physical disease: in no case referred for psychological reasons was the mental factor regarded as strong enough for interruption of the pregnancy.

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Before the war the Department of Scientific and Industrial Research produced a series of twelve leaflets, "Methods for the Detection of Toxic Gases in Industry." Leaflet No. 7, "Carbon Monoxide," has just been completely revised and now describes a new, simpler, and more accurate method of detection developed during the war at the Royal Aircraft Establishment. Dangerous concentration of carbon monoxide may occur in many industries, particularly steelworks, foundries, gas works, coke oven plant, and wherever gas producers and water gas plant are used. It is most dangerous when formed unknowingly, as by the improper use of geysers, boilers, braziers; in mine explosions ("after-damp"); in the smoke from fires; and in the exhaust gases from internal combustion engines. In the new test a sample of air is drawn through an indicator tube which is stained by the carbon monoxide. The length of the stain gives the concentration present in the air. Complete instructions for carrying out the test are given in the leaflet (H.M.S.O. Price 6d., 15 cents U.S.A., by post 7d.).

HABITUAL ABORTION

PROPHYLACTIC VALUE OF PROGESTERONE PELLET IMPLANTATION

BY

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For the purpose of this study "habitual abortion" is defined as "idiopathic" abortion before the end of the fifth month of pregnancy, occurring on two or more consecutive occasions immediately preceding the pregnancy, in which pellet implantation has been used. Abortion is regarded as "idiopathic" if no recognized organic cause has been found. "Primary" habitual abortion refers to the condition in which all previous pregnancies have resulted in abortion. "Secondary" habitual abortion indicates that one or more previous pregnancies have proceeded beyond the 28th week.

Material

The present series consists of 45 patients who have received an implant of six 25-mg. pellets of progesterone during the pregnancy under consideration. The implantation was carried out according to the technique described elsewhere (Bishop, 1949).^{*} No other treatment or precautionary regime was prescribed. These 45 cases represent all the patients with a history of habitual abortion treated by this method at the Chelsea Hospital for Women since 1947. It has been possible to obtain direct information concerning the outcome of the treated pregnancy in each of these cases.

Of these patients, 33 fall into the group of "primary" habitual abortion and 12 into the group of "secondary" habitual abortion.

Implantation was performed as early as possible—that is, as soon as the patient was referred to us for treatment. In most cases this was before the tenth week of pregnancy.

Results

TABLE I.—Results

No. of Successive Abortions Immediately Preceding the Treated Pregnancy	No. of Patients	Outcome of Treated Pregnancy		Percentage Successful Results
		Success	Failure	
A. Primary Habitual Abortion				
2	20	18	2	90
3	8	7	1	88
4 or more	5	3	2	60
B. Secondary Habitual Abortion				
2	8	6	2	} 100
3	1	1	0	
4 or more	3	3	0	
C. Primary and Secondary Habitual Abortion Combined				
2	28	24	4	86
3	9	8	1	89
4 or more	8	6	2	75

^{*}It should be emphasized that progesterone pellets, unlike other compounds suitable for implantation, tend to extrude unless implanted deeply: in this series the pellets were implanted beneath the deep fascia of the thigh.

The case recorded as a failure in the primary habitual abortion group, in which there had been three previous abortions, was that of a patient who started to bleed on her way home from hospital after the implantation, and the abortion was completed the following day (Table I). There would therefore have been no time for the progesterone to have any effect in this case. Of the two failures in the group having had four or more abortions one had had five previous abortions and the other seven.

A successful result was defined as one in which the pregnancy proceeded to 28 weeks. In fact, 26 of the 28 patients who were "successfully" treated for primary habitual abortion had live babies. In one of the two cases in which the baby died caesarean section was performed for fulminating toxæmia at the 28th week of pregnancy and the baby lived only 30 minutes: in the other case there was a stillborn breech delivery at the 36th week.

One case recorded as a success in the secondary habitual abortion group (Table I, B) in which there had been more than four abortions had miscarried nine times before the implantation.

All 10 successfully treated patients in this group had live babies. One of these was born with osteogenesis imperfecta, but the mother had previously had one child suffering from the same condition. This was the only case in the whole series in which there was any foetal abnormality.

Four other cases of repeated abortion treated by pellet implantation were not included in this series of 45 cases, because they did not conform strictly to our definitions of primary and secondary habitual abortion. A summary of these four cases is given.

Cases Not Included in the Series

Case 1.—Primary habitual abortion: three abortions at six weeks, then one abortion at 22 weeks. The next pregnancy carried to 33 weeks with an implant, and the baby lived. This case (a success) was excluded from the series because one pregnancy before the treated pregnancy had carried to more than five months.

Case 2.—Primary habitual abortion: two abortions at four and a half months and one abortion at three months, followed by another abortion at five and a half months. The next pregnancy carried to 30 weeks with an implant, but the baby lived only a few hours. This case (strictly a success according to our definition) was discarded for the same reason as Case 1.

Case 3.—Primary habitual abortion: one abortion at two months followed by two abortions at five months. Another abortion at five and a half months preceded the treated pregnancy, which carried only to 22 weeks after an implant. This case (a failure) was discarded for the same reason as Cases 1 and 2.

Case 4.—Primary habitual abortion: two abortions at five months followed by an abortion with twins at 28 weeks after an implant. One twin was born macerated and the other lived 32 hours. This case (strictly a success) was not included in the series, because it so barely conformed with our requirements.

Had these cases been included in the series there would have been no alteration in the success rate of 90% in the primary habitual abortion cases (group A) with two successive abortions, nor in the success rate of 86% in the same group under C. The success rate in A with four or more successive abortions would have risen to 62% and fallen in the same group in C to 72%.

Incidence of Habitual Abortion

In studying reports of many thousands of pregnancies in women attending antenatal clinics and birth-control

centres it was concluded by the Biological and Medical Committee of the Royal Commission on Population (1949) that "the proportion of all pregnancies ending in spontaneous abortion may be placed between the relatively narrow limits of 7 and 11%."

Complete information regarding the incidence of habitual abortion is not yet available. In order to obtain a true random sample it would be necessary to have details of all the pregnancies of the total population of a certain area, such as a borough or an urban or rural district.

Most of the figures at present available are derived from studies of patients attending antenatal clinics or obstetric departments. For instance, Javert (1948) analysed 56,803 pregnancies cared for at the Woman's Clinic of the New York Hospital during the 15-year period 1933-47, and classified 189 as cases of "primary habitual abortion (i.e., having had three or more consecutive spontaneous abortions beginning with the first pregnancy) and 115 as cases of secondary habitual abortion." He concluded that this corresponded to an incidence of 1 in 300 (0.3%) for primary and 1 in 493 (0.2%) for secondary habitual abortion.

Malpas (1938), studying about 6,000 pregnancies, found that 84 women had three or more consecutive abortions or stillbirths, an incidence of 1.4%.

These incidences have been calculated by relating the number of cases of habitual abortion to the number of pregnancies seen, whereas they might more usefully be related to the number of women.

Bishop (1937) analysed 2,687 case histories from Guy's Hospital Maternity Service and found that 0.4% of women had more than one initial idiopathic abortion at less than five months, and 0.1% (i.e., three cases) had three initial idiopathic abortions.

The "Spontaneous Cure Rate"

Various attempts have been made to calculate the likelihood of a pregnancy proceeding spontaneously beyond the 28th week, or to term, when preceding pregnancies have terminated in abortion. Though some believe that any series of consecutive abortions may be due to coincidence, it is generally thought that there is a recurrent factor in abortion sequences. The figures most commonly quoted are those of Malpas (1938) and Eastman (1947). The "spontaneous cure rate," according to the calculations of Malpas, is as shown in Table II.

TABLE II.—Malpas's Figures

No. of Previous Abortions	Spontaneous Cure Rate of a Subsequent Pregnancy
1	50 to 78%
2	9 " 62%
3	7 " 27%
4	0.3 " 6%

Eastman's calculations are based on the assumption that 10% of pregnancies terminate in spontaneous abortion and that a recurrent factor causes 0.4% to abort repeatedly. (This is the 0.4% in Bishop's series of 2,687 cases, mentioned above.) With these figures in mind he follows 100,000 hypothetical women through successive pregnancies (Table III).

Assuming the validity of these two sets of calculations, it is clear that the chances of a fourth pregnancy going to term are considerably less than those of a third pregnancy. This assumption is the basis of the definition of "habitual abortion" as representing three, rather than two, preceding abortions. It will, however, be obvious that a

TABLE III.—*Eastman's Figures*

No. of Cases	Previous Abortion	Will Abort from Accidental Causes	Will Abort from Recurrent Causes	Total Abortions	Per cent. will Abort	Spontaneous Cure Rate
100,000	0	9,600	400	10,000	10.0	—
10,000	1	922 (9.6% of above figure)	400 (Same 400)	1,322	13.2	86.8
1,322	2	88 (9.6% of above figure)	400 (Same 400)	488	36.9	63.1
488	3	8 (9.6% of above figure)	400 (Same 400)	408	83.6	16.4

sequence of three or more consecutive abortions represents a rare occurrence, and it is therefore unlikely that any individual set of observers will be able to present an impressive series of three or more consecutive abortions. In the present series there were only 17 such cases. We have therefore included details of 28 cases with two previous abortions.

Significance of Results Obtained in the Present Series

Accepting Eastman's figures and projecting them further to include the spontaneous cure rate of four (or more) previous abortions as 2%, the probabilities of obtaining by chance the results obtained in the present series of primary habitual abortions (see Table I) are:

With 2 previous initial abortions	..	..	0.007594
* " 3 " " "	..	..	0.000018
" 4 " " "	..	..	0.000078

Combining the probabilities together, the overall probability is much less than 0.001 ($P = 0.001$ for $\chi^2 = 22.5$ and $n = 6$; in this instance $\chi^2 = 50.5$).

If, however, recurrent factors operate less often, say in 0.1% of women, the expected success rates increase to 82%, 44%, and 8%, and the probabilities of obtaining the present figures are:

With 2 previous initial abortions	..	..	0.2758
* " 3 " " "	..	..	0.0157
" 4 " " "	..	..	0.0045

and the combined probability lies between 0.01 and 0.001.

If the true incidence of abortion due to recurrent factors is still less, say 0.01%, the expected success rates increase to 89%, 82%, and 45% (i.e., reasonably close to the observed figures) and the probabilities of obtaining the present results are:

With 2 previous initial abortions	..	..	0.62
* " 3 " " "	..	..	0.56
" 4 " " "	..	..	0.41

and the combined probability lies between 0.50 and 0.70.

Thus, provided the "normal" incidence of spontaneous abortion is of the order of 10% and the incidence of abortion due to recurrent factors is not much less than 0.1%, it is reasonable to conclude that the present figures indicate an effect of treatment. Should, however, the true incidence of "recurring" abortion be of the order of 0.01%, the present results could easily be attributed to chance. If the secondary habitual abortions are included the results are not materially affected.

*In calculating these probabilities we have assumed that all the patients referred to in Table I as having had four or more successive abortions had had four abortions. In fact, several had had five or more, but there were not enough of these for separate consideration. This approximation results in the calculated probability being slightly higher than the real one, so that the test errs on the strict side.

Discussion

If there is a recurrent factor in habitual abortion it is obviously not easy to identify, and prophylactic treatment is therefore difficult to assess. Rest in bed, sedatives, correction of vitamin, nutritional, and thyroid deficiencies, and even psychotherapy, have been cited as useful prophylactic measures, apart from the administration of sex hormones. Smith (1948) has propounded the theory that many of the disorders of pregnancy, including habitual and threatened abortions, toxæmia, pre-eclampsia, and eclampsia, are due to an imbalance of placental hormones (excessive chorionic gonadotrophin and deficiency of oestrogen and progesterone), and that they can be counteracted by administration of oestrogens, and especially stilboestrol, in doses increasing from 5 mg. daily at the sixth week to 115 mg. daily at the 35th week, when treatment is discontinued. In a series of 127 patients with a history of habitual abortion (some of whom had previously had live births, and some of whom were treated for threatened abortion), she obtained the results shown in Table IV.

TABLE IV.—*Smith's Series*

Previous Abortions	No. of Cases	Carried to 28 Weeks	Live Babies
2	67	84%	81%
3	38	87%	87%
4	17	65%	59%
5	5	40% } 59%	20% }
Total	127	80%	77%

It will be noted that this series (which is much larger than ours) has yielded substantially similar results. It was possible to obtain such a large number of cases by enlisting 117 obstetricians to co-operate in the study and to conform to certain standards in recording the results. Some doubt has been expressed, however, with regard to Smith's contention that stilboestrol stimulates the placenta to produce adequate quantities of oestrogen and progesterone (Davies and Fugo, 1947; Sommerville *et al.*, 1949), and it should be noted that this series of cases included both primary and secondary habitual abortions as well as cases of threatened abortion.

It has always seemed to us that the most important hormone for the maintenance of pregnancy is progesterone and that habitual abortion in many cases may be directly due to lack of this hormone. Attempts have been made in the past to counteract this deficiency by means of injections of progesterone given at intervals up to a week; indeed, some of the patients in the present series had been unsuccessfully treated in previous pregnancies with progesterone injections or ethisterone by mouth. We have been impressed, however, with the necessity for maintaining a constant level of exogenous administration. This can be achieved adequately only by means of pellet implantation, and it is for this reason that we have used this mode of administration. The choice of dosage has been arbitrary and may well seem to be low. It should, however, be pointed out that pellet implantation provides the most effective means of complete as well as constant absorption, and we feel that this route of administration may be more efficient than other methods of progesterone therapy.

The substantially similar results obtained by Smith (1948) and ourselves suggest the following possibilities: (1) That administration of oestrogen leads to adequate endogenous secretion of progesterone, and that a constant exogenous supply of progesterone is equally effective in preventing abortion due to recurrent factors. (2) That any therapeutic

discipline will induce the patient to take the necessary precautions to prevent another abortion from occurring. (3) That each of the "successfully" treated pregnancies proceeded beyond the 28th week by chance.

The second possibility seems to us unlikely. The last suggestion has been fully considered above. As to the first possibility, our results would indicate that progesterone is the essential hormonal factor for maintaining pregnancy, and that adequate progesterone therapy should not be discounted as a method of preventing the recurrent factor in abortion sequences. The results certainly do not conform with Hamblen's (1939) warning that exogenous progesterone may hinder the intrinsic metabolism of progesterone, nor do they support the contention (Hoffman, 1944) that progesterone therapy should be employed only in cases in which the pregnanediol level has been shown to be subnormal.

Summary

A series of 45 cases of habitual abortion treated prophylactically with progesterone pellet implantation (six 25-mg. pellets) yielded successful results in 86% of the patients with a history of two previous abortions, 89% with three previous abortions, and 75% with four or more previous abortions.

The series was subdivided into "primary" habitual abortion (in which all previous pregnancies had resulted in abortion) and "secondary" habitual abortion (in which one or more previous pregnancies, but not those immediately preceding the treated pregnancy, had proceeded beyond the 28th week). In these groups the results for primary habitual abortion were: 90% success with two previous abortions, 88% success with three previous abortions, and 60% success with four or more previous abortions; and for secondary habitual abortion, 75% success for two consecutive abortions immediately preceding the treated pregnancy and uniform success for the four cases of three or more abortions.

If the true incidence of "recurring" abortion is not much less than 0.1% these results indicate that the treatment was of value.

Statistical Methods Used.—The probabilities of obtaining the observed number of successes and failures in each group have been calculated direct from the binomial theorem, using the three different sets of estimates of the expected success rates. The combined probabilities for each set of three groups have been calculated from the formula: $\chi^2 = -2 \sum \log_e p$.

Our thanks are due to Professor A. Bradford Hill and Mr. P. Armitage for their interest and advice concerning the statistical methods used, and to members of the staff of the Chelsea Hospital for Women, who have referred many of the cases in this series to us for implantation.

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HAEMATEMESIS AND MELAENA

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Widely differing opinions have been expressed concerning the risk to life which accompanies bleeding from non-malignant ulceration of the stomach or duodenum (Chiesman, 1932; Cullinan and Price, 1932; Burger and Hartfall, 1934; G. Gordon-Taylor, 1937; Hurst and Ryle, 1937; Andresen, 1939; Meulengracht, 1939).

Some of the fallacies which abound in the published statistics relating to this condition have been critically discussed by Smith (1945) and also by Avery Jones (1947), who treated a large series of cases in a special gastro-enterological unit, with a mortality of 7.8%. He considered that the mortality has declined to between 5 and 10% during the past decade, but Baker (1947), reporting a series of 576 cases treated in a general hospital, found a mortality of 13.4%, and a recently published series by Lewin and Truelove (1949) showed a mortality of 19.5%. These figures are more likely to be representative of the results obtained in most hospitals, and they show that the management of gastro-duodenal haemorrhage is still far from satisfactory, many patients dying and many more causing grave anxiety and uncertainty regarding the best course to be adopted in their treatment.

More precise knowledge of the features which are of value in assessing the prognosis of the individual patient under the usual routine treatment would be very useful in distinguishing at an early stage which patients are in grave danger of dying from the haemorrhage. Until this particularly serious group of patients can be distinguished it will often be difficult to know whether one can reasonably persist with the routine conservative regime, or whether some other form of treatment should be considered. Much useful information regarding prognostic indications may be obtained from a study of the many papers published on the subject, in particular, Cullinan and Price (1932), Rafsky and Weingarten (1942), Heuer (1946), Baker (1947), Avery Jones (1947), and Lewin and Truelove (1949). But we believe it to be useful to see what further information may be obtained from an analysis of a large series of patients treated recently in the North-east of Scotland, more especially since some characteristics of peptic ulceration—for example, G.U./D.U. ratio—vary with the geographical area (Jamieson, Smith, and Scott, 1949), and it is possible that some features of gastro-duodenal bleeding might vary in the same way.

Present Series

This is a consecutive series of 476 cases of haematemesis and/or melaena admitted as emergencies because of bleeding to the three general medical units of the Aberdeen Royal Infirmary from January, 1941, to December, 1948, inclusive. The series is presumed to include only patients bleeding from peptic ulcers or erosions, because the notes of all cases of haematemesis and melaena from all causes were reviewed, but all those where some other cause was found—for example, gastric carcinoma, portal hypertension with oesophageal varices, blood dyscrasia—

The British Standards Institution has published a British Standard on "Industrial Safety-Gloves." The material, size, and dimensions of many types of safety-gloves are specified, and appendices list the information to be given when ordering the gloves. The specification is obtainable from the institution at 24-28, Victoria Street, London, S.W.1 (4s., post free).