in average P.E.F. rates in the morning or in the evening. All patients who were symptomatically better had an increase in P.E.F., including the three patients who had a smaller F.E.V.₁; the use of a peak flow meter is of considerable value in following the response to treatment in asthmatics over a period of days or weeks, and in this trial it provided useful confirmation of symptomatic benefit (Epstein *et al.*, 1969). The degree of symptomatic improvement did not correlate with initial F.E.V.₁ results.

Moran *et al.* (1968) reported a greater improvement in the younger patients, but in our series the reverse obtained.

In the nine patients there was a reduction in average values of F.R.C. and R.V. Woolcock and Read (1966) found a greater reduction in T.L.C. in many of their cases, whereas only one of our patients showed a fall of as much as 1 litre. The difference may be due to the fact that Woolcock and Read's patients were studied during and after severe status asthmaticus.

We did not find any improvement in exercise capacity in those who were symptomatically better despite an increase in ventilatory capacity as judged by F.E.V.₁ and specific conductance of airways. It would seem that ventilation did not limit exercise capacity in our subjects, though it would be expected to do so with a greater degree of airway obstruction. The reduction in pulse rate is unexplained.

Altounyan (1964) showed that during attacks of asthma associated with allergy there is a poor response to inhaled atropine methylnitrate compared with isoprenaline sulphate, but that treatment with corticosteroids increases the atropine response. Patients with non-allergic airway obstruction usually have a high atropine response. In the present study the six asthmatics having steroids had a much greater atropine response than those not having steroids. Furthermore, those not having steroids had an increase in atropine response after treatment with disodium cromoglycate. If a poor atropine response indicates an allergic basis for increased airway resistance, both steroids and disodium cromoglycate appear to interrupt this allergic process, not necessarily by the same mechanism. Pepys *et al.* (1968) showed that previous inhalation of disodium cromoglycate inhibited allergic reactions produced by inhalation of appropriate allergens in asthmatic patients.

We included sensitive tests of airway resistance and lung volumes, using the body plethysmograph, and of exercise performance in our study because we thought that these methods might show a physiological basis for subjective improvement

in the absence of improvement in F.E.V.₁. In fact these more elaborate techniques proved less useful than the simple daily measurement of P.E.F. It seems that Howell and Altounyan's (1967) failure to show objective improvement in patients whose symptoms were diminished by disodium cromoglycate was due to the unreliability of isolated measurements in asthmatic patients. The value of daily measurements of P.E.F. recommended by Epstein *et al.* (1969) is confirmed by this study.

Grant (1968) criticized claims that have been made of benefit from disodium cromoglycate on the ground that the degree of improvement obtained has been too small to be worth while in most cases. It can be seen from our results that there was a very marked symptomatic improvement in the nine patients who were benefited and that they showed on average a 30% improvement in P.E.F. rate accompanied by a 65% improvement in specific conductance. These changes appear to us to be well worth while.

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Preliminary Communications

Progesterone Oral Contraception and Blood Coagulation

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Summary: The effects on blood coagulation of oral contraception with continuous progesterone (chlormadinone acetate, 0.5 mg. daily) have been studied in a group of 76 volunteers. The women in this trial not having previously received conventional oral contraceptives showed no evidence of increased coagulability or increased platelet aggregation in the first three months, though possibly fibrinolytic activity was raised. Women previously taking combined oestrogen-progesterone preparations showed significantly raised levels of clotting-

factors VII and X at the start of the trial. Both of these progressively fell over the three months, and by the third month the factor VII level was no longer different from the normal group. Factor X levels, however, have not yet fallen to normal. The results so far suggest that the thrombogenic constituent of conventional oral contraception may have been eliminated by the use of progesterone alone, though further investigation will be required to substantiate this.

INTRODUCTION

Oral contraception with conventional oestrogen-progesterone combinations produces significant rises in specific blood-clotting factors—that is, factors VII and X (Thomson and Poller, 1965). The rise becomes significant from the third

month onwards (Poller and Thomson, 1966), and is not diminished by using low-dose preparations (Poller *et al.*, 1968).

In the present trial a pure progesterone preparation, chlormadinone acetate, was studied in a group of women volunteers. The results with this progesterone preparation are in such sharp contrast to those we have reported previously that we are presenting our preliminary findings at the three-month stage.

METHOD OF STUDY

The women in this investigation volunteered following a public appeal for participants in a trial of progesterone oral contraception. The hormone used was chlormadinone acetate, which was given continually in a daily dosage of 0.5 mg. Investigations were performed before starting and subsequently at monthly intervals.

The women in this progesterone study totalled 76 and were divided into two groups. The first were those taking an oral contraceptive for the first time and the second group were those already taking some conventional combined or sequential preparation. A normal group consisted of an equal number of women not taking the "pill," but of a similar age group, and included women in group 1 before they started to take chlormadinone. The normals were tested in parallel. The normals and the volunteers for the study were asked to attend the department between 9 and 10 a.m., and a venous blood sample was collected. All subjects were made to rest for at least five minutes before venepuncture.

Technique.—The methods for measuring the one-stage prothrombin time, the cephalin time, the kaolin-activated cephalin time, and the factor VII and factor X assays were as described previously (Thomson and Poller, 1965; Poller and Thomson, 1966). These tests were carried out on every sample in the progesterone study and the controls. In group 1 only the following additional tests were performed: fibrinogen (Ratnoff and Menzie, 1951) in 20 women; the dilute whole blood clot lysis time (Fearnley *et al.*, 1957, modified) in all cases; thromboelastography (Hartert) in 10 women; and platelet aggregation by Chandler's tube and an adenosine-diphosphate-induced optical density method (Poller *et al.*, 1969) in 18 women.

RESULTS

Of the 40 women in group 1 who had not previously taken oral contraceptives, 37 kept all their appointments up to the three-month stage. Of the 36 in the second group who had changed to chlormadinone, 23 made their four visits. Those women who did not keep their four appointments were excluded from the study. There has been no fall-out because of pregnancy.

The women in the group not having taken oral contraceptives previously showed no statistically significant change in any of the clotting-tests or specific coagulation assays over the first three cycles. Results for dilute whole blood clot lysis times, which was modified by using a 1/20 dilution, are given in the Table. From the second month onwards a significant shortening of the clot lysis time was noted. In the 10 patients followed by thromboelastography no alteration in their thromboelastographic pattern was observed. Platelet aggrega-

tion studies showed no significant change with either coagulation-induced (Chandler's tube) or adenosine-diphosphate-induced methods.

The second group of women had been taking some conventional oestrogen-progesterone combination for an average of 14 months. There was a significant shortening of the prothrombin time and significantly raised levels of factor VII and factor X before starting chlormadinone. Cephalin times were not shortened. The results of factor VII and X assays over the three months of chlormadinone administration are shown in Fig. 1. By the second month the prothrombin time had returned to the normal range and by the third month the factor VII level was no longer significantly increased. The factor X level, though falling, was still significantly high.

FIG. 1.—Factor VII and X assays during three months of chlormadinone administration. "Pill" group expressed as percentage of mean control times. — Chlormadinone acetate group not having taken oral contraceptives previously. ---- Group who had changed to chlormadinone acetate from other "pill" preparations.

DISCUSSION

There is clinical evidence that oestrogens promote haemostasis, and they have been used for some time as haemostatic agents in certain clinical states (Blackburn, 1963; Berkarda *et al.*, 1965). There is also believed to be an increased thrombotic tendency in women whose lactation is suppressed by oestrogens (Daniel *et al.*, 1968). Whether the action of oestrogens in haemostasis is due to an effect on blood-clotting factors, on blood platelets, or on the blood vessel wall is not certain (Ulutin, 1969).

The absence in this progesterone trial of rises in factors VII and X is in direct contrast to our results with all previous types of oral contraceptive. Even more encouraging, however, is the dramatic reduction seen in Fig. 1 of the raised levels of clotting-factors present in the women on conventional oestrogen-progesterone preparations when they change to progesterone alone.

Although factor X levels were considerably reduced after three months' progesterone administration in women who had taken conventional oestrogen-progesterone compounds previously, the level was still higher than normal. Further study will show whether factor X levels return to normal at a later date in this group.

An interesting additional feature is the reduction of dilute clot lysis time, suggesting an increase in fibrinolytic activity in normal women during the first three months of taking chlormadinone. This obviously needs more careful investigation and, if confirmed, suggests that progesterone may exert a protective influence against thrombosis. The absence of a rise in fibrinogen level with chlormadinone contrasts with our findings in a group on the combined preparations, Ortho-Novin and Norinyl-1, studied in parallel, though the latter had been

Dilute Whole Blood Clot Lysis Times in Women Not Previously Taking Oral Contraceptives

	No. of Women	Lysis Time (Hours)	Standard Deviation
Before starting chlormadinone ..	37	3.86	2.38
1st month chlormadinone ..	38	3.31	1.38
2nd month chlormadinone ..	38	3.23	1.00
3rd month chlormadinone ..	38	3.25	0.98

on oral contraception longer—that is, 18 months (unpublished data). Brakman and Astrup (1964) reported raised fibrinogen levels in women on oral contraceptives.

FIG. 2.—Thromboelastographic patterns. A, a normal pattern after three months on chlormadinone acetate. B, hypercoagulability after 12 months on a conventional oestrogen-progesterone compound. C, extreme hypercoagulability pattern of a patient suffering from a deep-vein thrombosis after oral contraceptive administration.

The normal thromboelastographic pattern so far also contrasts with our findings during the administration of conventional preparations, as Fig. 2 shows. An extreme form of thromboelastographic hypercoagulability pattern in a patient who had been receiving an oestrogen-progestin compound and suffered a deep-vein thrombosis is illustrated for comparison.

The absence so far of changes in platelet aggregation is likewise reassuring, as in parallel studies we have shown significant shortening of the platelet aggregation with the Chandler tube in women taking both high-dose and low-dose forms of combined preparations (Poller and Priest, 1969).

We should emphasize that these results, though extremely encouraging, reflect only the first three cycles of administration, and a long-term study must of course be performed to

exclude a delayed or cumulative action. In so far as it is possible to be certain at this stage the investigation does suggest that the thrombogenic constituent of conventional oral contraception may have been eliminated by the use of progesterone alone.

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Medical Memoranda

Urinary Oestriol Excretion in Pregnant Patient Given Large Doses of Prednisone

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A recent report of pregnant patients receiving corticosteroids throughout pregnancy suggests that perinatal mortality is increased (Warrell and Taylor, 1968). The present report is of a patient who was taken off corticosteroids when she was found to be pregnant, but therapy had to be restarted when her condition deteriorated. Urinary oestriol and pregnanediol estimations were carried out throughout the second course of treatment until delivery.

Wallace and Michie (1966) reported a case of impetigo herpetiformis in which 30 mg. of prednisone was given each day throughout pregnancy and a consistently low oestriol excretion count of about 4 mg./24 hours was found from the 29th to the 33rd week of gestation. As it was feared that continuation of the pregnancy would jeopardize the foetus, caesarean section was performed at the 34th week. The birth weight of the baby was only one standard deviation below the

mean weight for duration of gestation, and the authors believed that the pregnancy could have been allowed to continue until near term. This report of a patient who received a much higher dose of prednisone confirms their belief.

CASE REPORT

A 24-year-old primigravida was admitted to hospital on 20 April 1968 for investigation of recurrent stomal ulceration when 24 weeks pregnant. The condition had been present intermittently for the previous 18 months. It had been diagnosed as erythema multiforme and in the past had responded to treatment with cortisone. Her last menstrual period was on 12 October 1967.

Examination showed that she had, in addition to the stomal ulceration, patches of what appeared to be eczema on the lower abdomen and in front of the left ankle. There was a normal 24-week intrauterine pregnancy.

The haemoglobin was 11.7 g./100 ml., packed cell volume 36%, M.C.H.C., 33%, E.S.R. 14 mm./hour, white blood count 7,300/cu. mm., blood urea 14 mg./100 ml., alkaline phosphatase 7 units, bilirubin 0.2 mg./100 ml., serum vitamin B₁₂ 325 µg./100 ml. The platelet count was 160,000/cu. mm., the serum electrolytes were normal (sodium 139 mEq/l., potassium 44 mEq/l., chloride