practically certain that these antigen injections have less immunizing effect on tuberculous patients than on healthy controls.*

Our data are not extensive enough to allow of further analyses, especially with respect to a possible difference between the effect of immunization on acute and on chronic patients. Any differences there may be cannot be shown to be statistically significant. There is some indication that the tuberculous patients consist of two groups—that is, those who still do not show any increased titre values after from three to six weeks and those who reach fairly high titre values two to three weeks after the second injection of antigen. Or, to put it differently, there are tuberculous patients who did not react at all throughout the experiment and there are patients who did react albeit somewhat tardily, while at the same time the level of the titre values for the latter may be lower than with healthy persons.

However, these are but vague indications, and only a more extensive investigation can show what they are worth.

Discussion

Our findings with regard to the immunization of tuberculous patients appear to be essentially the same as the results obtained with sarcoidosis patients by the English investigators mentioned above.

Consequently the question now arises whether a chronic disease—that is, sarcoidosis or tuberculosis—causes a lesion or an exhaustion of the reticulo-endothelial system (R.E.S.) (which, we believe, plays an all-important part in the formation of antibodies). Greenwood *et al.* assume that the sarcoidosis infiltrates the R.E.S., as a result of which there can be no adequate reaction to the antigen stimulus (any more).

On the other hand, there is the possibility of there being a primary disorder of the R.E.S. which has caused the inability to resist these diseases.

Our limited material comprises both very recent and chronic infections.

The reaction pattern we found showed no difference in the antibody production of the two groups of patients. So the analysis of the antitoxin formation after the administration of the two tetanus P.T. injections did not enable us to find any correlation with the clinical picture.

Summary

A number of tuberculous patients were immunized against tetanus with two injections of tetanus phosphate toxoid. Compared with a control group consisting of normal healthy persons these tuberculous patients showed in general a diminished antibody production.

REFERENCE

Greenwood, R., Smellie, H., Barr, Mollie, and Cunliffe, A. C. (1958). *Brit. med. J.*, **1**, 1388.

APPENDIX

All sera from patients were titrated according to a logarithmic scale For practical reasons this logarithmic scale was divided into three subscales:

Scale 1: 0.001, 0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.128, 0.256 unit/ml. of serum.

Scale 2: 0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.28, 2.56 unit/ml. of serum.

Scale 3: 0.10, 0.20, 0.40, 0.80, 1.60, 3.20, 6.40, 12.8, unit/ml. of serum.

So each scale gives nine titre values (scale 3 only eight). From all serum-toxin-saline mixtures (4 ml.) 0.4 ml. was injected subcutaneously into a mouse.

Every series of titrations of an unknown serum was compared with a control titration with standard serum. For this reason our own standard serum (titrated against the International Standard Serum from the Statens Serum Institute, Copenhagen) was used.

For titrations according to scale 1 the standard serum was diluted to 0.001 unit/ml.; for titrations according to scale 2 the dilution was to 0.01 unit/ml., and for scale 3 to 0.1 unit/ml.

To 1 ml. of this standard serum dilution was added the corresponding quantity of test toxin and the total volume of the mixture brought to 4 ml. with saline. Of this mixture, 0.4 ml. was injected subcutaneously into a mouse. This last-mentioned quantity of the mixture therefore contained 0.0001 viz. 0.001, 0.01 unit, and so much toxin that the mice normally died four days after the injection. These toxin quantities therefore were L+/10,000, viz. L+/1,000. L+/100.

To get a good insight into the course of the serum titrations, and especially to obtain a good check of the "control mixtures," all titrations with the diluted standard serum were performed with three different quantities of diluted standard serum (D.S.S.):

0.9 ml. D.S.S.+1 L+/10,000 (1,000, 100) test toxin
1.0 ml. „ +1 L+/10,000 (1,000, 100) test toxin
1.1 ml. „ +1 L+/10,000 (1,000, 100) test toxin

All mixtures were made up to 4 ml. with saline, and 0.4 ml. was injected into mice.

The injected mice were observed daily for four days.

*It should be noted that actually this conclusion may only be drawn if the 16 tuberculous patients and the 11 controls have been taken at random. As it is usually very difficult to fulfil this condition in investigations like the present, the general validity of this interpretation must as yet be accepted with some reserve.

COMPARATIVE TRIALS OF NEW ORAL PROGESTOGENIC COMPOUNDS IN TREATMENT OF PREMENSTRUAL SYNDROME

BY

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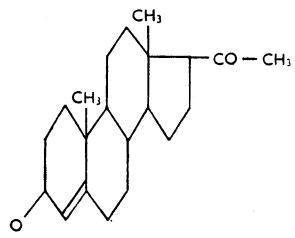
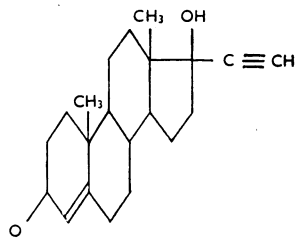
Progesterone usually provides complete symptomatic relief in cases of premenstrual syndrome (Greene and Dalton, 1953). Against this successful treatment must be set the high cost of progesterone and the inconvenience and discomfort of frequent deep intramuscular injections. Several progestogenic compounds have recently been developed which, being oral preparations, could conveniently replace progesterone if they were as completely successful in their action. Two of these new progestogenic compounds were tested in a comparative trial of 58 patients suffering from premenstrual syndrome who had all obtained complete symptomatic relief with progesterone.

The oral preparations used were ethisterone (anhydrohydroxyprogesterone or ethinyltestosterone) and the two new oral preparations norethisterone (anhydrohydroxy-19-norprogesterone or ethinylnorprogesterone) and

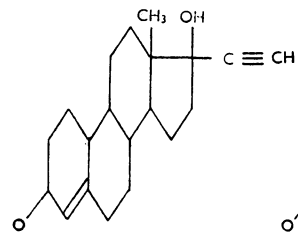
dimethisterone (6α-21-dimethylethisterone). The chemical formulae of progesterone and the above three preparations are as follows:



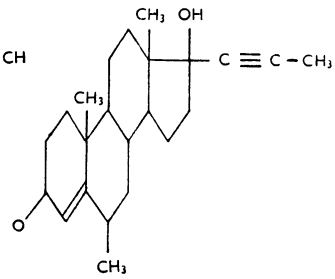
Progesterone



Ethisterone



Norethisterone



Dimethisterone

All these preparations had been shown by the Clauberg test to give progestogenic secretory response to the endometrium of oestrone-primed ovariectomized rats. The norethisterone and dimethisterone were several times more potent than ethisterone (Ferin, 1957).

Selection of patients for the trial was limited to members of the practice suffering from premenstrual syndrome who had obtained complete relief with progesterone, and whose diagnosis had been confirmed by the use of a menstrual chart for a minimum of three months. The 58 patients had received doses of progesterone varying individually from 25 mg. on alternate days to 100 mg. daily during the two weeks prior to menstruation. Twenty-four of these patients had previously received progesterone implants of 0.5 to 1 g., now exhausted, and consequently the symptoms had returned. Seven of the patients had previously been reported in a paper on premenstrual syndrome (Greene and Dalton, 1953). Another seven patients had previously had a hysterectomy and now had cyclical symptoms occurring at the time of the menstrual equivalent, and three patients were post-menopausal also with cyclical symptoms. Most patients were poly-symptomatic, and their symptoms are shown in Table I.

TABLE I.—*Premenstrual Symptoms of 58 Patients*

	Patients	%		Patients	%
Headache	38	65	Vomiting	7	12·0
Depression	22	37·8	Backache	6	10·3
Lethargy	22	37·8			
Abdominal pain	10	17·2	Asthma, epilepsy, dyspnoea, and acne		1 each
Tension	9	15·5			

Results

Ethisterone.—Patients enjoying complete symptomatic relief with progesterone are usually given a trial with ethisterone. A daily dose of ethisterone is used which is approximately four times the optimal strength of progesterone. The results in Table II show that only 59% reported good or moderate relief.

TABLE II.—*Results of Treatment*

Preparation	Good		Moderate		Poor		Total
	No.	%	No.	%	No.	%	
Progesterone	58	100	—	—	—	—	58
Ethisterone	14	36	9	23	16	41	39
Dimethisterone	6	32	1	5	12	63	19
Norethisterone	19	40	9	19	19	40	47

Dimethisterone was the first of the new progestogens to be tried. In view of the known endometrial response a dosage of 10 mg. daily was recommended by the manufacturers. This was later raised to 40 mg. daily, but produced little improvement on the final result. Only 37% reported good or moderate relief.

Norethisterone was next tried. The daily dose of 15 mg. was based on the known endometrial response and the manufacturer's recommendation, but this dose was later increased to 45 mg. The most successful dose was 15 mg. daily, and 59% reported good or moderate relief, a result similar to that from ethisterone.

Patients who responded to one oral preparation did not necessarily respond to another. Of the 58 patients there remained 18 (31%) who required progesterone injections. In order to ascertain which patients are likely to respond to an oral preparation the 58 patients were analysed according to clinical severity, duration, types of symptoms, overweight and underweight, age, parity, marital status, and history of toxaemia of pregnancy. No significant difference was found among the responders to oral preparations when compared with the non-responders, though there was an increase in non-responders among women with two or more children (60%) compared with responders (36%).

From the foregoing it might be concluded that patients failing to respond to one oral preparation should be tried with another. In practice, however, this presents difficulties, for patients who have obtained no relief from one or two oral preparations prefer to return to progesterone injections; this was found to be particularly the case where a recurrence of symptoms had resulted in loss of time from work or the need for bed rest.

Side-effects were reported with the new progestogens, including headache 4, tiredness 4, mastitis 2, nausea 2, vertigo 1, dysmenorrhoea 1, and acne 1. Greenblatt and Jungck (1958) advise patients to take norethisterone at night to avoid excessive tiredness and nausea. A gain in weight of over 4 lb. (1,800 g.) a month was noted by seven obese patients. Both dimethisterone and norethisterone delayed menstruation if treatment was not stopped at the time of the expected menstruation. One patient became pregnant after two months' treatment with norethisterone.

Comparative Costs

Table III shows there is little difference in the cost of one month's treatment with progesterone, ethisterone, or norethisterone, but in many instances the cost of the

TABLE III.—*Basic National Health Cost of One Month's Treatment*

Preparation	Average Daily Dose	Month's Cost
Progesterone	25 mg.	21s. 0d.
Ethisterone	75 ,,	24s. 6d.
Dimethisterone	15 ,,	22s. 6d.
Norethisterone	15 ,,	22s. 6d.

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 toxaemia 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 toxaemia 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 toxaemia 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.

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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