An Investigation of Cases of Recurrent Abortion and their Treatment with Progesterone

BY

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It is recognized that the preparation of the uterine endometrium and the process of implantation of the fertilized ovum are initially associated with the persistence of the corpus luteum of pregnancy. Abortion or absorption of foetûs can be induced in the experimental animal by the removal of the corpus luteum, but in the human it has been shown that pregnancy can continue to term after the removal of the corpus luteum in early pregnancy.[1] It has, therefore, been suggested that, in man, some other structure takes over the function of the corpus luteum, for pregnandiol, an end-product of progesterone metabolism, has been recovered from the urine after the corpus luteum has been removed. The placenta probably functions in this way,[1] and it may, therefore, be supposed that the corpus luteum itself is responsible for the embedding of the ovum and its nutrition in the early phase of pregnancy, but that later this role is, or can be, taken over by the functioning placenta. An active corpus luteum is dependent, in its turn, on the supply of an anterior pituitary hormone, and there is evidence of overfunction of the anterior pituitary in early pregnancy.

Evidently, failure of a pregnancy to continue to term would result from a deficiency of either or both of these hormones, but before it is possible to draw any conclusions from their amount in cases of recurrent abortion, it is obviously necessary to know the quantities secreted in normal pregnancy. It is not feasible at present to estimate the concentration of these hormones in the blood, and accordingly the concentration in the urine of the hormones themselves or their metabolic products has been

studied as a measure of their production. The hypophyseal hormone can only be determined biologically, and although the substance estimated during the earliest phase of pregnancy may be a true hypophyseal hormone, it seems likely that the chorionic epithelium elaborates a somewhat similar hormone. Progesterone, the corpus luteum hormone, is not excreted as such, but pregnandiol, which is probably its main breakdown product, can be recovered chemically from the urine, in which it appears chiefly as a diglucuronide.

Once knowledge of hormonal behaviour in normal pregnancy has been obtained, it becomes possible to inquire how far failure of the hormone control is responsible for abortion, and to study intelligently the possibility of preventing abortion by hormone therapy. Obviously, information on these points can best be obtained from a series of cases in which there is a reasonable expectation that pregnancy will, if untreated, end in abortion. Now the number of women with a history of one previous abortion is much greater than the number with two abortions, and as the number of successive abortions increases, the number of possible cases progressively decreases. It is, therefore, important to know what number of successive abortions may be taken as indicating the existence of some intrinsic defect which is preventing a pregnancy at term. Malpas[2] suggests 3 abortions as a minimum, showing that by the laws of probability it is highly unlikely that a sequence so long would be due to accidental causes of abortion. The figures given by Malpas strikingly support his view. There is, however, the possibility that a hormonal defect may occasionally be non-recurrent, and if such a defect appeared in one pregnancy but not in a subsequent one, it would be one of the accidental causes of Malpas. It is impossible, in fact, to say that hormonal deficiency as a cause of abortion is limited to those 1 per cent of pregnancies which fulfil Malpas's conditions for inclusion in the number of cases incapable of continuing pregnant to term.

For experimental purposes, however, it is obviously unfair to include in the series women with a history of only a single abortion, for in such cases the probability is high that the previous abortion was accidental. Ideally, the criterion of Malpas should be taken, and only those women included who have had a sequence of 3 abortions. In practice, we have been unable adhere to this ideal, and have investigated cases in which women have had two or more successive abortions, though admittedly, on the basis of Malpas's calculations, this does

increase the difficulty of interpreting the results of treatment. We suggest, however, that Malpas's estimate of the likelihood of recurrent abortion is rather low, and that his estimate of the likelihood of a successful pregnancy following a sequence of two abortions is consequently rather high.

Our Table I is abstracted from Malpas's Tables I and II, and gives the results of calculations which show a close correlation with the data on frequency of abortion collected by Whitehouse. Malpas suggests that the figures for the expected percentage of abortions, calculated on the assumption that a recurrent cause is operating in 1 out of 18 cases of abortion, correlate very well with the observations of Whitehouse. He points out, quite rightly, that close correlation cannot be expected in the cases of more than 3 successive abortions, since in practice one has to reckon with avoidance of pregnancy after a series of abortions. It seems to us, however, that the correlation between the calculated and the observed figures is, for women with up to 3 abortions, just as good if one assumes a recurrent cause in 2 out of 18 cases, and with this assumption the chances of a successful pregnancy following 3, or even 2, abortions are markedly reduced. Probably the truth lies somewhere between these extremes, and we are justified in believing that after 2 successive abortions the probability of abortion in a third pregnancy is about 50 per cent, that after 3 abortions the probability of abortion in the fourth pregnancy is about 80 per cent, and that the probability rises to over 90 per cent after

TABLE I.

No. of previous successive abortions.	Percentage chance of successive pregnancies.		No. of abortions per 100 women in successive pregnancies.		
			Expected		Observed*
	(*a*)	(*b*)	(*a*)	(*b*)	
0	82.00	82.00	18.00	18.00	18.0
1	78.40	74.70	3.89	4.56	4.3
2	62.00	47.00	1.48	2.41	2.1
3	27.00	14.60	1.08	2.06	0.7
4	6.00	3.00	1.01	2.01	0.6

(*a*) Assuming 1 abortion in 18 to be due to a recurrent cause.
(*b*) Assuming 2 abortions in 18 to be due to a recurrent cause.

* *From data given by Sir Beckwith Whitehouse.*

a sequence of 4 abortions. Thus, in a series of cases with at least 2 successive abortions, but including a number with 3, the expectation of abortion in the next pregnancy is about 65 per cent. This reduced expectation of abortion as compared with that in a series of cases with a succession of at least 3 abortions is, however, compensated for by the much greater number of cases available.

Methods of Investigation.

At first we treated empirically women with a sequence of two or more abortions, giving progesterone in small doses throughout the pregnancy and attempting to evaluate the results on a semi-statistical basis. Soon, however, we realized the practical impossibility of gauging the proper dose of progesterone without some knowledge of the amount normally produced and metabolized. Further, it seemed possible that estimations of the actual hormone production in the cases studied might give information as to which in fact were producing abnormally low amounts and which, therefore, might be expected to benefit from administration of the hormone. We therefore estimated the excretion of the gonadotropic hormone and of pregnandiol diglucuronide (representing progesterone) at short intervals during normal pregnancies and also in cases of recurrent abortion. In the latter group of cases, of course, the estimations were begun before treatment. An estimate of oestrogenic hormone excretion was not made. All estimations were made on 24-hour collections of urine, for the completeness and accuracy of which, however, we had to depend entirely on our patients, most of whom were living at home throughout the period of observation. It is possible that some irregularities in our figures may be due to collection errors. For the same reason, namely, that our subjects were out-patients, we were unable to make the estimations either as frequently or as regularly as we should have liked.

Pregnandiol was determined by the method of Venning,[3] which was found to work well, and does not need any description here. It should perhaps be mentioned that since this method depends upon the actual isolation of the pregnandiol derivative, the results are really minimal quantities present, and in particular, a negative result merely means that the amount present, if any, was too small to be isolated.

Since various methods exist for the estimation of the gonado-

tropic hormone, it is desirable that the one we used should be briefly described. The gonadotropic hormone was extracted from the urine by the alcohol precipitation method. An equal volume of alcohol was added to 150 cubic centimetres of the urine under test, and the mixture was centrifuged. The supernatant fluid was poured into 600 cubic centimetres of alcohol. (The alcohol used in these procedures was 95 per cent ethyl alcohol.) An hour later the liquid was centrifuged, and the precipitate, which contained the hormone, was suspended in 100 cubic centimetres of ether, separated again by centrifuging, and dried in a desiccator. The dry powder was dissolved in 60 cubic centimetres of distilled water for testing, and 10 cubic centimetres of this solution were diluted with 20 cubic centimetres of distilled water for a second test. The first solution, of which 3 cubic centimetres were equivalent to 7.5 cubic centimetres of urine, is referred to as "dilution 1/1", and the diluted solution, of which 3 cubic centimetres were equivalent to 2.5 cubic centimetres of urine, as "dilution 1/3". For testing each dilution, 10 immature female rats, weighing between 38 and 45 grammes, were used. Each rat received subcutaneously 1 cubic centimetre of the appropriate test solution daily for 3 days The rats were killed on the fifth day, and the ovaries were immediately dissected from their capsules and rapidly weighed on a torsion balance. For determining the increase in weight due to the hormone, we took 10 milligrams as the average weight of the ovaries of rats of the size and strain (Wistar) used, a figure which resulted from the examination of 40 control animals. A series of experiments with graded doses of a single preparation of gonadotropic hormone showed that for increases of ovarian weight up to 35 milligrams there was a roughly linear relation between amount of hormone and increase in ovarian weight. Beyond that, however, the response to increased dosage rapidly decreased. For assay purposes, therefore, we accepted the results using "dilution 1/1" only when the average increase in ovarian weight was less than 35 milligrams: when it exceeded that figure the results from the series with "dilution 1/3" were used. The unit was taken as the amount of gonadotropic hormone (i.e. the volume of urine) required to produce a 5 milligram increase in ovarian weight.

Both for pregnandiol and gonadotropic hormone, the daily output was calculated rather than the concentration per litre of urine.

Results and Discussion.

Excretion of Gonadotropic Hormone.

The quantitative excretion of gonadotropic hormone throughout pregnancy has been determined by several workers, and their results agree in indicating that there is a peak in the amount of hormone excreted daily during the early months of gestation. Thus Browne and Venning[4] found that the concentration of the hormone in the urine rises rapidly between the fortieth and the fiftieth day after the beginning of the last menstrual period, and reaches a maximum between the fiftieth and sixtieth days; this maximum is maintained for only a few days and is followed by a rapid fall in the concentration to a low and constant level which is maintained until parturition. The assays of the gonadotropic hormone excretion in our normal cases agree generally with these findings (Fig. 1) although we have not been able to determine the excretion of the hormone before the fifty-fifth day of pregnancy. We find, however, a tendency for the gonadotropic hormone excretion to increase somewhat in the later months of pregnancy, and thus to run parallel with the excretion of pregnandiol.

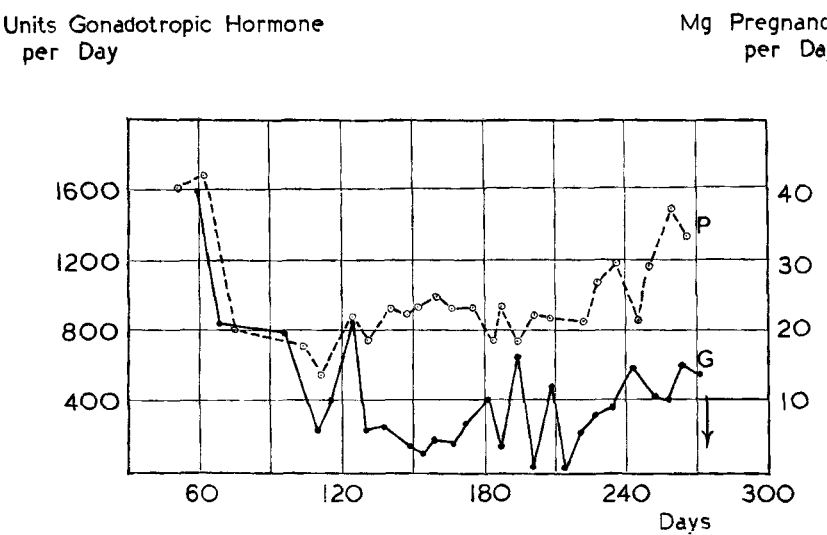

Fig. 1.

Excretion of gonadotropic hormone and pregnandiol in a normal pregnancy.

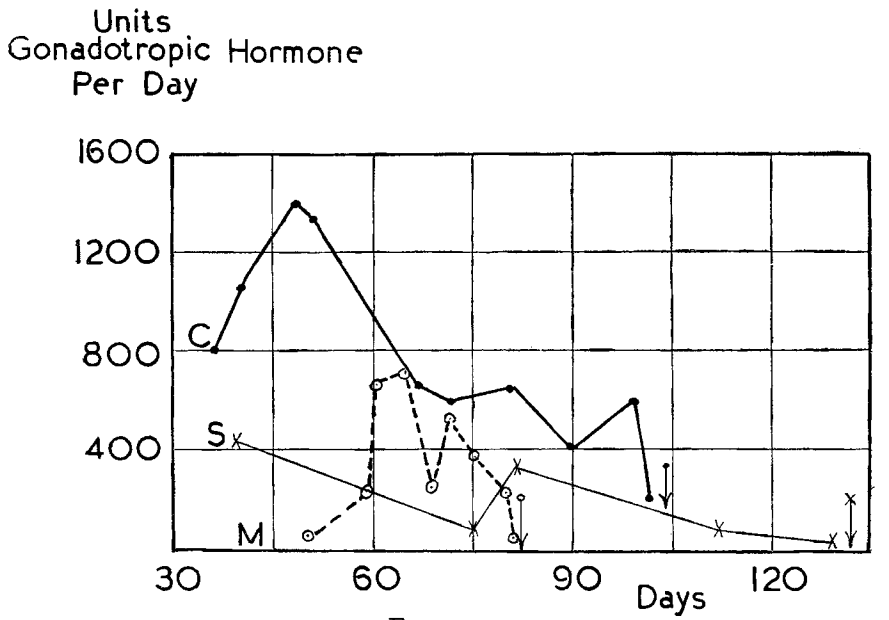

FIG. 2A.

Excretion of gonadotropic hormone in three cases which aborted while receiving progesterone treatment. Treatment was begun on forty-third day (S), fifty-eighth day (C), and sixty-fourth day (M).

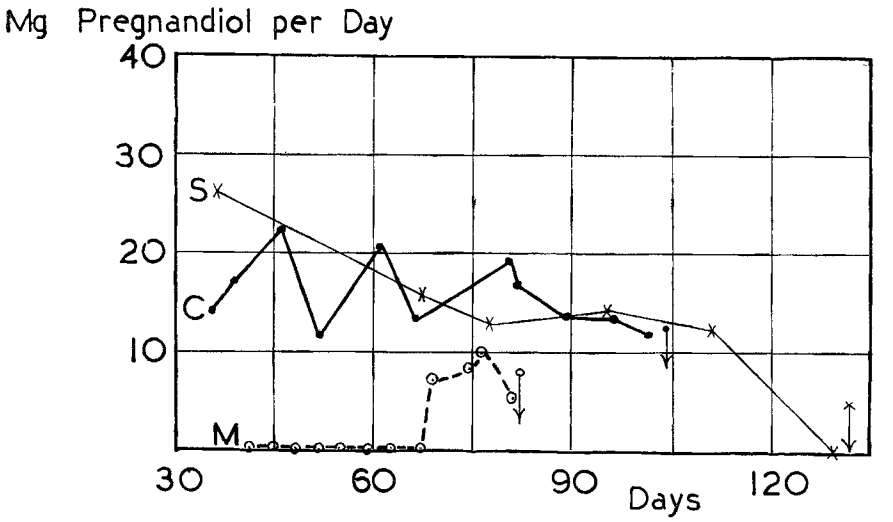

FIG. 2B.

Excretion of pregnandiol in the same three cases.

A study of the women who aborted shows that there was a low excretion of gonadotropic hormone at the time when the excretion should be high, and that the progesterone therapy was not appreciably affecting it. Figure 2A shows the excretion of the gonadotropic hormone in 3 women who aborted while under treatment. Two of them, *C* and *M*, show a peak in the excretion at about the expected time, but in both, and especially in *M*, the magnitude was much less than in the normal cases. In the third case shown, *S*, the peak may have been missed owing to the infrequency of the assays, a regrettable circumstance which was beyond our control. In a subsequent preg-

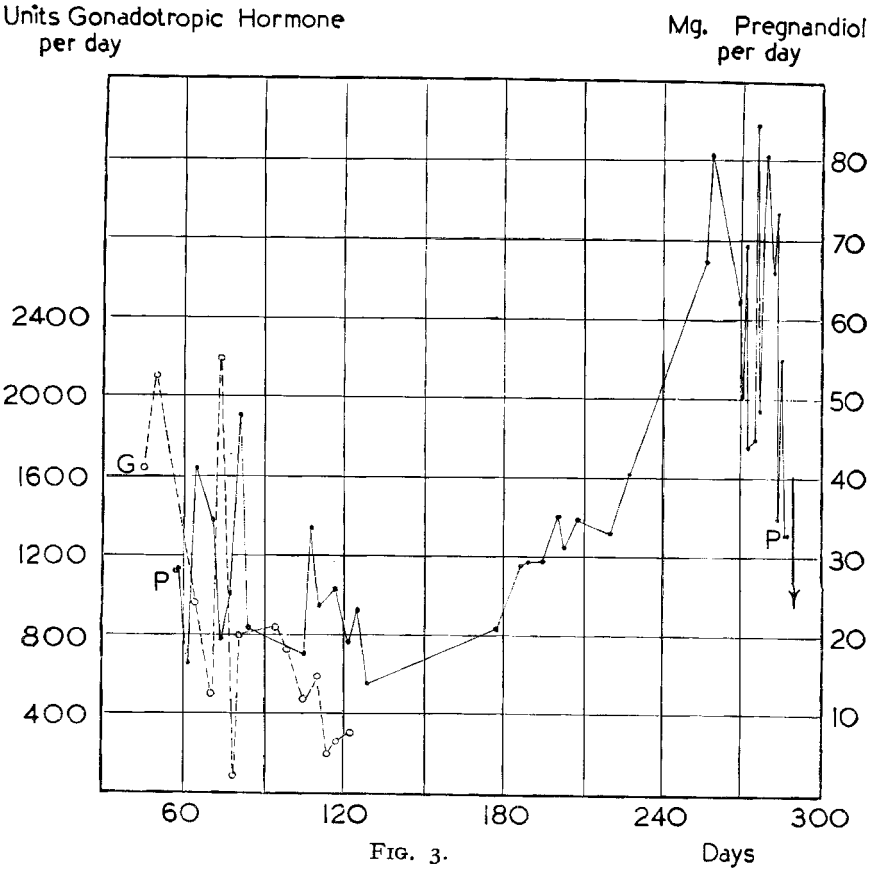

FIG. 3.

Excretion of gonadotropic hormone and pregnandiol in a successful case of progesterone therapy. This case had aborted on a previous occasion, which is shown in FIG. 2C. Therapy was begun on the forty-fourth day.

nancy, and with increased doses of progesterone, the pregnancy of one of these women, *C*, continued to term, and on this occasion the high excretion of gonadotropic hormone duly occurred between the sixtieth and seventieth days of the pregnancy. (Fig. 3.) On the other hand, successful results were obtained with progesterone therapy in one case (Fig 4) which did not show the normal early high excretion of hormone. In this case assays were made with sufficient frequency to exclude the possibility of the normal increase having escaped observation; all that could have occurred was a small and fleeting increase.

Whether or not the early high excretion occurred, the women in whom, under progesterone therapy, the pregnancy successfully continued to term, showed a steady, continued excretion of gonadotropic hormone, whereas those who aborted showed a steady fall, often to zero.

Excretion of Pregnandiol.

In a normal pregnancy our results (Fig. 1) show the pregnandiol excretion to be relatively high between the sixtieth and eightieth days of pregnancy, i.e. at the time when the excretion of gonadotropic hormone is also high. Thereafter, along with the gonadotropic hormone, it falls to a relatively low level at which it remains until about the two hundred and fortieth day, when it again rises rather sharply. This second high level is maintained until immediately before parturition. After parturition pregnandiol appears in the urine for a day or two, and then only in decreased amounts. These results agree only partly with those of Browne, Henry and Venning,[5] who found a daily excretion of 4 to 10 milligrams of pregnandiol up to the sixtieth day of pregnancy, and increase dating from the eightieth to the hundredth day, reaching 40 milligrams per day at the hundred and fiftieth day, and continuing to a peak in the eighth month, when two women showed an excretion of 80 and 70 milligrams respectively. These authors point out, however, that they cannot from their results determine the limits of normal variability. Our results differ from theirs chiefly in the high early excretion, an excretion which roughly parallels the high excretion of gonadotropic hormone at the same time, and which occurs too regularly in our series to be merely fortuitous.

As to the treated cases of recurrent abortion, the essential for success seems to be the maintenance, during the period from the sixtieth day to the two hundredth day of gestation, of a pregnandiol excretion about the normal level (Figs. 3 and 4; con-

trast Fig. 2B). There may or may not be a greatly increased excretion about the sixtieth day, depending, apparently, upon whether or not the gonadotropic hormone excretion is high at that time (Fig. 2B). There may even be some rise in the pregnandiol excretion during treatment followed by abortion, if the subsequent fall reaches too low a level. Irrespective of the height of the excretion-rate about the sixtieth day of pregnancy, in all successful cases the women show a maintained excretion during the middle months of about 20 milligrams per day of pregnandiol. The general tendency in all cases, successful or otherwise, was for the pregnandiol excretion to parallel the gonadotropic hormone excretion.

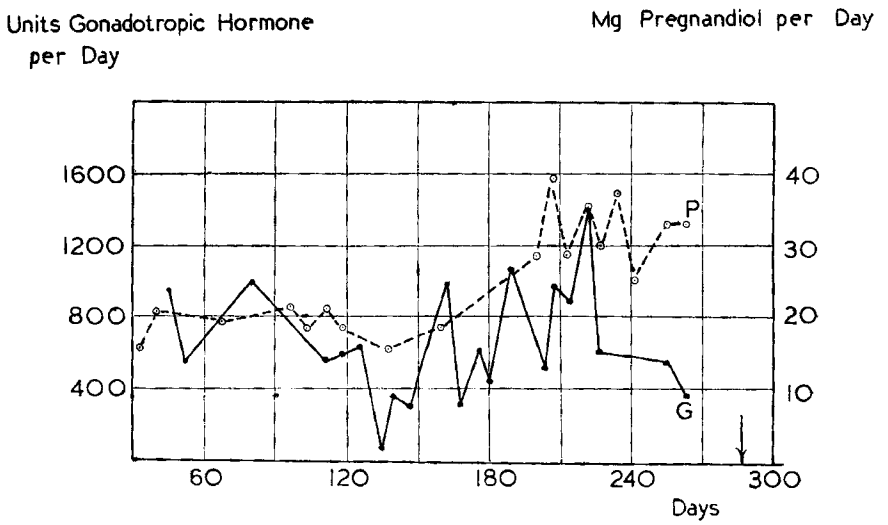

FIG. 4.

A successful case of progesterone therapy in which the normal high excretion of hormone at the third month of gestation did not occur. Therapy was begun on the fifty-first day.

Discussion.

The hypothesis to which these results have led us is briefly as follows. The high production of gonadotropic hormone at about the fiftieth to the sixtieth day of pregnancy, possibly of trophoblastic origin, causes intensive stimulation of the corpus luteum, possibly by the mediation of oestradiol, and, therefore, a high production of progesterone. This is responsible for effective placental growth. Given this stimulus, the placenta is able, by the eightieth or ninetieth day, to form a sufficient supply

of progesterone to maintain the pregnancy, and the corpus luteum can decrease in activity without danger of abortion. Though not essential to the hypothesis, there is evidence to suggest that the continued production of gonadotropic hormone also becomes a function of the placenta. The idea of production of progesterone by the placenta is supported by the work of, for example, Jones and Weil,[3] who found that it was possible to maintain pregnancy and to extract pregnandiol from the urine after the corpus luteum had been removed at the third month of pregnancy. We regard it as probable that the placental formation of progesterone is largely, though not necessarily entirely, independent of the gonadotropic hormone. Otherwise it becomes difficult to explain the increased pregnandiol excretion towards the end of pregnancy at a time when Venning and Browne[4] and others, as well as ourselves, have not observed any very marked corresponding increase in the excretion of gonadotropic hormone.

The sequence of events we visualize is: the pituitary gland through its secretion of gonadotropic hormone stimulates the ovary and so the production of progesterone; this in turn stimulates placental production of gonadotropic hormone which reacts on the ovary; the corpus luteum ultimately stimulates placental activity to the point at which it also begins to secrete progesterone; thereafter the corpus luteum diminishes in activity.

On this hypothesis the danger period in pregnancy is during the time when placental activity is developing and the corpus luteum activity is retrogressing. It is well known, in fact, that this danger period is towards the ninetieth day of pregnancy, just the time when the early high excretion of hormones is settling down to a steady, relatively low rate.

The hypothesis adequately explains:

(*a*) The fact that in hypophysectomized animals pregnancy can be maintained by administration of gonadotropic hormone [6] or oestradiol,[7] or progesterone.[8]

(*b*) The maintenance of pregnancy when the corpus luteum is removed at a time when the placenta is producing, or is on the verge of producing, progesterone.

(*c*) The common occurrence of abortion in the third month of pregnancy.

(*d*) The observed fluctuations in the excretion of gonadotropic hormone and pregnandiol.

Although we suggested the placenta as the probable site of progesterone and gonadotropic hormone formation during the

later months of pregnancy, it is possible that other glands, for instance the adrenals, may be concerned. That the placenta is at least the main site is, however, suggested by the rapid disappearance of pregnandiol and gonadotropic hormone from the urine after parturition.

The Clinical Results.

In Table II we have summarized the history with respect to previous abortions and the results of treatment in 20 patients. No case in which women had fewer than 2 successive abortions is included, and prior to progesterone treatment, 65 pregnancies had, altogether, resulted in only 10 live births. In none of these patients could any cause be found for the recurrent abortions—other, that is, than the hormone deficiency revealed in many of them during our investigation. Of the 22 pregnancies during which progesterone was given, there were, on the other

TABLE II.

Case No.	No. of previous abortions.	Mg. of progesterone administered.	Result.
1.	3	68	Success
2.	4	70	Success
3.	3	73	Success
4.	2 *a*	45	Failure
	3 *b*	410	Success
5.	2	15	Failure
6.	2	120	Success
7.	3 *a*	3	Failure
	4 *b*	33	Failure
8.	3	85	Success*
9.	2	66	Success
10.	3	80	Success
11.	3	23	Success†
12.	2	190	Success
13.	3	10	Failure
14.	4	50	Failure
15.	2	12	Failure
16.	2	55	Success
17.	2	43	Success
18.	3	74	Success
19.	2	49	Success
20.	4	8	Failure

* Z.A. weak, positive at beginning of pregnancy.

† Child lived only one day.

hand, only 8 which ended in abortion, whereas 14 resulted in a living child at term.

Superficially this appears a striking result in favour of progesterone therapy, but it is necessary to examine it a little critically. According to the calculations of Malpas the chance of a full-time pregnancy following a sequence of 2 abortions is 62 per cent, following 3 successive abortions 27 per cent, and following 4 successive abortions 6 per cent. If it be accepted that our suggestion as to the incidence of recurrent abortion agrees better with the data of Whitehouse, these figures are reduced to 47 per cent, 14.6 per cent, and 3 per cent respectively. The 22 women receiving progesterone treatment in our series had all a previous history of at least 2 abortions, and the percentage of live births was 64, a figure not significantly above the 62 of Malpas, though definitely above the 47 per cent which we have suggested. However, 13 of the women in our cases had 3 or more successive abortions prior to the treated pregnancy and, if this be taken into account, the expectation of a full-time pregnancy becomes only 40 per cent on Malpas's calculations, or 27 per cent on our own. Obviously the observed 64 per cent of successes in the women receiving progesterone is definitely greater than the percentage to be expected without treatment. The same conclusion is reached if one considers separately those women with a previous sequence of only 2 abortions and those with a sequence of 3 or more. In the former group (9) there were six successes and three failures, almost exactly the figures to be expected on the calculations of Malpas. In the second group (13), however, there were eight successes, whereas only three were to be expected without specific therapy.

The results we have obtained are in full agreement with those reported by other workers. Thus in a series of cases given by Bishop,[9] 8 with a history of 2 or more successive abortions the women were treated with progesterone to completion; of these 6 resulted in delivery at term, whereas the expected number was not more than 4. Kane[10] reported 40 pregnancies treated with progesterone, of which 36 went to term; from the previous history of these cases the expected number of pregnancies at term can be calculated as 26. In Elden's[11] series of 8 cases, 6 were successful. Malpas[2] also reports observations of his own and refers to others, concluding that "progesterone therapy probably represents the most effective method we possess of treating some cases of threatened abortion". He believes,

however, and we agree, that more chemical data are needed to determine the scope of the treatment.

Even as they stand, we are of the opinion that our figures definitely support the use of progesterone therapy in cases of recurrent abortion, and it should be noted that we have included in the series as "failures" cases in which treatment was only begun when abortion was actually threatening. We believe that when progesterone is given early enough, the proportion of successes can be still further increased. The majority of our failures occurred early in the investigation, when we were using very small doses of progesterone—for example, 1 milligram twice weekly—in conformity with current practice. More recently, in the light of our measurements of pregnandiol excretion, we have increased the dose, first to 3 milligrams and later to 5 milligrams, or even 10 milligrams and 20 milligrams twice weekly, with intensive therapy in cases of threatened abortion. Even these doses are surprisingly small to be effective, and there is almost an air of the miraculous about the results reported by various observers on doses which are almost infinitesimal in comparison with the amount of progesterone produced in normal pregnancy.

The mode of action of progesterone is obscure, but there is no doubt that its presence in adequate amounts is necessary for the maintenance of pregnancy. A study of the hormone excretion in cases of recurrent abortion at once indicates that in them there is a decreased output of the hormones during the early weeks of pregnancy as compared with normal cases. It has been shown,[12] too, that if progesterone is present in excessive amounts at term, parturition does not occur, and pregnancy is prolonged. The inference is that in cases of recurrent abortion, either the pituitary stimulus to the corpus luteum is weak, thus causing imperfect placental development, or the response of the corpus luteum to anterior pituitary stimulation is weak, thus giving the same result. The simplest explanation of the action of progesterone therapy in preventing abortion would be that it provides, by replacement, an adequate supply of an essential hormone until, whether by its stimulant action on the placenta or by an independent placental development, the deficiency is made good from natural sources. When one considers the smallness of the doses which appear to be effective in relation to the normal daily output of pregnandiol, it seems that this simple explanation of replacement therapy can only be correct if the margin between an adequate and an inadequate proges-

terone production is extraordinarily narrow. This, however, is not entirely impossible, though it seems unlikely in view of the case reported by Jones and Weil in which pregnandiol could not be detected in the urine for nearly a week after removal of the corpus luteum and yet the pregnancy continued to term. There is this consideration, of course, that during the critical period the patient in this case was, presumably, resting in bed after an abdominal operation.

It may well be, and indeed it is suggested by many facts, that while a temporary deficiency of progesterone does not in itself necessarily lead to abortion, it does make abortion an almost inevitable consequence of slight trauma or strain which would otherwise be without effect. If such is the case, the possibility arises that some accidental abortions may be potentiated by a temporary deficiency of progesterone due to some non-recurrent cause.

The administration of progesterone in relatively small amounts may be sufficient to maintain, or even stimulate, placental function over the critical period when the corpus luteum secretion decreases and the placenta is becoming a secretory organ. A study of the hormone excretion in normal pregnancy has suggested that this critical period is round the ninetieth day of gestation, and this is recognized as a common period for abortion to occur. In recurrent abortion, however, the critical period may be much earlier, as the hormone excretion may be at a sub-normal level at a very early stage.

Although an injection of a few milligrams of progesterone represents only part of a normal day's production as measured by the pregnandiol excretion, it gives, for a short time, an abnormally high concentration of the hormone in the blood. It is possible that this high concentration, repeated at intervals though not lasting long on each occasion, may provide sufficient extra stimulus to the developing placenta, and so enable it to take over its proper work of hormone production.

Neither of these explanations is entirely satisfactory, but on the evidence at present available we are unable to suggest one that is. The two are not mutually exclusive, and though we ourselves incline to the first as a working hypothesis, we recognize that both may contain some element of the truth but that, on the other hand, both may be wrong. Either, it may be noted incidentally, leads to the conclusion that progesterone therapy throughout pregnancy is usually unnecessary, and that most cases of recurrent abortion should be successfully treated by

administration of progesterone until the end of the fourth month of gestation. If further work should show this not to be the case, then both explanations fall to the ground.

ACKNOWLEDGMENTS.

We have to thank Messrs. Organon Ltd. for the progesterone used in this work, and the Medical Research Council for a grant which provided us with technical assistance and defrayed the cost of materials. Our thanks are also due to various colleagues who have placed cases at our disposal, and to Professor F. A. E. Crew for facilities in the Institute of Animal Genetics. We wish also to acknowledge the conscientious work of our technical assistants, Mr. Rae, Miss Wilson, and Miss Sanders.

REFERENCES.

1. Jones, W. H., and P. G. Weil. *Journ. Amer. Med. Assoc.*, 1938, cxi, 519.
2. Malpas, P. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1938, xlv, 932.
3. Venning, E. M. *Journ. Biol. Chem.*, 1937, cxix, 437.
4. Browne, J. S. L., and E. M. Venning. *Lancet*, 1936, ccxxxi, 1507.
5. Browne, J. S. L., J. S. Henry, and E. M. Venning. *Journ. Clin. Invest.*, 1937, xvi, 678.
6. Robson, J. M. *Journ. Physiol.*, 1937, xc, 145.
7. Robson, J. M. *Journ. Physiol.*, 1939, xcv, 83.
8. Robson, J. M. *Journ. Physiol.*, 1936, lxxxvi, 415.
9. Bishop, P. M. F. *Guy's Hosp. Reports*, 1937, lxxxvii, 366.
10. Kane, H. *Amer. Journ. Obstet. and Gynecol.*, 1936, xxxii, 110.
11. Elden, C. A. *Amer. Journ. Obstet. and Gynecol.*, 1938, xxxv, 648.
12. Snyder, —. *Bull. Johns Hopkins Hosp.*, 1934, liv, 1.

Discussion on Dr. Macgregor's paper at the Eleventh British Congress of Obstetrics and Gynaecology (April 1939).

Dr. BETHEL SOLOMONS asked the following questions:—

(1) Was the ovum examined for degeneration in any of the cases in which abortion had occurred?

(2) Were other treatments, such as wheat germ oil, or rest, used?

(3) Was the male examined for faulty spermatogenesis?

He had had several cases of habitual abortion due to the last cause. He said that the cost of a treatment as outlined by Dr. MacGregor would be nearly prohibitive, and suggested that this disadvantage could be removed if the firms making hormonic preparations could induce veterinary surgeons to make more use of them in their work. The greater the amount prescribed, the cheaper would be the cost.

This was the kind of paper which was an example to writers for future congresses.