district nurse's time should be added to the cost of progesterone injections.

Discussion

There can be little doubt that both norethisterone and dimethisterone are powerful progestogenic agents if measured by the Clauberg test on the endometrial proliferation of oestrogen-primed ovariectomized rabbits (Hertz *et al.*, 1954) or of rats (Ferin, 1957). In oestrogen-primed women with long-standing amenorrhoea Swyer (1959) found that 150–200 mg. of norethisterone would produce complete endometrial changes; this is also the amount of progesterone required, but by comparison ethisterone appears to require a total dose of 2,500 to 4,000 mg. (Wied and Davis, 1958) in order to produce the same result. Greenblatt and Jungck found norethisterone so consistent in delaying menstruation that they have suggested this criterion as a new clinical measurement of the comparative effectiveness of progestogenic compounds.

In the comparative trials of treatment of premenstrual syndrome neither ethisterone nor the new progestogens were as completely effective as progesterone itself. This suggests that their effectiveness in the treatment of premenstrual syndrome bears little, if any, relationship to the progestational activity on the endometrium. This can perhaps be explained by the findings of Landau and his colleagues (1955, 1957, 1958), who have demonstrated that progesterone in physiological doses causes a rise in urinary sodium and chloride excretion in man, and also that progesterone inhibits the sodium-retaining influence of aldosterone in man. Nevertheless they have shown that several progestational compounds, which from the chemical point of view are closely related to progesterone, have failed to show this sodium-dissipating action of progesterone, and this may well apply to ethisterone, dimethisterone, and norethisterone.

The many points of similarity of premenstrual syndrome and toxæmia of pregnancy have already been noted (Dalton, 1954), for both are characterized by salt retention, gain in weight, and oedema, and both these conditions respond to progesterone if given from mid-cycle or mid-pregnancy respectively (Dalton, 1957). It may well be that it is this action of progesterone on urinary sodium and chloride excretion which exerts the beneficial effect in premenstrual syndrome and toxæmia of pregnancy, and not the progestational secretory response on the endometrium. Progesterone differs in its action in man from that in other species, for progesterone has a salt-retaining action in dogs (Thorn and Engel, 1938) and in adrenalectomized ferrets and rats (Gaunt and Hays, 1938). Significantly the human species is also the only species to suffer from toxæmia of pregnancy.

Summary

These comparative trials of 58 patients suffering from premenstrual syndrome have shown that ethisterone, dimethisterone, and norethisterone are not as specific in their action as progesterone. This is not to say that they do not possess comparable progestogenic activity as shown by the secretory response of the endometrium, the evidence for which has already been demonstrated. But these oral preparations fail to produce the action of progesterone, peculiar to the human species, of increasing the urinary sodium and chloride excretion. If an oral preparation can be produced possessing this salt-dissipating action of progesterone in man then one

may anticipate a universal substitute for progesterone in the premenstrual syndrome.

I am indebted to Dr. J. L. Hunt, of British Drug Houses Ltd., and Dr. Jürgen Friebel, of Schering A.G.B. Berlin, for the supplies of the dimethisterone and norethisterone and for the help and encouragement they have both given me.

REFERENCES

- Dalton, K. (1954). *Brit. med. J.*, **2**, 1071.
 — (1957). *Ibid.*, **2**, 378.
 Ferin, J. (1957). *J. clin. Endocr.*, **17**, 1252.
 Gaunt, R., and Hays, H. W. (1938). *Science*, **88**, 576.
 Greenblatt, R. B., and Jungck, E. C. (1958). *J. Amer. med. Ass.*, **166**, 1461.
 Greene, R., and Dalton, K. (1953). *Brit. med. J.*, **1**, 1007.
 Hertz, R., Tullner, W. W., and Raffelt, E. (1954). *Endocrinology*, **54**, 228.
 Landau, R. L., Bergenstal, D. M., Lugibihl, K., and Kascht, M. E. (1955). *J. clin. Endocr.*, **15**, 1194.
 — and Lugibihl, K. (1958). *Ibid.*, **18**, 1237.
 — — — Bergenstal, D. M., and Dimick, D. F. (1957). *J. Lab. clin. Med.*, **50**, 613.
 Swyer, G. I. M. (1959). *J. Endocr.*, **18**, No. 2, p. v.
 Thorn, G. W., and Engel, L. L. (1938). *J. exp. Med.*, **68**, 299.
 Wied, G. L., and Davies, M. E. (1958). *Ann. N.Y. Acad. Sci.*, **71**, 599.

Medical Memoranda

Acute Haemolytic Anaemia Associated with Sulphadimidine Therapy

The possible complications affecting the haemopoietic system due to the administration of the sulphonamides are acute haemolytic anaemia, aplastic anaemia, leucopenia, agranulocytosis, thrombocytopenia, and methaemoglobinaemia (Wintrobe, 1956). Dacie (1954) regards acute haemolytic anaemia as the most serious of these complications, and its frequency varies with the different sulphonamides: 2–4% with sulphanilamide, 0.6% with sulphapyridine, and more rarely with sulphathiazole and sulphadiazine (Dacie, 1954; Wintrobe, 1956). One case of acute haemolytic anaemia following sulphadimidine administration was reported by Sterndale (1956), and the following report summarizes the clinical and laboratory findings in another case.

CASE REPORT

The patient, a boy aged 7 years, was admitted to hospital on June 30, 1958. The only relevant information in his history was that at the age of 4 years he developed measles followed by otitis media, for which sulphadiazine (1.5 g.) was administered; therapy was suspended because of abdominal pain and the passage of a small, loose, brown stool.

The child was healthy until June 22, 1958, when he complained of sore throat. The following evening his temperature rose to 104° F. (40° C.). Acute tonsillitis was diagnosed on June 23, and sulphadimidine (suspension), 1 g. four-hourly, was prescribed. As the temperature did not subside, intramuscular penicillin was started the next day. Protein was found in the urine on June 26, and the child was put on a nephritic diet. His general condition remained good until the next day, when it rapidly deteriorated, and he became drowsy, pale, and icteric. He also passed a dark-coloured urine. Sulphadimidine and penicillin were stopped on June 28, a total of 28 g. of sulphadimidine having been administered over a period of

five days. Tetracycline (125 mg. four-hourly) therapy was then instituted. That same evening drowsiness and icterus became more pronounced, and a large volume of dark-coloured urine was passed.

On admission to hospital his general condition was poor, jaundice and pallor were obvious, and there was an appreciable degree of air-hunger and of restlessness. The pulse rate was 120 and regular; temperature, 100.4° F. (38° C.); B.P., 130/180. The fauces and tonsils were congested; the liver was slightly enlarged, but the spleen was not palpable. There were no other physical findings.

Laboratory Findings.—The principal haematological findings are set out in Table I. Other laboratory findings on June 30 were: Coombs test, direct and indirect, negative; foetal Hb. 1.4%; electrophoresis of Hb showed the presence of only adult Hb. The van den Bergh reaction was negative; plasma bilirubin, 3.2 mg./100 ml. The serum was dark brown, and both oxyhaemoglobin and methaemalbumin (Schumm's test) were detected spectroscopically. The serum haemoglobin was increased ($\times 5.2$ normal control). Serum electrophoresis showed some reduction in the albumin component, an appreciable increase in both α_1 - and α_2 -globulins, a normal beta-fraction, and a considerable fall in gamma-globulin (see Table II). An additional distinct band was discernible in the α_2 -beta position, and was attributed to the presence of free haemoglobin in the serum. The blood urea was 35 mg./100 ml. The Wassermann and Kahn reactions were negative.

The urine was reddish-brown in colour; protein ++; Benedict's test was negative; ketone bodies absent; bilirubin absent; no urobilinogen or urobilin was detected; the o-tolidine and benzidine tests were very strongly positive. Microscopy of the centrifuged deposit showed occasional erythrocytes, few leucocytes, fine granular casts (+), and transitional epithelial cells (+).

Acute haemolytic anaemia was diagnosed, and treatment was instituted on the day of admission. The child was

transfused with 150 ml. of group O Rh positive blood, and was given prednisone, 30 mg. daily, for the first four days, and 20 mg. daily for the next two days. Crystalline penicillin intramuscularly (1 mega unit daily for the first three days, reduced to 0.5 mega unit daily for the subsequent three days) was also started.

Retention of urine developed on July 1 and was relieved by catheterization, when 24 oz. (680 ml.) of dark-coloured urine was voided. Some improvement in the patient's general condition was, however, noticeable. Proteinuria was more pronounced, urobilin was present, and sulphona-mide crystals were seen in microscopical examination of the urine deposit. The patient was afebrile on July 2, and his general condition continued to improve.

On the fourth day the plasma bilirubin level was 1 mg./100 ml.; free haemoglobin was still detectable ($\times 2.5$ normal control) in the serum; spectroscopy showed only weak methaemalbumin bands. Plasma proteins, 7.7 g./100 ml.; albumin 5 g./100 ml. Serum electrophoresis now showed a further reduction in the albumin fraction and that the gamma-globulin fell within normal limits, while the α_1 -, α_2 -, and beta- components were essentially unaffected (see Table II). An additional band in the α_2 -beta position was again equally distinct. The blood urea level was 15 mg./100 ml.

Steady progress was maintained, the urine becoming of a lighter colour, and only a trace of protein was present when the patient was discharged on July 9.

The child was observed as an out-patient for a prolonged period and remained well.

COMMENT

The risk of toxic effects of sulphadimidine is still thought to be very small. Our observations are in agreement with those of Sterndale (1956), and favour hypersensitivity rather than a direct haemolytic action as being the cause of the acute anaemia. Early diagnosis and immediate institution of treatment to counteract the rapidly progressive anaemia are of major importance.

J. L. GRECH, M.D.,
E. A. CACHIA, M.B., D.C.H.,
St. Luke's Hospital, Malta.

REFERENCES

- Dacie, J. V. (1954). *The Haemolytic Anaemias*, p. 392. Churchill, London.
Sterndale, H. (1956). *Brit. med. J.*, 2, 1101.
Wintrobe, M. M. (1956). *Clinical Hematology*, 4th ed., p. 624. Kimpton, London.

TABLE I.—Principal Haematological Findings

	June 30	July 4	July 31
Hb (g. 100 ml.)	5.50	7.58	13.30
R.B.C. (mill. c.mm.)	1.80	2.55	4.0
P.C.V. (%)	15.50	25.75	40.0
Reticulocytes (%)	5.8	22.2	2.0
W.B.C. (per c.mm.)	23,900	7,100	6,000
Platelets (per c.mm.)	241,200	33,210	—
R.B.C. fragility, } Begins	0.76	0.44	—
NaCl g. % } Ends	0.30	0.30	—
Film appearance	Anisocytosis ++	Anisocytosis +	Anisocytosis slight
	Anisochromia ++	Hypochromia ++	Normochromia
	Macrocytosis +	Macrocytosis +	Macrocytosis slight
	Microcytosis +	Microcytes rare	—
	Poikilocytosis +	Poikilocytosis slight	—
	Basophilia + Schistocytosis +	Basophilia +	—
Normoblasts (per 100 W.B.C.)	18	3	0
Myelocytes (per c.mm.)	239	142	0
Metamyelocytes (,,)	9,321	1,775	0
Poly neutrophils (,,)	7,648	3,479	2,623
„ eosinophils (,,)	478	0	244
Lymphocytes (,,)	5,494	1,491	2,440
Monocytes (,,)	717	213	793

Heinz bodies were not detected on repeated examination.

TABLE II.—Results of Paper Electrophoresis of Serum Proteins. Values Expressed as Percentage of Total Protein

	Albumin	Globulin				Hb
		α_1	α_2	Beta-	Gamma-	
Normal values	39	6	13	17	25	0
Standard deviation	± 4.5	± 2.3	± 2.6	± 2.6	± 4.5	—
Patient:						
June 30	34	10	18	15	19	4
July 4	31	9	17	16	23	4

More than 5,000 soldiers, sailors, and airmen have come to St. Dunstan's since it was first started 44 years ago, says St. Dunstan's 44th annual report for the year ended March 31, 1959—*The Art of Blindness*. To-day 2,500 St. Dunstaners survive—1,300 from the first world war and 1,200 from the second—and new cases are still being admitted as a late result of injuries, often mustard-gas poisoning, received many years ago. During the year the council of St. Dunstan's has established a scientific committee to study the whole field of sensory reading and guiding devices. The chairman, Lord Fraser of Lonsdale, states in his foreword that, if a reasonable measure of support continues for a few more years and there is no devaluation crisis, St. Dunstan's should have sufficient funds to carry out its programme in regard to blinded Service men and women. It has accordingly been decided to abate the most highly organized forms of competitive money-raising and rely upon subscriptions, donations, deeds of covenant, and legacies.