There have been no accidents as a result of the test, and the patients are not distressed by it. Indeed, when a patient is given a good prognosis concerning her baby, considerable peace of mind is derived from such news.

Summary

A report is given of liquor amnii tests on 101 sensitized rhesus-negative women. It has been found that: (1) the liquor must be tested fresh before the 35th week; and (2) an accurate prediction can be obtained in at least 94.9% of cases.

This work has been made possible by the willing co-operation of all members of the medical and nursing staffs of St. Mary's Hospitals, Manchester. I wish to thank Professor W. F. Gaisford, Dr. G. M. Komrower, and Dr. R. F. Jennison for their constant advice and enthusiasm in this research; and also my obstetrical colleagues who so kindly entrusted their patients to my care, and to Dr. D. C. A. Bevis for much generous assistance.

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TOXAEMIA OF PREGNANCY TREATED WITH PROGESTERONE DURING THE SYMPTOMATIC STAGE

BY

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While investigating the use of progesterone for the relief of premenstrual syndrome (Greene and Dalton, 1953) a high incidence of toxaemia of pregnancy (19.1%) was recognized among sufferers from this syndrome. A further investigation, undertaken to ascertain the incidence of premenstrual syndrome in those who had previously suffered from toxaemia of pregnancy, revealed that 86% of the 237 women thus affected at one time or another during the previous twelve years also suffered from premenstrual syndrome (Dalton, 1954). Furthermore, direct questioning and a scrutiny of records of these patients showed that before the full development of the signs of toxaemia—that is, oedema, hypertension, and albuminuria—most had earlier in the pregnancy experienced a symptomatic stage characterized by relatively minor afflictions—for example, lethargy 43%, headache 48%, visual aura 37%, vertigo 29%, nausea and vomiting 16%, irritability 14%, depression 9%, and backache 6%. In fact, only 7% disclosed freedom from these symptoms during a toxaemic pregnancy. Of the 237 women, 92 (38.8%) had experienced both a normal and a toxaemic pregnancy, and 72 (78%) contrasted the sense of well-being associated with a normal pregnancy with the malaise and minor symptoms characteristic of the toxaemic condition.

The striking feature of these early minor symptoms of toxaemia was their close resemblance to those of premenstrual syndrome noted in an earlier investigation (Greene and Dalton, 1953), most patients confirming that the minor symptoms during their toxaemic pregnancy were similar, though of increased severity, to those experienced in the premenstruum, irrespective of whether the onset of premenstrual syndrome had preceded or followed the toxaemic pregnancy.

Apart from the similarities of these minor symptoms in the two conditions, other points in common were noted. For example, day-to-day observations of sufferers of premenstrual syndrome had shown that, apart from minor symptoms, some developed oedema, hypertension, and albuminuria during the premenstruum, with spontaneous improvement during menstruation. This appeared to be analogous to the spontaneous resolution of oedema, hypertension, and albuminuria following delivery. Furthermore, if symptoms remain untreated either in premenstrual syndrome or in toxaemia both diseases may culminate in fits, epileptic in the one case, eclamptic in the other.

In an earlier investigation one of the reasons for using progesterone in the treatment of premenstrual syndrome had been that some patients suffering from this condition were symptom-free during pregnancy. It was considered that the corpus luteum and placenta supplied enough progesterone during pregnancy to keep these patients symptom-free. Others were not only unrelieved of their premenstrual symptoms during pregnancy, but, as already indicated, developed symptoms closely resembling those of the premenstruum and culminating in toxaemia. It was therefore thought possible that the development of toxaemia might in such cases arise from failure of the corpus luteum and placenta to produce sufficient progesterone.

In the light of similarities between premenstrual syndrome and toxaemia, and the fact that treatment of the former with progesterone not only relieved the symptoms (Greene and Dalton, 1953) but also prevented the development of oedema, hypertension, and albuminuria in the premenstruum (Dalton, 1954, 1955), it was decided to carry out a trial, employing large doses of progesterone in patients disclosing early minor symptoms of toxaemia, in an attempt to arrest full development of that condition.

Methods and Material

This investigation was carried out in a maternity hospital and midwifery training centre with 71 beds. Here a clinic for mothers up to the 28th week of pregnancy is run by the midwives, who were asked to devote particular attention to those patients who, in the middle trimester, showed a deterioration in general health. Those complaining of nausea and/or vomiting, lethargy, irritability, depression, vertigo, fainting, and paraesthesia (generally between the 16th and the 28th weeks but sometimes earlier) were referred to me. After interviewing them, but without clinical examination, I recommended a test dose of progesterone. Patients responding to the test dose were subsequently treated with progesterone or ethisterone in a dosage individually determined. Those showing toxaemic or other signs after the 28th week were referred directly to the consultant, with whom any decision to admit such patients for routine toxaemic treatment rested.

Test Dose of Progesterone.—As at this stage there is no reliable biochemical test for detecting progesterone deficiency or potential toxaemic symptoms, a therapeutic test with progesterone was made. A controlled investigation into the value of this test injection is in progress at a London teaching hospital, where progesterone test injections and similar injections containing inert oil are being used. These results will be embodied in a subsequent paper. In the preliminary investigations a test dose was given for such toxaemic symptoms as occurred at any time before the 28th week. Initially 50 mg. of progesterone in oil was used, and if the symptoms were not relieved the test was later repeated, the dosage being doubled. It soon became apparent that better results were obtained with an initial dose of 100 mg., and this was subsequently adopted as standard. This test dose was injected deep into the buttock. If the symptoms were not relieved when the patient was seen two days later it was

assumed that they were unrelated to early toxaemia. If relief was obtained for one or two days, the symptoms were regarded as those which might later lead to toxaemia. For the purpose of this investigation toxaemia was defined as the presence, on one or more occasions, of blood pressure of 140/90 mm. Hg or over, together with oedema or albuminuria in a catheter specimen after the 28th week and before the onset of labour, provided that prior to the 28th week the blood pressure had been below 140/90 mm. Hg and there had been no albuminuria.

Progesterone-responsive Symptoms.—The symptoms responding to a test dose of progesterone are shown in Table I.

TABLE I.—*Symptoms Responding* (136 *Patients*)

	Patients	
	No.	%
Nausea and vomiting	103	75·7
Lethargy	107	78·7
Headache	71	52·2
Depression and irritability ..	49	36·0
Backache	48	35·4
Vertigo	39	28·7
Fainting	21	15·4
Paraesthesia	17	12·5

It was noted that 72.1% of patients with progesterone-responsive symptoms had complained of three or more unrelated symptoms; indeed, 51.5% admitted to four or more. The fact that these combinations of varied symptoms are all relieved by progesterone adds further support to the theory that such symptoms arise from deficiency of progesterone or progesterone-like substance.

Subsequent Treatment with Progesterone

Continued treatment with progesterone was limited to those patients responding favourably to the test injection. The aim was to give a dosage high enough to bring continuous and complete relief and low enough to avoid symptoms of overdosage, which manifests itself first as dysmenorrhoea-like pains resembling false labour. Euphoria is a sign that the dose is too high, and may be reduced. Progesterone in oil was used, and the injections were given either daily or on alternate days, according to the duration of relief obtained from the test dose. The initial dose was determined by the severity of symptoms, the degree of relief obtained from the test injection, and the presence of excessive weight gain. Thus a patient with four different symptoms and a weekly weight gain over the previous month of 1½ lb. (680 g.) was given 100 mg. of progesterone daily or on alternate days. If she remained symptom-free when seen a week later, the dose was reduced to 75 mg. daily or on alternate days, but if the symptoms recurred it was increased to 125 mg., 150 mg., or 200 mg. Another patient with few symptoms and a weight gain of 1 lb. (450 g.) weekly was given 25 mg. of progesterone, the dose being increased if and when necessary. When the patient remained symptom-free for two or three weeks the dose was gradually reduced, and if symptoms did not recur it was ultimately discontinued. If symptoms recurred treatment was immediately resumed.

Progesterone-responsive symptoms may occur in the early months of pregnancy. I have shown that in some cases increasing severity of the symptoms during the early weeks may end in abortion (Dalton, 1954). For this reason progesterone treatment was instituted during the early months in the presence of an increase in the severity of progesterone-responsive symptoms, or where there was a history of previous abortion or toxaemia. In many cases when progesterone treatment was given in the early months it was discontinued after the fourth or fifth month, but, where necessary, treatment was maintained throughout the entire pregnancy, as in the following case.

A dressmaker aged 31 had a history of two previous abortions at 12 weeks. L.M.P. May 8, 1955. At 6 weeks she complained of backache and lethargy; the Hogben test was negative. A test injection of 25 mg. of progesterone brought complete symptomatic relief and 25 mg. of progesterone was given on alternate days. At eight weeks the Hogben test was positive and a 200-mg. progesterone implant was given. At 10 weeks she reported a return of backache and lethargy which responded to test injections of 100 mg. of progesterone. Injections of 100 mg. were given twice weekly. At 12 weeks the injections were discontinued, but the following week she reported a recurrence of backache, lethargy, and nausea, and the dose of 100 mg. twice weekly was resumed. A break in the injections was tried at the 16th and the 20th week, but on each occasion the symptoms rapidly returned. At 22 weeks, as she complained of backache and lethargy on the third day after injection, 100 mg. of progesterone was given on alternate days. At 34 weeks lethargy, backache, and nausea recurred and slight oedema of her ring-finger was noted; the injections were increased to 100 mg. daily. At the 37th week she had a spontaneous delivery of twin boys weighing 4 lb. 1 oz. and 3 lb. 13 oz. (1,840 and 1,730 g.). Her blood pressure had remained in the range of 100–130/65–75 mm. Hg, and no albuminuria had been detected throughout the pregnancy.

If progesterone was discontinued in a patient nearing full term she was seen every two to four days, as alarming toxaemic signs can develop suddenly within a few days of the termination of progesterone therapy (Dalton, 1954, Case 8).

There is some evidence that progesterone therapy may cause post-maturity, but this was not found in this hospital series. Six treated patients (5.7%) of a total of 106 whose dates were accurate continued their pregnancy beyond 42 weeks and delivered babies over 5½ lb. (2.5 kg.), compared with 30 patients (9.5%) of 315 similar untreated patients delivered in the same hospital between October 1 and December 31, 1955. If progesterone-treated patients do go beyond term there appears to be no contraindication to medical or surgical induction.

Replacement of Progesterone with Ethisterone.—Ethisterone (anhydrohydroxyprogesterone, or ethinyltestosterone), an oral progestogen, is of some value in the treatment of selected cases, but its action is not always identical with that of progesterone. Stolte (quoted by Overbeek and de Visser, 1956) has shown that in rats ethisterone possesses two actions: a favourable progestational effect on the non-pregnant uterine mucosa, and an unfavourable effect on pregnant rats, causing abortions, which he suggested may be due to its androgenic properties. The effect of ethisterone in the premenstrual syndrome was found to be variable compared with progesterone (Greene and Dalton, 1953). Its use in the prophylaxis of toxaemia was therefore limited to those patients with mild progesterone-responsive symptoms, and with no excessive weight gain, history of previous abortion, or hirsutism. In all, 87 patients with progesterone-responsive symptoms were given a week's trial of 100 mg. of ethisterone daily. Of these, 52 (59.8%) reported symptomatic relief. As with progesterone, the dosage of ethisterone was determined on a symptomatic basis and a dosage ranging from 50 to 200 mg. daily was used. If the symptoms recurred late in pregnancy, indicating the need for a larger dose, progesterone was substituted.

Progesterone Implant.—The use of progesterone implants in non-pregnant women suffering from premenstrual syndrome has shown a wide variation in the duration of action. Implantation was used in two cases only in these hospital trials, 500 mg. of progesterone in the form of 100-mg. pellets being implanted into the fat of the abdominal wall at 30 and 32 weeks respectively. But within four weeks the symptoms recurred in both cases and it was necessary to resume progesterone injections. Both had normal full-term deliveries. It is therefore suggested that, though implants may be employed during the early months when small doses are required, their use during the later months should be confined to those refusing injections or in cases where daily injections are not convenient. It does not seem to be a useful method for routine treatment during the last trimester of pregnancy.

Other Adjuncts to Progesterone Therapy.—In the hospital trials no other method of prophylaxis was used—for instance, low-salt diet or rest. In private practice it has been found that if progesterone is temporarily discontinued

and toxaemic signs develop, these signs usually respond rapidly to resumption of progesterone. When oedema or excessive weight gain has occurred during cessation of progesterone, acetazolamide or mersalyl can be given with progesterone to produce a more rapid result.

Results of the Progesterone Trial

Between January, 1951, and September 30, 1956, there have been 7,156 deliveries at the maternity hospital. Figures earlier than January, 1951, cannot be included, as the hospital was then housed in different premises. Prior to the introduction of the experimental scheme in June, 1955, the quarterly incidence of toxaemia had varied between 6.2% and 11%, giving an average of 9% for some 5,307 deliveries. This 9% incidence of toxaemia is similar to that for local maternity hospitals. The first progesterone-treated patients were delivered in September, 1955, and in the third quarter of 1955 the incidence of toxaemia fell from 7.2% to 3.9%, with further declines in subsequent quarters to 2.5%, 1.9%, 1.0%, and 1.3% (see Chart). Prior to the introduction of the scheme there were 12 deliveries for every toxaemic patient, whereas after its introduction there were 47.6 deliveries for every toxaemic patient.

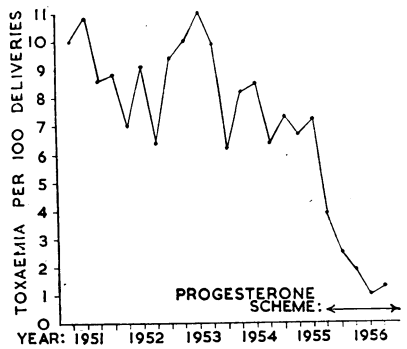

Chart showing quarterly incidence of toxaemia.

The 141 patients seen with symptoms between the 16th and the 28th week of pregnancy have been delivered. Of these, four were transferred to other hospitals and nine did not attend to report the effect of the test dose. Of these nine, two subsequently aborted and there was one maternal death, with stillbirth, from antepartum and post-partum haemorrhage and toxaemia. Twenty patients with symptoms not relieved by progesterone were delivered, of whom one developed toxaemia. Of 109 patients treated with progesterone, five developed toxaemia and there were two stillbirths (one hydrocephalic monster and one disproportion). Two of these five toxaemic patients were receiving 50 or 100 mg. of progesterone respectively on alternate days at the time of onset of toxaemic signs, and the remaining three had temporarily ceased taking ethisterone. It should be noted that all five cases, as soon as they developed toxaemia, came under the care of the consultants, and no more progesterone was administered. They were treated with bed rest, sedation, and low-salt diet, but in three of these five cases the blood pressure rose higher when progesterone or ethisterone was discontinued.

TABLE II.—*Weight Gain Before and After Progesterone* (13 *Cases*)

No.	Weight Gain in 4 Weeks Before Progesterone		Weight Gain in 4 Weeks After Progesterone	
	lb.	kg.	lb.	kg.
1	6½	2·9	4	1·8
2	8	3·6	5½	2·5
3	7	3·2	4½	2·0
4	7½	3·4	3½	1·6
5	6	2·7	5	2·3
6	7½	3·3	1¾	0·8
7	7½	3·4	5	2·3
8	6	2·7	4½	2·0
9	10	4·5	6	2·7
10	7	3·2	Lost 2	0·9
11	7	3·2	1½	0·7
12	7½	3·4	0	
13	8½	3·9	1½	0·7
Average	7·4	3·36	3·1	1·4

Decreased Weight Gain on Progesterone Therapy.—Hamlin (1952) has stressed the importance of excessive weight gain during the middle trimester as an early toxaemic sign. It is significant that patients with progesterone-responsive symptoms and an excessive gain in weight before the 28th week show a decrease in weight gain when the symptoms are controlled with progesterone. Among the 109 treated patients were 13 whose weight gain during the four weeks immediately before treatment was 6 lb. (2.7 kg.) or over. In every instance the weight gain during the first four weeks after the commencement of treatment was less than before treatment (Table II).

Limitations of Progesterone Therapy in Toxaemia

Progesterone therapy is essentially prophylactic and effective only if started during the early symptomatic stage and before the onset of signs. In treated patients, should toxaemic signs develop when progesterone is temporarily withheld (owing to failed attendance or improvement in symptoms), a return to progesterone usually effects a rapid amelioration of signs. On the other hand, should patients not under progesterone treatment develop toxaemic signs, even massive doses of up to 300 mg. of progesterone given intravenously usually prove ineffective and the toxaemia takes its uninterrupted course.

It may be argued that this method of treatment, dependent on symptoms alone, is unreliable, and that neurotic patients may receive progesterone therapy needlessly. However, with experience it was easy to distinguish between symptoms due to a specific cause—for example, headache after being involved in a road accident—and those due to pregnancy.

There appears to be a minority of patients who develop toxaemia although symptom-free during the middle trimester. In this series the incidence of toxaemia was reduced under the progesterone scheme from 9% to 2.1%, but in this 2.1% were included some patients who did not report any symptoms during the middle trimester. Again, in retrospective interviews with mothers who had previously suffered from toxaemia, 7% stated that they had remained symptom-free during pregnancy (Dalton, 1954). It is suggested that the development of toxaemia in this minority without a symptomatic stage may be due to a sudden catastrophe of the placental circulation—embolism, thrombosis, or concealed haemorrhage—which causes placental infarction and an abrupt reduction in placental output of progesterone. It seems that one is unable to prevent such fulminating cases of sudden onset with progesterone therapy.

Discussion

Considerable supporting evidence is available to demonstrate the importance of progesterone in the maintenance of pregnancy. Robson and Paterson (1937) have shown that convulsions, acute toxic conditions, and finally death can be produced experimentally in rabbits by depriving them of the luteal or gonadotrophic hormone during the latter part of pregnancy, and that these effects could be prevented by injections of gonadotrophic hormone or progesterone. Nelson *et al.* (1951) found that the high foetal mortality in rats fed on a diet deficient in vitamin B_6 could be avoided by the administration of progesterone and oestrone. Similarly, Nelson and Evans (1953) showed that rats bred on a protein-free diet have a 90–100% foetal mortality, which can be overcome by injections of progesterone and oestrone. Lyons (1943) has demonstrated that pregnancy can be maintained in rats oophorectomized and hypophysectomized after conception if progesterone and oestrone are artificially supplied. The work of Nelson, Lyons, and others has further demonstrated the importance of the ratio of progesterone to oestrone. The fact that animals receiving high doses of oestrone showed an increased foetal death rate suggests that this occurs when there is insufficient progesterone to balance the oestrin available.

It has long been recognized that toxaemia is frequently associated with beriberi, and in these cases both diseases are susceptible to the administration of vitamin B. Hamlin (1952), in Australia, has reduced the incidence of toxaemia by recognizing excessive weight gain as an early sign of toxaemia and by impressing on such patients the importance of lowering their weight by a high-protein, low-carbohydrate, and high-vitamin diet. The importance of the protein and vitamin in Hamlin's work, and the vitamin B in treatment of beriberi cases, is corroborated by the work of Nelson and his colleagues, who found that pregnancies in rats bred on a diet deficient in protein and vitamin B_6 could be maintained only with progesterone. I have already demonstrated the value of the administration of progesterone in the treatment of toxaemia in its early symptomatic stage.

From this it would appear that there is a close connexion between progesterone, protein, and vitamin B_6 in the maintenance of pregnancy. On the one hand, Hamlin has reduced the incidence of toxaemia with a high-protein and high-vitamin diet, and, on the other, the administration of progesterone achieves a like result, while Nelson and others have shown the close connexion between both treatments in their experiments on rats. If the role of progesterone is similar in humans and in rats it would suggest that protein and vitamin B_6 play an important part in the production of progesterone in the body. Should this be so, would it not explain the enigma of the success of vitamin B in the toxaemic beriberi cases and its failure when applied in the prophylaxis of toxaemia in Britain? Does it not also explain the success of Hamlin's slimming diet in Australia and its failure when applied here? The essential element for success in each instance is sufficient dietary protein, which in this country is lacking. The prohibitive cost of a high-protein diet for the average mother in Britain compels her to resort to a low-protein, low-carbohydrate diet for reducing her weight in pregnancy.

Conclusion

Toxaemia of pregnancy is one of the greatest dangers both to the pregnant mother and to the unborn child. Its aetiology is still unknown, and whatever light can be thrown on this subject may help towards eliminating this serious condition. Evidence is produced that lack of progesterone may be one of the important factors in the causation of the disease, and the prophylactic treatment with progesterone seems to have achieved worth-while results in its first year of experimental operation by reducing the incidence of toxaemia from 9% to 2.1%.

This preliminary study has certainly yielded interesting and encouraging data, and it is hoped that similar trials will be instituted elsewhere, for the subject obviously merits further study.

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LACTATION AND HEREDITY

BY

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In recent years investigations have shown that only about 50% of our babies are breast-fed for three months (Hughes, 1948; Dummer, 1949) and that the cause of failure is unknown in about one-half of the cases (Robinson, 1943; Royal College of Obstetricians and Gynaecologists, 1948). Although a wide variety of environmental factors are known to affect the duration of breast-feeding, yet basically the outcome will often depend upon the initial adequacy of the lactation—that is, the quantity and quality of the milk produced. Hytten (1954a, 1954b, 1954c, 1954d, 1954e) has pointed out that this may be genetically determined. We have found only four papers which make any attempt to assess the effect of heredity upon human lactation; their results, together with our own, are summarized in Table I.

TABLE I.—*Relation Between Mother's and Daughter's Breast-feeding Performance: Comparison Between Published and Present Series*

	Mother a "Good Nurse*"		Mother Not a "Good Nurse"	
	No.	Proportion with Daughters who are "Good Nurses"	No.	Proportion with Daughters who are "Good Nurses"
Bunge (1900)	237	53%	147	1%
Winternitz (1922) ..	115	61%	15	73%
Robinson (1939) ..	81	76%	19	53%
Pfändler (1949)	217	83%	118	49%
Present series	397	60%	63	43%

* In each series the relationship in question is between the mother and one specified daughter (the propositus). Widely differing criteria of a "good nurse" have been used (see text).

Bunge accepted a woman as a good nurse only if *all* her children (with a few specified exceptions) had been fully breast-fed for nine months, but Winternitz was less rigorous and used only three months' breast-feeding of one specified daughter as a criterion. Neither appeared to recognize the cardinal difficulty of distinguishing between environmental and hereditary effects. On the other hand, Robinson and Pfändler both concluded that the association they demonstrated was the result of environmental factors, though Pfändler believed also in a genetic one. We have tried to throw further light on the problem by investigating the capabilities of two generations of women and also by means of a twin study.

Present Investigation

The investigation included 943 women who first attended an antenatal clinic (A.N.C.) in Edmonton between April, 1952, and June, 1953. It will be convenient to refer to these women as the "subjects." Whenever the word "mother" is used it will refer to the subject's mother; the mother-daughter relationship is that between the subject's mother and the subject. The "current" infant is the one born to the subject after the pregnancy for which she attended the A.N.C.

Omissions.—As a criterion of successful breast-feeding applicable to the current infant we chose the maintenance of uncomplemented breast-feeding of a single normal infant for eight weeks. The reason why we chose this period was