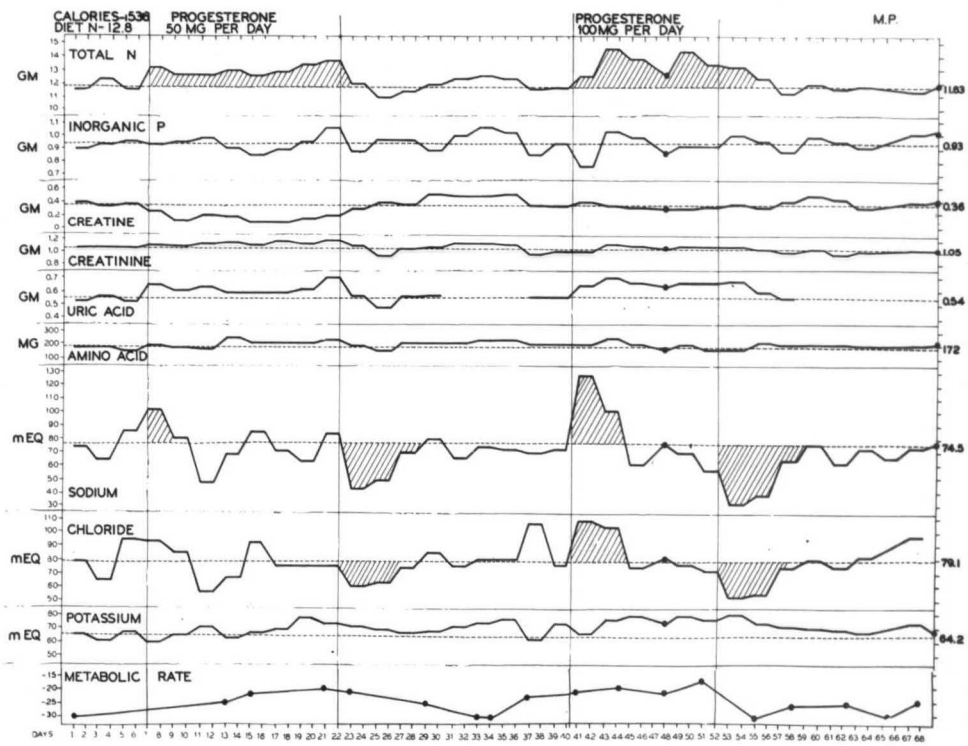

FIG. 3. The effect of 50 mg. and of 100 mg. per day of progesterone in an amenorrheic woman, **M.P.**, on the excretion of several urinary constituents and on the basal metabolic rate. Broken horizontal lines indicate the averages of pre-treatment control values. The diet consisted of 141 Gm. carbohydrate; 81 Gm. protein (nitrogen, 12.8); 72 Gm. fat; calories, 1,536.

tained approximating that previously lost. Urinary chloride excretion tended to parallel the foregoing shifts in sodium, but in all instances the movement of chloride was substantially less than that of sodium. The volumes of urine also tended to follow the trends in sodium excretion, but shifts in the output were never spectacular.

In patients with Addison's disease who were fully treated with both cortisone acetate and desoyxcorticosterone acetate the metabolic influence of progesterone was more intense and enduring, and the salt losses were

substantially greater than in normal subjects. The first of these subjects, V.W. (Fig. 5), received the most vigorous course of progesterone. Her urinary nitrogen excretion began to increase on the fifth day of treatment with 50 mg. per day, reached a level averaging 2.1 Gm. in excess of the control average, and then rose another gram when a dose of 100 mg. per day was given. The Addisonian crisis which developed on the last day of treatment prevented her from consuming the full diet, but despite the lower caloric and protein intakes during the two succeeding days, urinary nitrogen remained elevated for eight days after treatment was stopped. A spontaneous compensatory nitrogen retention, which averaged 1.6 Gm. per day at its maximum, ensued. In contradistinction to the results in subjects with active adrenal glands, the enhanced nitrogen excretion was

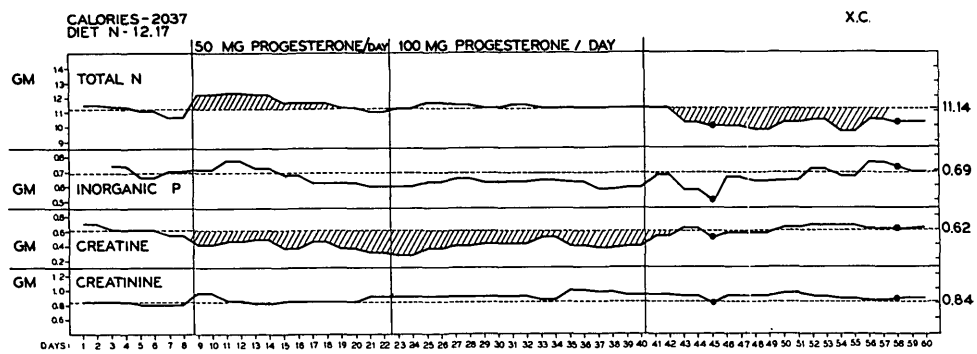

FIG. 4. The effect of 50 mg. and 100 mg. of progesterone per day in an arthritic woman, **X.C.**, on the urinary excretion of total nitrogen, inorganic phosphorus, creatine and creatinine. The broken horizontal lines indicate the averages of control values. The diet was 179 Gm. carbohydrate; 76 Gm. protein (nitrogen, 12.2); 113 Gm. fat; calories, 2,037.

paralleled by an elevation in urinary inorganic phosphorus, potassium and creatine.

Similar results were obtained in 2 men with Addison's disease. In V.V. (Fig. 6) there was a positive nitrogen balance of about 2 Gm. per day (dietary nitrogen, 13.3 Gm.; control urinary nitrogen, 10.3 Gm.) when pregesterone was started. On 50 mg. per day his total nitrogen excretion rose 4.2 Gm., and took eight days to return to a new baseline which approximated nitrogen equilibrium. Inorganic phosphorus and potassium were also lost during this catabolic phase. Urinary uric acid rose slightly. J.B. (Fig. 7), the third Addisonian, was recovering from the inanition of uncontrolled adrenal insufficiency and showed a positive nitrogen balance of approximately 6 Gm. per day when progesterone treatment was begun (dietary nitrogen, 19.2 Gm.; control urinary nitrogen, 12.3 Gm.). Despite

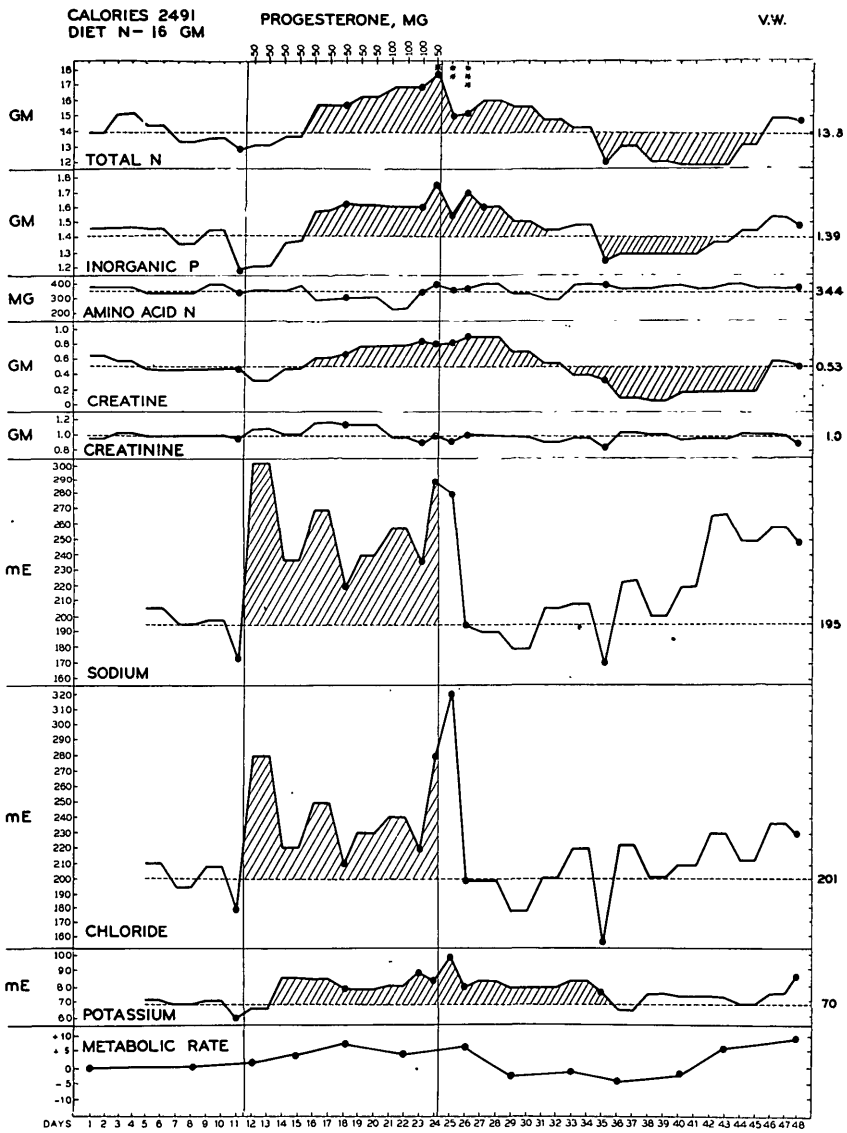

FIG. 5. The effect of 50 mg. and 100 mg. per day of progesterone in an Addisonian woman, **V. W.**, on the excretion of several urinary constituents, and the metabolic rate. Horizontal lines indicate the averages of control values. She received 50 mg. of cortisone acetate and 3 mg. of desoxycorticosterone acetate per day throughout. Her diet was 318 Gm. carbohydrate; 100 Gm. protein (nitrogen, 16.0); 153 Gm. fat; calories, 2,491.

* Normal saline, 500 ml. intravenously.

** Normal saline, 1,000 ml. intravenously. Dietary intake—146 Gm. carbohydrate; 65 Gm. protein; 73 Gm. fat; calories 1,501.

*** Dietary intake—204 Gm. carbohydrate; 93 Gm. protein; 123 Gm. fat; calories, 2,283.

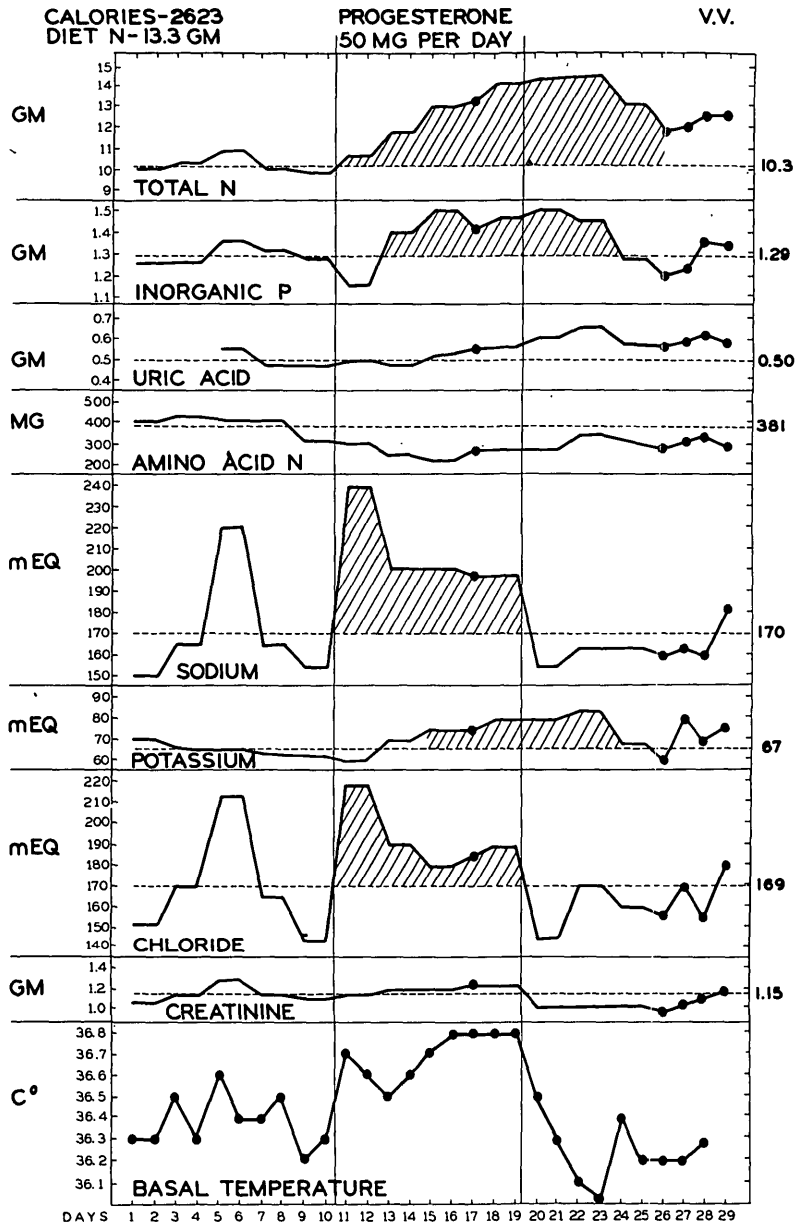

FIG. 6. The effect of 50 mg. per day of progesterone in a 42-year-old laborer with Addison's disease, **V.V.**, on the excretion of several urinary constituents and on the basal body temperature. He received 2 mg. of desoxycorticosterone acetate and 25 mg. of cortisone acetate per day throughout the study. Broken horizontal lines indicate the averages of control values. The diet was 278 Gm. carbohydrate; 83 Gm. protein (nitrogen, 13.3); 132 Gm. fat; calories, 2,623.

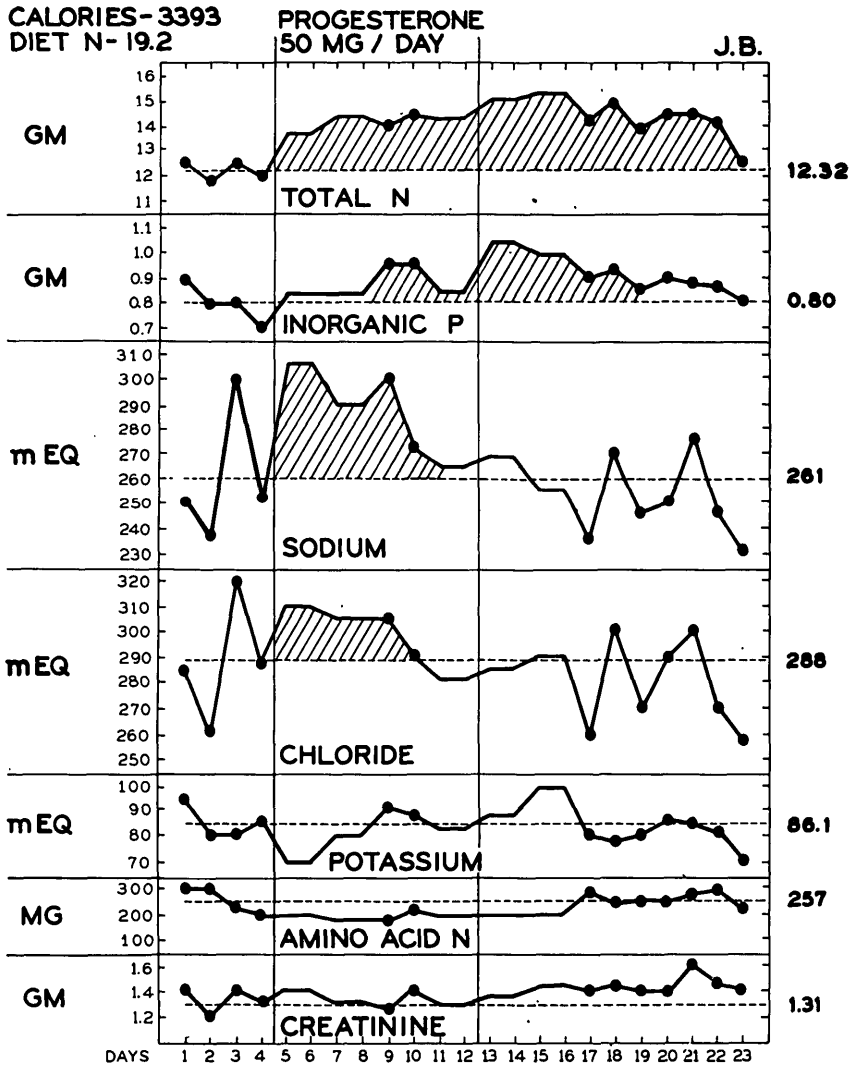

FIG. 7. The effect of 50 mg. per day of progesterone on the excretion of several urinary constituents in **J.B.**, a 26-year-old man with Addison's disease. He received 25 mg. cortisone acetate and 1 mg. desoxycorticosterone acetate each day. Horizontal lines indicate the averages of control values. His diet was 366 Gm. carbohydrate; 120 Gm. protein (nitrogen, 19.2); 161 Gm. fat; calories, 3,393.

this vigorous anabolic impulse, 50 mg. of progesterone per day led to an elevated nitrogen excretion which averaged 15.4 Gm., or 3.2 Gm. per day greater than the control value. Following treatment urinary nitrogen declined slowly, and required eleven days to return to its original level. As in the other Addisonians, inorganic phosphorus excretion was also enhanced, but potassium excretion was not affected in this subject.

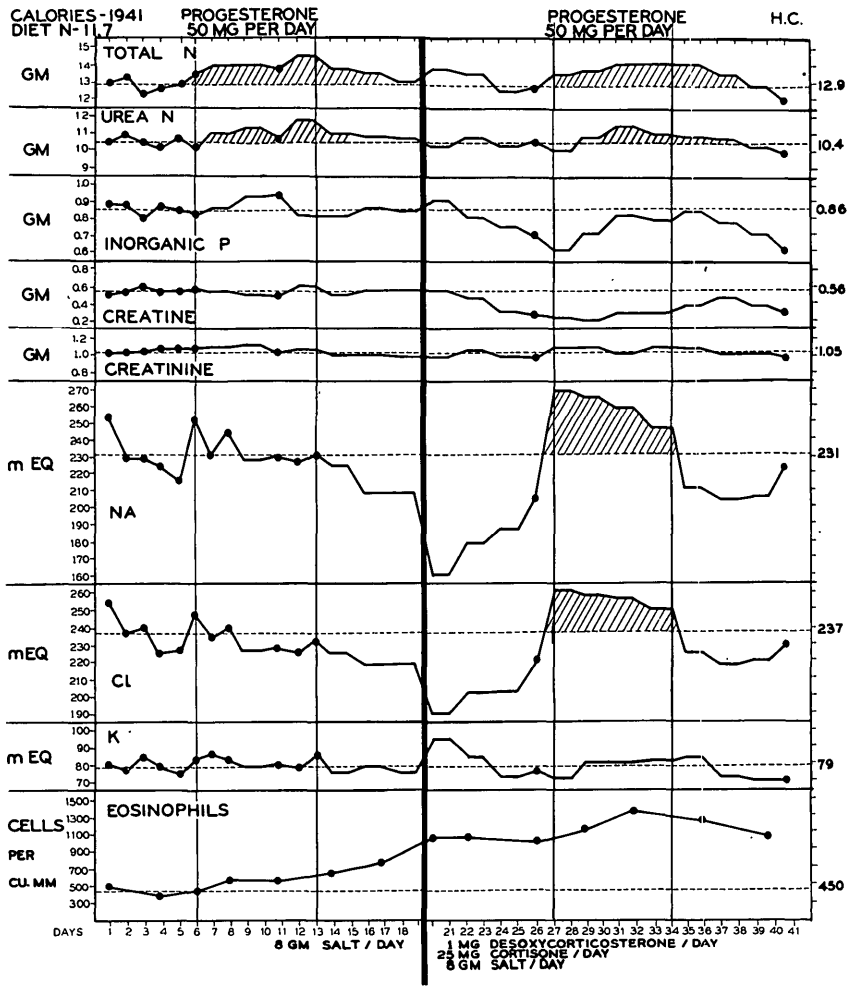

FIG. 8. The comparative effects of 50 mg. per day of progesterone given to **H.C.**, a 40-year-old man with Addison's disease, before and after treatment with 1 mg. of desoxycorticosterone acetate and 25 mg. of cortisone acetate daily, on the excretion of several urinary constituents and on circulating eosinophils. The heavy vertical line indicates the change in treatment of the adrenal deficiency; broken horizontal lines indicate the averages of the initial control values. His diet was 176 Gm. carbohydrate; 73 Gm. protein (nitrogen, 11.7); 105 Gm. fat; calories, 1,941.

Amino-acid nitrogen excretion was uninfluenced in all of the patients with adrenal deficiency.

The natriuresis and chloruresis induced in the hormone-treated Addisonians were dramatic, despite sizable control variations in sodium and chloride excretion. Accompanying increases in urine volume were moderate. In V.W. the urinary sodium loss (quantity in excess of the control average)

was 819 mEq. and the chloride loss 546 mEq. In V.V. the sodium loss was 342 mEq. and that of chloride, 207 mEq. J.B. lost 198 mEq. of sodium and 128 mEq. of chloride. These losses were unquestionably substantial and they were of clinical importance in at least one of the patients. In V.W. the sodium loss was probably the dominating factor in the crisis which developed, though the serum sodium concentration did not reach a spectacularly low level (132 mEq./L). Sodium and chloride losses were greatest during the first forty-eight hours of progesterone treatment, as was usual in the patients with apparently normal adrenal function; but a more sustained loss of these ions was observed during the succeeding days of declining excretion in patients with Addison's disease. Only in J.B. (Fig. 7) did compensation occur during treatment. The salt loss did not continue after progesterone was stopped, but no distinct post-treatment retention of sodium and chloride developed in these patients, although the losses incurred were much greater than those induced in the non-Addisonians.

In order more clearly to evaluate the role played by adrenal hormones in the development of these effects of progesterone, H.C. (Fig. 8), a man with adrenal deficiency, was given 50 mg. daily of progesterone while he was maintained on only 8 Gm. of added salt, and again when cortisone and desoxycorticosterone had been added in approximately replacement quantities. In both circumstances the magnitude and the duration of the induced catabolic processes were somewhat less than had been previously observed in Addisonians. The patterns of urinary nitrogen excretion were almost superimposable in the two instances. The urinary nitrogen elevation averaged 1.0 Gm. per day before steroid replacement and 1.0 Gm. afterward; in both experiments the nitrogen increment continued for four days after the last day of progesterone administration. As in M.K. (Fig. 1), most of the increase in urinary nitrogen was urea.

Initially, urinary inorganic phosphorus was uninfluenced by progesterone administration in H.C. (Fig. 8). The introduction of cortisone and desoxycorticosterone, however, was followed by a distinct and progressive lowering of phosphorus excretion. The second progesterone course then induced a rise in urinary phosphorus which coincided with that of nitrogen, and returned to the original low point after treatment. Urinary creatine was also unaffected by the first progesterone course. The spontaneous creatinuria, like inorganic phosphorus excretion, was suppressed by the introduction of cortisone and desoxycorticosterone treatment; subsequently, a questionable rise paralleled the foregoing increases in nitrogen and phosphorus. Urinary potassium was not noticeably influenced by either course of progesterone, although it rose as expected following the introduction of adrenal replacement therapy.

The influence of progesterone on urinary sodium and chloride was

strikingly different before and after the administration of cortisone and desoxycorticosterone. When H.C. was treated only with 8 Gm. of added salt, no effect was observed. The slowly diminishing course of excretion of these ions seemed undisturbed by the progesterone. Desoxycorticosterone and cortisone then caused the expected sharp retention of sodium and chloride. Following this, progesterone induced a loss of both ions (sodium 232 mEq.; chloride 160 mEq.) which was of the order previously noted in the other Addisonians.

The anticipated slight elevation in basal body temperature during treatment with progesterone was observed in every subject, but there was no fever. Metabolic rate determinations performed approximately twice a week in M.K., J.S., M.P., and the Addisonian V.W. (Figs. 1, 2, 3 and 5) furnished no conclusive evidence for a rise due to progesterone administration. In both M.P. and M.K. there might have been a slight increase in B.M.R. In M.P. (Fig. 3), the B.M.R. before progesterone was −29 per cent, and the peaks were −20 per cent on 50 mg. and −16 per cent on 100 mg. daily. In M.K. (Fig. 1) the controls averaged −17 per cent, the high point on progesterone was −10 per cent, and a value of −9 per cent was obtained two days after treatment. The slight malaise usually associated with progesterone therapy could have accounted for these questionably significant elevations. The very gradual and delayed upward trends in V.W. and J.S. could be explained by the developing crisis in V.W. and an increase in the severity of arthritic symptoms in J.S.

Circulating eosinophils were either uninfluenced, or there was a delayed and protracted increase in concentration as noted in J.S. and H.C. (Figs. 2 and 8). The rising eosinophil counts seem to have resulted from a reaction to the sesame oil and benzyl benzoate medium in which the progesterone was dissolved, since injections of the oil alone induced similar elevations in the eosinophil count in other subjects. However, the vehicle did not account for the metabolic effects described. Its administration to 2 arthritics (data not shown here) did not influence nitrogen metabolism or salt excretion, although progesterone dissolved in the same amount of oil evoked the usual catabolic response.

Urinary 17-ketosteroid excretion was not increased as a result of progestrone treatment. A systematic 3-mg. decline and subsequent recovery was observed in the young Addisonian, J.B. (Fig. 7), possibly reflecting a suppression of testicular androgen secretion.

The excretion of urinary pregnanediol during progesterone administration tended to be somewhat greater than anticipated in those subjects in whom it was determined. M.K. (Fig. 1) excreted 1.2 mg. daily prior to therapy and 16.2 mg. per day in the sixth two-day pool during treatment. The control level in M.P. (Fig.3) was 1.24 mg. In the last two days of the

50-mg. dosage period she excreted 12.9 mg. of pregnanediol daily, and in the next to the last pool, while receiving 100 mg. per day, the excretion was 22 mg. daily. J.S. (Fig. 2) excreted 11.5 mg. of pregnanediol daily in the middle of his course of 50 mg. of progesterone per day, and 13.3 mg. daily at the end of the course. The level of pregnanediol excretion in H.C. (Fig. 8) reached 7.7 mg. daily the last two days of his first series of injections. In X.C. (Fig. 4) the level rose to 8.1 mg. daily during treatment with 50 mg. of progesterone daily, and only reached 8.9 mg. before the discontinuance of the 100-mg. daily dosage of progesterone. The 50-mg. dosage thus produced pregnanediol elevations of 7 to 15 mg. per day. From these results it would appear that daily doses of 50 mg. of progesterone are probably slightly in excess of the maximum rate of progesterone secretion during the progestational phase of the menstrual cycle. However, the quantities of pregnanediol excreted indicate that 50 and 100 mg. daily are both within the range of the amount of progesterone secreted per day during pregnancy.

DISCUSSION

The administration of progesterone increased urinary nitrogen excretion in 12 subjects reported here, establishing that the hitherto isolated and unappreciated report of Abels and Dobriner (10) is truly representative. The benzyl-benzoate sesame-oil medium in which the progesterone was dissolved was metabolically inactive, although the eosinophilia occasionally seen after progesterone was reproduced by the oil alone. Minor local irritations at the sites of injection occurred only occasionally. Except for the 1 Addisonian in whom a crisis was induced by exaggerated metabolic effects, and 1 arthritic whose rheumatoid process was apparently intensified, the progesterone provoked very slight malaise or none at all. No fever was induced. The progesterone used had a high chemical standard of purity. Accordingly, although a description of the effects of this hormone as secreted is essential, the nitrogen dissipation so consistently seen here commands attention as a response which is probably of physiologic significance.

The large amounts of nitrogen lost in a long experiment suggest a rather general catabolic response. Although the daily nitrogen increments were never extreme, the accumulated loss from a protracted course of progesterone represented considerable protein destruction. For example, in J.S. (Fig. 2) in whom the increase in nitrogen excretion averaged just 1.0 Gm. daily, the aggregate loss of protein calculated from the nitrogen loss during the thirty days of treatment approximated 750 Gm. Such amounts could hardly be restricted to a single tissue or organ, with the exception of muscle.

The composition of the nitrogen loss offers no especial clue as to its source. The increments in urinary nitrogen consisted mainly of urea, indicating that the normal course of protein catabolism was followed. There was no increase in amino-acid excretion and urinary uric acid rose very slightly. Creatinuria was increased in only 1 subject, the Addisonian, V.W. (Fig. 5). Since a crisis was developing at the time, however, the creatinuria may have been secondary to the adrenal insufficiency itself rather than a primary effect of progesterone. The development of an enhanced creatine excretion only in this unusual circumstance cannot be accepted as evidence that muscle is a site of action of progesterone when nitrogen is lost.

Certain tissues may well be more or less selectively influenced by progesterone, just as the lymphoid tissues appear to be more sensitive to the catabolic influence of excesses of adrenal corticoids (21). In all likelihood the uterus, breast parenchyma and perhaps other tissues were spared here. However, no conclusions concerning the locus of the effect can be drawn from the data presented.

There was no evidence to suggest that the catabolic effect of progesterone was the result of stimulation of the adrenal or the thyroid. The slight elevations in uric acid excretion did not resemble the prompt and substantial rise in urinary uric acid characteristic of adrenal stimulation and no other indications of adrenal activation, such as a rise in urinary 17-ketosteroids (22), were observed. The response in Addisonians was even greater than in subjects with normal adrenals.

The elevations in basal metabolic rate that were occasionally seen were not always correlated with the loss of nitrogen, nor were they consistent enough or of sufficient magnitude to suggest activation of the thyroid gland. An increase in urinary creatine, which might suggest a thyroid effect, did not occur with regularity. Furthermore the failure of urinary alpha amino-acid nitrogen excretion to rise as part of the catabolic process distinguishes this response from the catabolism induced by adrenal and thyroid hormones (23). It is therefore likely that the acceleration of protein catabolism is a metabolic property of progesterone itself.

The data suggest a comment concerning the means by which progesterone accelerates protein catabolism. The rise in basal body temperature of 0.3–0.4 degrees Fahrenheit due to progesterone is probably too small to increase the basal metabolic rate detectably. However, calculations based on basal calories indicate that a portion of the nitrogen loss might be accounted for by the increased caloric requirement, provided the movement of fat into the metabolic pool was simultaneously inhibited by progesterone. For example in V.V. (Fig. 6), the basal calories of 1,370 per day would be augmented by 27 calories as a result of the temperature elevation. On a constant diet, 6.8 Gm. of protein must be mobilized to supply this energy.

The metabolism of this quantity of protein would produce an increment in urinary nitrogen slightly in excess of 1.0 Gm. Nitrogen excretion actually rose 4.2 Gm. in V.V. as a result of the administration of progesterone, and the elevation continued for six days after the basal temperature had returned to its initial level. Accordingly, only a portion of the catabolic effect could be accounted for by this mechanism, and other perhaps more direct processes for accelerating protein catabolism must be involved.

Although progesterone did not exert its catabolic force by acting through the adrenals, the presence of active adrenal glands did affect the character of the response. The catabolic process was generally more intense and enduring in the patients with adrenal deficiency. Nitrogen losses were greater in the Addisonians, and were accompanied by parallel increases in urinary inorganic phosphorus. Potassium excretion was also enhanced in 2 of these subjects.

Several explanations can be offered for the more limited catabolic effect of progesterone in subjects without adrenal defects. Although a final decision between alternatives cannot be made at this time, the matter is of sufficient importance to warrant outlining the possibilities here. The homeostatic influence of adrenal secretion could be exerted in four ways: 1) A stable quantity of corticoids may promote a situation conducive to the maintenance of nitrogen equilibrium without exerting a direct influence on protein metabolism (24). 2) Varying quantities of corticoids operating in an indrect fashion may be required for the optimum support of protein metabolism under different circumstances (24). 3) A direct protein-supporting effect may be exerted by an increased secretion of corticoids. 4) A specific anabolic secretion of the sort which has been previously proposed (25, 26) may be elaborated to counteract the progesterone effect. Of these, only the first suggestion does not involve an added secretion. If the catabolic effect of progesterone were opposed in such an indirect manner, the less intense catabolism induced in normal subjects could be explained by the greater effectiveness of native corticoids as compared with the cortisone and desoxycorticosterone used in treating the Addisonians. On the other hand the more rapid termination of the catabolic response after the discontinuance of progesterone in most of the subjects without adrenal disease could be an indication of the active participation of the adrenal glands in any of the manners suggested. The possibility that active adrenal opposition was generated in response to the progesterone received some support from the data on the effect of progesterone on sodium and chloride excretion.

The consistent sodium and chloride dissipating influence of progesterone came as a surprise, in view of its previously noted salt-retaining effects in intact dogs and in adrenalectomized dogs, ferrets and rats (3–6), and in

view of the absence of effect of progesterone on chloride excretion in an Addisonian treated with added salt (8). The apparent disagreement was reconciled in part by the observations made on H.C. (Fig. 8). Results of this study in an Addisonian demonstrated that the effect of progesterone on sodium and chloride excretion differed, depending on the presence or absence of circulating adrenal hormones. The characteristic salt loss was induced by progesterone while he was treated with desoxycorticosterone and cortisone, but when he was maintained on salt alone, sodium and chloride excretion was not influenced.

This difference in response between the treated and untreated Addisonian can be best explained as an inhibition of the salt-retaining influence of desoxycorticosterone and cortisone by progesterone. Presumably this interaction occurs in the kidney. The natriuresis and chloruresis induced by progesterone generally displayed the same pattern which has been reported to follow the withdrawal of adrenal secretions or of active adrenal preparations (27, 28). The peak excretion of sodium and chloride always occurred soon after progesterone treatment started, and the maximal excretion of these ions characteristically developed during the first few days of adrenal deficiency. In both circumstances the losses of sodium substantially exceeded those of chloride. This competitive type of reaction, so clearly demonstrated in the Addisonian H.C., would similarly account for the salt loss in subjects with intact adrenals in whom the progesterone opposed the intrinsic salt-retaining adrenal secretions. Thorn (29) has suggested a similar competitive reaction between cortisone and desoxycorticosterone.

Thus, in the doses employed, progesterone may have no influence on sodium and chloride excretion in the absence of adrenal secretions, and a salt-dissipating effect in the normal subject or in the hormone-treated adrenal-deficient human subject by virtue of a competitive inhibition of adrenal steroids. The salt-retaining influence of progesterone in intact dogs (5, 6) could be an effect peculiar to that species. However, large amounts of progesterone are also salt-retaining in adrenalectomized dogs, rats and ferrets. Much larger amounts of progesterone than those employed here might also be salt-retaining in man.

The influence of progesterone on sodium and chloride excretion was modified by the presence of active adrenals. Salt losses were less intense and of shorter duration in normal subjects than in the treated adrenal-deficient patients, and a compensatory retention of sodium and chloride after progesterone was discontinued developed only in the subjects with intact adrenal glands. The smaller losses of sodium and chloride induced in the non-Addisonians could be accounted for by a less effective inhibition of endogenous salt-retaining hormones by the administered progesterone. However, the post-treatment retention of salt in these individuals cannot

be so readily explained in this manner. In constantly maintained Addisonians, the lack of development of a sharp compensatory response despite greater salt losses would suggest that the permissive role of adrenal hormones cannot account for this protective reaction. Accordingly, the enhanced secretion of a salt-retaining adrenal steroid is postulated to explain this process. Such increased adrenal secretory activity could also account for the limitation of salt losses in the normal subjects. The particular secretion involved here may be aldosterone (30).

Although the dosages cannot be said to apply to all of the natural circumstances during which progesterone may be secreted, these results indicate that the physiologic influence of progesterone in man cannot be considered as being restricted to sex-linked structures. Androgen and estrogen, the other sex hormones, have previously been shown to possess general anabolic properties (31). The catabolic effect so consistently produced by progesterone in these studies places it, too, among the hormones which may play a role in the regulation of the growth process. This aspect is particularly important in pregnancy, when very large amounts of progesterone are secreted. Its role here in the face of the rapid growth of the fetus and certain maternal tissues is obscure. However, the possibility that it inhibits the general deposition of protein in the maternal organism in order to favor the growth of selected tissues and the fetus must be given serious consideration.

This demonstration that progesterone may competitively inhibit the salt-retaining influence of adrenal hormones and effect thereby a loss of sodium and chloride is also particularly pertinent in its relationship to pregnancy. In this manner progesterone could exert an inhibitory influence on the tendency of the pregnant organism to store salt and water.

These results also prompt a reconsideration of the role of progesterone in the physiology of the menstrual cycle. The progesterone secreted in the normal woman may exert an inhibitory influence on somatic growth and could also be expected to enter into the control of salt and water excretion. In these connections it is imperative that these studies be extended to include smaller dosages of progesterone.

SUMMARY

1. Approximately physiologic amounts of progesterone (50 to 100 mg. daily) exerted a mild to moderately intense catabolic influence in men and women.

2. The catabolic response was not mediated by the adrenal glands and there was no decisive evidence that thyroid activation resulted from progesterone administration. It was concluded that the accelerated protein catabolism was an effect of progesterone itself.

3. The nitrogen losses were usually greater in the patients with adrenal deficiency. In these subjects the enhanced nitrogen excretion was usually accompanied by an increase in urinary inorganic phosphorus, and in 2 cases urinary potassium was also elevated. The excretion of these constituents was not increased in non-Addisonians. Creatine retention accompanied progesterone treatment only in several normal subjects. These differences indicated that the catabolic effect of progesterone was opposed by adrenal secretions.

4. The same dosages of progesterone induced sharp rises in urinary sodium and chloride excretion, which were considerably greater in Addisonians treated with cortisone and desoxycorticosterone than in subjects with apparently normal adrenal function. The sodium losses exceeded those of chloride. Subjects with functioning adrenals retained sodium and chloride in the immediate post-treatment period.

5. In a patient with Addison's disease, progesterone induced no loss in urinary sodium and choride when given prior to hormone replacement therapy, and induced the usual natriuresis and chloruresis during treatment with cortisone and desoxycorticosterone. It was accordingly suggested that progesterone induced the salt loss by virtue of a peripheral (renal) competitive inhibition of salt-retaining corticoids.

6. The post-treatment retention of salt which developed only in normal subjects was suggestive of an enhanced secretion of salt-retaining corticoids. Such increased adrenal secretory activity could also explain the more limited salt losses in subjects without adrenal defects.

7. These metabolic effects of progesterone should be considered both in relation to the physiology of pregnancy and the menstrual cycle, and to the hormonal regulation of somatic growth.

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REFERENCES

1. Pincus, G.: The physiology of ovarian hormones, *in* The Hormones, ed. by Pincus, G. and Thimann, K. V. New York, Academic Press Inc., 1950, vol. 2, p. 1.
2. Folley, S. S., and Malpress, F. H.: Hormonal control of mammary growth, *Ibid.* 1948, vol. 1, p. 695.
3. Gaunt, R.; Nelson, W. O., and Loomis, E.: Cortical hormone-like action of sex hormones and non-effect of sex hormones on water intoxication, *Proc. Soc. Exper. Biol. & Med.* **39**: 319, 1938.
4. Gaunt, R., and Hays, H. W.: The life maintaining effect of crystalline progesterone in adrenalectomized ferrets, *Science* **88**: 576, 1938.

5. THORN, G. W., and ENGEL, L. L.: The effects of sex hormones on the renal excretion of electrolytes, *J. Exper. Med.* **68**: 299, 1938.
6. THORN, G. W.; NELSON, K. R., and THORN, D. W.: A study of the mechanism of edema associated with menstruation, *Endocrinology* **22**: 155, 1938.
7. INGLE, D. J.: The work performance of adrenalectomized rats treated with corticosterone and chemically related compounds, *Endocrinology* **26**: 472, 1940.
8. LOEB, R. F.; ATCHLEY, D. W.; FERREBEE, J. W., and RAGAN, C.: Observations on the effect of desoxycorticosterone esters and progesterone in patients with Addison's disease, *Tr. A. Am. Physicians* **54**: 285, 1939.
9. HASKIN, D.; LASHER, M., and ROTHMAN, S.: Some effects of ACTH, cortisone, progesterone and testosterone on sebaceous glands in the white rat, *J. Invest. Dermatol.* **20**: 207, 1953.
10. ABELS, J. D., and DOBRINER, K.: *in* Transactions of the Seventh Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing. New York, Josiah Macy, Jr. Foundation, 1944, p. 121.
11. LANDAU, R. L.; BERGENSTAL, D. M.; LUGIBIHL, K., and KASCHT, M. E.: The metabolic effects of progesterone in man, (abstract) *J. Clin. Invest.* **33**: 950, 1954.
12. VENNING, E. H., and BROWNE, J. S. L.: Studies on corpus luteum function. I. The urinary excretion of sodium pregnanediol glucuronidate in the human menstrual cycle, *Endocrinology* **21**: 711, 1937.
13. SOMMERVILLE, I. F., and MARRIAN, G. F.: Urinary excretion of pregnanediol in human subjects following the administration of progesterone and of pregnane-3:20-diol, *Biochem. J.* **46**: 290, 1950.
14. GUTERMAN, H. S.: Progesterone metabolism in the human female, *in* Recent Progress in Hormone Research, ed. by G. Pincus. New York, Academic Press Inc., 1953, p. 293.
15. REIFENSTEIN, E. C., JR.; ALBRIGHT, F., and WELLS, S. L.: The accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen, *J. Clin. Endocrinol.* **5**: 367, 1945.
16. KENYON, A. T.; KNOWLTON, K.; SANDIFORD, I.; KOCH, F. C., and LOTWIN, G.: A comparative study of the metabolic effects of testosterone proprionate in normal men and women and in eunuchoidism, *Endocrinology* **26**: 26, 1940.
17. STIMMEL, B. F.: A procedure for concomitant photometric estimation of pregnanediol and estrogens in human urine, *J. Clin. Endocrinol. & Metab.* **12**: 371, 1952.
18. RANDOLPH, T. G.: Blood studies in allergy. The direct counting chamber determination of eosinophils by propylene glycol aqueous stains, *J. Allergy* **15**: 89, 1944.
19. CONWAY, E. J.: Microdiffusion Analysis. London, Crosby and Lickwood and Sons, Ltd., 1950.
20. BARKER, S. S.: The direct colorimetric determination of urea in blood and urine, *J. Biol. Chem.* **152**: 453, 1944.
21. DOUGHERTY, T. F., and WHITE, A.: Effect of pituitary adrenotropic hormone on lymphoid tissue, *Proc. Soc. Exper. Biol. & Med.* **53**: 132, 1943.
22. FORSHAM, P. H.; THORN, G. W.; PRUNTY, F. T. G., and HILLS, A. G.: Clinical studies with adrenocorticotropin, *J. Clin. Endocrinol.* **8**: 15, 1948.
23. BERGENSTAL, D. M., and LUGIBIHL, K.: Effect of TSH and ACTH on amino acid metabolism, *J. Clin. Endocrinol. & Metab.* **12**: 929, 1952.
24. INGLE, D. J.: The role of the adrenal cortex in homeostasis, *in* Yoffey, J. M.: The Suprarenal Cortex. London, Butterworth Scientific Publications, 1952.

25. KENYON, A. T.: Comparative metabolic influences of testicular and ovarian hormones in man, *Biol. Symposia* **9**: 11, 1942.
26. ALBRIGHT, F.: Cushing's syndrome, *Harvey Lectures* **38**: 123, 1943.
27. LOEB, R. F.; ATCHLEY, D. W.; BENEDICT, E. M., and LELAND, J.: Electrolyte balance studies in adrenalectomized dogs with particular reference to the excretion of sodium, *J. Exper. Med.* **57**: 775, 1933.
28. THORN, G. W.; EMERSON, K., and EISENBERG, H.: Oral therapy in adrenal insufficiency, *Endocrinology* **23**: 403, 1938.
29. THORN, G. W.; FORSHAM, P. H.; BENNETT, L. L.; RAKE, M.; REISS, R. S.; SLOSSER, A.; FLINK, E. B., and SOMERVILLE, W.: Clinical and metabolic changes in Addison's disease following the administration of compound E acetate, *Tr. A. Am. Physicians* **62**: 233, 1949.
30. SIMPSON, S. A.; TAIT, J. F., and BUSH, I. E.: Secretion of a salt-retaining hormone by the mammalian adrenal cortex, *Lancet* **2**: 226, 1952.
31. KNOWLTON, K.; KENYON, A. T.; SANDIFORD, I.; LOTWIN, E., and FRICKER, R.: Comparative study of metabolic effects of estradiol benzoate and testosterone propionate in man, *J. Clin. Endocrinol.* **2**: 671, 1942.