PROGESTERONE AND NORETHISTERONE IN CYCLICAL OEDEMA AND ASCITES

BY

JOHN S. JENKINS, M.A., M.D., M.R.C.P.
Senior Medical Registrar, St. George's Hospital, London

The action of progesterone and its synthetic analogues on the reproductive organs has been extensively studied, but the effects of these substances on electrolyte metabolism have received less attention. Thorn and Engel (1938) and Gaunt and Hays (1938) reported that progesterone caused sodium retention in animals such as the dog and ferret, but Landau *et al.* (1955, 1957a, 1957b) have presented evidence that in man it increased sodium excretion. Landau and Lugibihl (1958) further demonstrated that in patients suffering from Addison's disease an increase in urinary sodium could only be obtained with progesterone if aldosterone were given concurrently, and concluded that the action was that of an aldosterone antagonist.

In the treatment of the syndrome of premenstrual tension, of which recurrent oedema is the most important objective feature, progesterone has for many years been advocated, largely on the hypothesis of an oestrogen–progesterone imbalance (Israel, 1938). Later the oral synthetic progestational compounds, such as ethisterone (Greene and Dalton, 1953) and, more recently, norethisterone (Dalton, 1959) have been used on account of their greater convenience. It therefore seemed useful to investigate the action of progesterone and norethisterone on urinary electrolyte excretion in cases of oedema related to the menstrual cycle. It was also thought to be of interest, in view of its reported anti-aldosterone action, to study the effect of progesterone in hepatic cirrhosis with ascites, since in this condition there is marked sodium retention and aldosterone secretion is usually raised (Dyrenfurth *et al.*, 1957).

Material and Methods

Four women suffering from cyclical oedema were studied. In each case evidence of renal, cardiac, or gastro-intestinal disease was absent and the plasma-protein level was normal. All suffered to a varying extent from such symptoms as headache, depression, abdominal distension, and painful breasts, and all showed some degree of generalized oedema accompanied by rapid changes in weight. Two patients (Cases 2 and 3) were menstruating regularly and the symptoms were maximal during the two weeks before menstruation. Two others (Cases 1 and 4) had a similar history of premenstrual oedema, but, although the menopause had supervened at respectively one year and two years previously, they continued to be troubled by oedema which still tended to be cyclical in character.

The fifth patient, a man aged 56, had a history of excessive consumption of alcohol and was suffering from cirrhosis of the liver with marked ascites.

All patients were maintained on a constant intake of sodium, potassium, and fluid volume, and at least five days were allowed on this regime before beginning the study, which in the case of the premenopausal women occupied the latter half of the cycle. Progesterone was administered intramuscularly in doses ranging from 75 to 200 mg. daily for three or four days. Norethisterone was given orally in doses of 10 mg. three times daily for a similar period.

Results

Figs. 1–5 show that in all subjects an increase in urinary sodium excretion occurred during the administration of progesterone. The greatest effect was seen in Case 4 (Fig. 4) where on an intake of 22 mEq a maximum sodium output of 100 mEq/day was seen, using 200 mg. of progesterone daily. In Cases 1 and 2 (Figs. 1 and 2) an excretion of 50 mEq was seen, using 100 mg. of progesterone. In most cases the effect began to diminish by the fourth day of treatment, and after the cessation of progesterone a rebound retention of sodium occurred in every instance. Potassium excretion fell to a variable extent, and in three cases to more than 20 mEq below control levels. Chloride excretion (Fig. 4) increased in association with the sodium, but the loss was not so great.

In Fig. 1 the effect of chlorothiazide in a dosage of 2 g. daily is shown; approximately twice the level of sodium excretion was obtained as with 100 mg. of progesterone, although potassium excretion was increased. In contrast with the effect of progesterone, norethisterone in doses of 30 mg. daily caused no increase in sodium excretion; in fact after four days there was slight sodium retention in Cases 3 and 4 (Figs. 3 and 4). In Cases 1 and 2 (Figs. 1 and 2) the administration of norethisterone coincided with a period of rebound sodium retention which, however, seemed to be intensified. Norethisterone produced a decrease in potassium excretion in three cases, although in the fourth instance no significant fall occurred. The urine volume altered in relation to the degree of sodium excretion, and where this was only moderate no marked change resulted.

The effect of progesterone on the cirrhotic patient (Fig. 5) was similar to that seen in the previous patients, though the degree of sodium loss was not striking. In this case, however, control values of less than 1 mEq/day indicated that sodium retention was intense; in fact the sodium loss obtained with 200 mg. of progesterone daily was very similar to that resulting from 400 mg. of the aldosterone antagonist spironolactone, and the effect on reducing potassium excretion was also similar. A single injection of mersalyl produced no greater sodium excretion, but in this instance potassium was increased.

Discussion

The increase in urinary sodium, which was observed during the administration of progesterone to cases of cyclical oedema and ascites, is in agreement with the results reported by Landau *et al.* (1955, 1957a, 1957b) on patients without oedema. Potassium excretion was more consistently diminished in the cases described here, but this is in keeping with the view that progesterone acts as an aldosterone antagonist and is confirmed by the similar results obtained with spironolactone. In contrast, the diuretics chlorothiazide and mersalyl caused an increase in both sodium and potassium excretion. The tendency to salt retention shown by norethisterone in doses which have a full progestational effect on the endometrium (Swyer, 1959) emphasizes the

necessity of separating the effects on the uterus from those on general metabolism when considering the therapeutic use of these compounds.

The results obtained in this study provide some rational basis for the reported efficacy of progesterone in the treatment of premenstrual tension (Greene and Dalton, 1953) and also for the fact that norethisterone is often ineffective in cases where progesterone was beneficial (Dalton, 1959).

It is tempting to assign a physiological role to progesterone as a possible moderating influence on aldosterone activity in the maintenance of electrolyte balance in the normal female, but this cannot be adduced from the present study since the amounts of progesterone used are greater than those reached during the menstrual cycle and are of the order found in the latter half of pregnancy (Pearlman, 1957). Landau *et al.* (1957b), however, have reported some effect with

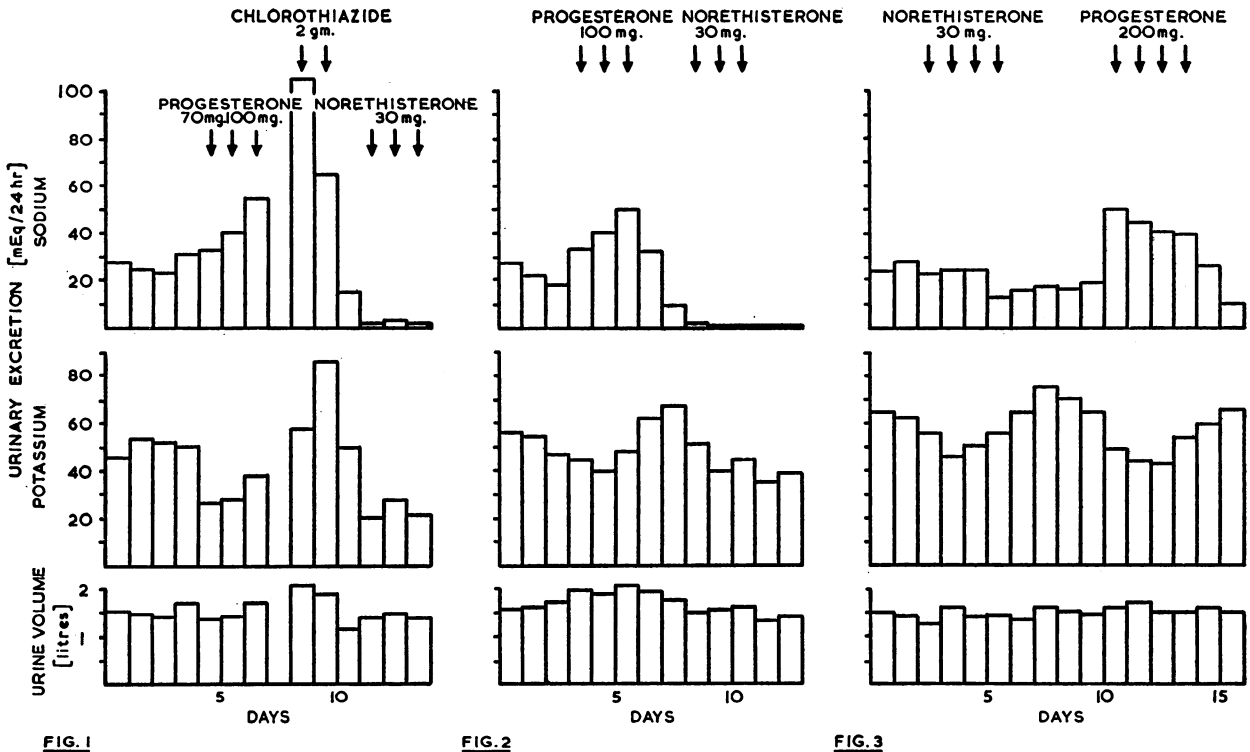

FIG. 1

FIG. 2

FIG. 3

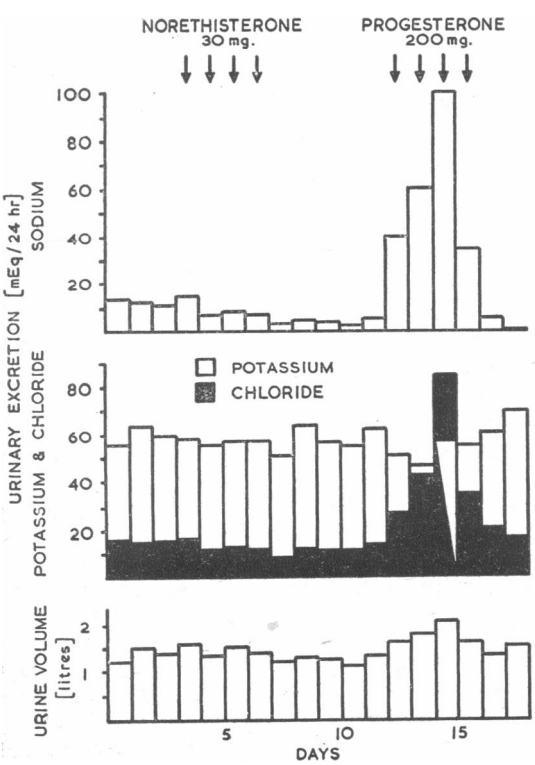

FIG. 4

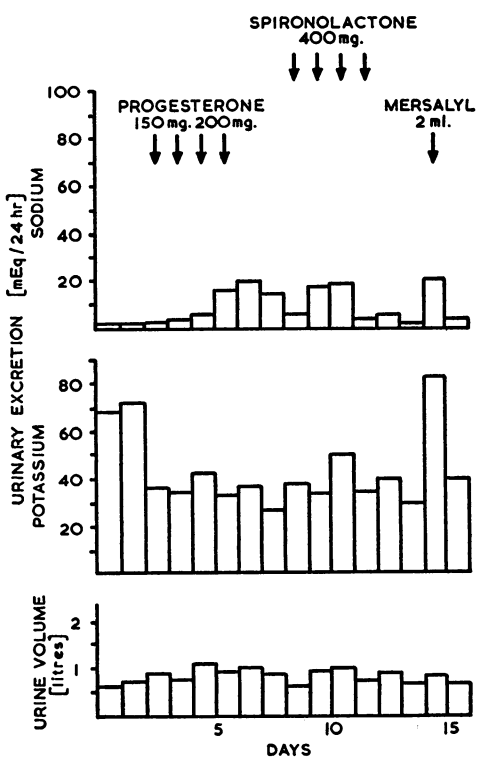

FIG. 5

FIG. 1.—Case 1. Woman aged 52. Cyclical oedema, two years post-menopausal. Intake: sodium 30 mEq, potassium 60 mEq, volume 1,500 ml. daily.

FIG. 2.—Case 2. Woman aged 45. Premenstrual oedema. Intake: sodium 22 mEq, potassium 80 mEq, volume 1,500 ml. daily.

FIG. 3.—Case 3. Woman aged 41. Premenstrual oedema. Intake: sodium 22 mEq, potassium 80 mEq, volume 1,500 ml. daily.

FIG. 4.—Case 4. Woman aged 51. Cyclical oedema, one year post-menopausal. Intake: sodium 22 mEq, potassium 80 mEq, volume 1,500 ml. daily.

FIG. 5.—Case 5. Man aged 56. Hepatic cirrhosis with ascites. Intake: sodium 30 mEq, potassium 80 mEq, volume 1,700 ml.

a dosage as low as 15 mg. daily. Whatever the physiological implications may be, the practical management of cyclical oedema seems to be more effectively and conveniently carried out by the use of oral diuretics such as chlorothiazide. It should be remembered, however, that premenstrual tension is a syndrome of which oedema is the important objective sign, and relief of the various subjective symptoms may be obtained on occasions by a variety of agents.

Summary

The effect of progesterone and norethisterone on urinary electrolyte excretion has been studied in four cases of cyclical oedema. Progesterone caused an increase in urinary sodium excretion, whereas norethisterone produced a tendency to sodium retention.

The action of progesterone in a case of hepatic cirrhosis with ascites was similar to that of the aldosterone antagonist spironolactone.

The implications of these findings in the treatment of premenstrual tension are discussed.

I thank Mr. H. S. H. Sculthorpe, F.I.M.L.T., of the department of chemical pathology, for the estimation of urinary electrolytes; Miss M. E. Carey, chief dietitian; and Dr. J. R. Nassim and Professor A. C. Dornhorst for permission to study cases under their care.

REFERENCES

Dalton, K. (1959). *Brit. med. J.*, **2**, 1307.
Dyrenfurth, I., Stacey, C. H., Beck, J. C., and Venning, E. H. (1957). *Metabolism*, **6**, 544.
Gaunt, R., and Hays, H. W. (1938). *Science*, **88**, 576.
Greene, R., and Dalton, K. (1953). *Brit. med. J.*, **1**, 1007.
Israel, S. L. (1938). *J. Amer. med. Ass.*, **110**, 1721.
Landau, R. L., Bergenstal, D. M., Lugibihl, K., and Kascht, M. E. (1955). *J. clin. Endocr.*, **15**, 1194.
—— —— —— Dimick, D. F., and Rashid, E. (1957a). Ibid., **17**, 177.
—— Lugibihl, K., Bergenstal, D. M., and Dimick, D. F. (1957b). *J. Lab. clin. Med.*, **50**, 613.
—— —— (1958). *J. clin. Endocr.*, **18**, 1237.
Pearlman, W. H. (1957). *Biochem. J.*, **67**, 1.
Swyer, G. I. M. (1959). *Proc. roy. Soc. Med.*, **52**, 515.
Thorn, G. W., and Engel, L. L. (1938). *J. exp. Med.*, **68**, 299.

"In the Norwegian health service the general practitioner is the corner-stone of the system. It is a basic principle that the patient should be free to choose his doctor. The system works on the following lines. The patient first consults his private practitioner, who decides the course to be taken and what treatment or further examinations are necessary. If the practitioner feels that the case is beyond his scope, he refers the patient to a specialist or sends him to a hospital. The insurance plan favours this procedure, and it does not usually refund the specialist's fee to the patient unless he has been referred to the specialist by a general practitioner. Parents may, however, go direct to the paediatrician with their children if they are under 2 years old. There are no open out-patient departments in Norway on the British pattern except in association with some university departments, where they are needed to provide material for teaching purposes. Compulsory health insurance for everyone was introduced in 1956. The relationship between the doctor and the health insurance scheme is relatively free. With very few exceptions it works on the fee system. The doctor is paid according to the amount of work performed, on the basis of a tariff established by the Norwegian Medical Association after informal discussions with the health authorities. Health insurance pays part of the doctor's fee, the remainder being covered by the patient." (Dr. O. K. HARLEM (department of paediatrics, University of Bergen, Norway), "Paediatrics in Bergen," *Cerebral Palsy Bulletin*, Vol. 3, No. 2, 1961.)

HUMAN-AMNION-TISSUE CULTURE IN THE ROUTINE VIRUS LABORATORY

BY

I. B. R. DUNCAN,* M.B., Ch.B.

AND

ELEANOR J. BELL, Ph.D., B.Sc.

From the University Virus Laboratory, Ruchill Hospital, Glasgow

Although tissue cultures of fresh human amnion have been employed in virology since 1955 (Zitcer *et al.*, 1955), few reports on the use of this tissue have appeared in the British literature, and it is doubtful if amnion is used in this country as widely as it deserves. After trial of several tissue-culture systems in this laboratory (Grist *et al.*, 1960), monkey-kidney-tissue cultures were chosen exclusively for the isolation of viruses from stool specimens in 1958. However, early in 1959, when the future supply of monkeys appeared uncertain, it was decided to compare the practical usefulness of monkey kidney and human amnion by testing the susceptibility of the two tissue-culture systems to laboratory strains of a wide range of enteroviruses and by using both in parallel for virus isolation from stool specimens submitted over the period of a year. From this experience we believe that amnion is a tissue suitable for use both in the large specialized virus laboratory and in the smaller bacteriological laboratory where only a limited amount of diagnostic virology is done.

Preparation of Amnion Cultures

Immediately after delivery the entire placenta and membranes are placed in a 2-litre beaker containing 400 ml. of sterile Hanks's solution and covered with sterile aluminium foil. If the placenta is obtained at night the beaker may be stored at room temperature for up to nine hours. At the laboratory the placenta is suspended by the umbilical cord and the amnion dissected free. Blood clot and mucus are removed with forceps from the amnion, which is then cut into six pieces and washed successively in four beakers each containing 100 ml. of sterile Hanks's solution. The amnion receives a preliminary trypsinization for 30 minutes at 37°C. in a tightly stoppered conical flask containing 200 ml. of 0.25% trypsin (Difco 1:250) in Hanks's solution brought to *p*H 7.6 with additional sodium bicarbonate solution. This trypsin is discarded and 200 ml. of fresh trypsin added. The flask is kept at 37°C. for four to four and a half hours and the amnion gently swirled in the flask every 30 minutes. After four to four and a half hours, when the fluid should be turbid from the release of amnion cells, the flask is shaken thoroughly.

The fluid is filtered through two layers of sterile gauze, and, after the amnion tissue has been shaken a second time in 100 ml. of Hanks's solution, this fluid is also filtered through gauze and pooled with the first filtrate. The pooled fluid is centrifuged at 1,000 r.p.m. for 10 minutes to deposit the amnion cells, the supernatant is discarded, and the cells are resuspended in 20 ml. of propagating medium and counted in a haemocytometer after further dilution to 1 in 10. The 20-ml. suspension

*Present address: Bacteriology Laboratory, St. Joseph's Hospital, London, Ontario, Canada.