minutes, the patient remaining asleep during the rest of the operation. This group accounted for $2\frac{1}{2}$ per cent. of the cases, or, if the upper abdomen be excluded, 3 per cent.

3. There is a small proportion of cases—0.5 per cent.—in which, in spite of apparently perfect technique, a spinal anaesthetic has no effect whatever: full sensation is present, there is no relaxation and no fall in blood pressure. In the absence of technical faults one is forced to fall back on the rather unsatisfying explanation of a "rachi-resistant" patient. This small number of cases comprised the only complete failures, and are ones that require supplementary full general anaesthesia.

Complications

The only complication to give any trouble during the performance of the subsequent operation was retching, occurring occasionally in upper abdominal operations, but very rarely otherwise. This phenomenon is most often observed in those patients in whom premedication has had little effect, and may occur at any time during the operation: it is fortunately temporary, and passes off spontaneously in a few moments.

There has been no mortality due to anaesthesia in this series of cases and, barring headache, no other complications that at various times have been attributed to spinal anaesthesia. Headache must not be regarded as the bogey of spinal anaesthesia; it occurs in about 7 per cent. of cases, is not of the intractable variety, and rarely lasts more than twenty-four hours. The incidence of this complication appears to be decreased by allowing cerebrospinal fluid to escape before injecting the percaine.

Summary

The results of observation on a series of cases of spinal anaesthesia administered by the time-diffusion technique are recorded. The series consisted of a total number, up to the time of writing, of 907 cases, in 551 of which dosage, timing, level of anaesthesia, etc., were carefully observed and correlated, and a further 356 cases administered as routine, which were not specially observed but which proved satisfactory.

The drug used throughout was light percaine, with the maximum dose of 12 c.cm. Presumably the results obtained would not hold good for other solutions.

The method appears to have a considerable margin of safety, is rapid, reasonably accurate, and has proved most satisfactory in practice.

The 551 cases were administered over a period of some seventeen months at the Anlaby Road Hospital, Hull, and for permission to publish them I wish to express my thanks to Dr. N. Gebbie, medical officer of health for Hull, to Dr. Tod, superintendent of the hospital, and to Mr. C. H. Corbett, consulting surgeon to the hospital. The remainder of the cases were administered at the Royal Infirmary, Sheffield, and for permission to publish these I wish to express my thanks to Mr. R. St. Leger Brockman, surgeon to the infirmary.

A circular letter from the Ministry of Health to medical officers in charge of venereal disease treatment centres states that under the arrangements being made for the examination and calling up of men liable for service under the Military Training Act, 1939, it may well happen that patients receiving treatment at the centres are affected. As it is most desirable that the treatment should not be interrupted, information regarding each case should be available to the Medical Board undertaking the examination; also details of previous treatment should be made known to the medical officer at the depot where the patient is called up. Each patient affected should therefore be supplied with Form V.15 setting out particulars of his case, and should be instructed to hand it to the medical officer concerned.

PREGNANEDIOL EXCRETION IN THE MENSTRUAL CYCLE

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The absence of a satisfactory method of determining the functional activity of the human ovary has been a serious obstacle to gynaecologists in the treatment of disorders of the menstrual cycle and of sterility. The difficulty of detecting the small amounts of gonadotrophic hormone and of oestrin excreted in the cycle renders such estimations of little value. In 1936 Venning and Browne isolated from human pregnancy urine the glucuronide of pregnanediol, and showed that its excretion during pregnancy and the menstrual cycle is directly related to corpus luteum hormone secretion in the body. The amount of pregnanediol recovered in the urine was found to be equal to 40 to 45 per cent. of the amount of corpus luteum hormone being secreted, on the basis of the quantity of pregnanediol recovered after injection of progesterone, the corpus luteum hormone. In a study of the excretion of pregnanediol by about twenty healthy women Venning and Browne (1937a, 1937b) found a considerable variation in the output, the range being from 3 to 60 mg.; they also found that variations existed in the excretion in different cycles of the same individual. As a general observation it was noted that where the amount of pregnanediol excreted was low—for example, less than 20 mg. in six days—and where the luteal phase was short, there was a history of functional sterility. No pregnanediol was found during the follicular phase—that is, the proliferative phase in the endometrium—but only during the luteal phase of the cycle—that is, from about two days after ovulation until one to two days before menstruation, covering a period roughly from the twelfth to the twenty-seventh day of the cycle, or a total excretion period of eleven to sixteen days. During the luteal phase, when pregnanediol occurs in the urine, the endometrium is no longer proliferative but secretory. It is thus possible to determine the existence of a functional corpus luteum in two ways: (a) by histological examination of endometrial scrapings, and (b) by estimation of the excretion of pregnanediol in the urine. In the present investigation the two methods were employed, and the result of each was given independently of the other and without knowledge of the finding obtained or information as to the stage of the cycle.

Methods and Results

The five patients mentioned in this report were suffering from sterility, and it was deemed advisable to estimate the activity of their ovarian luteal tissue as well as to examine the reaction of the uterine endometrium. Estimations of the excretion of pregnanediol will reveal, it is hoped, those cases of sterility and other abnormalities in which progesterone therapy is specifically indicated.

Pregnanediol.—The improved method of extraction of sodium pregnanediol glucuronide published by Venning in 1938 was used, and the weights of the glucuronide converted into pregnanediol by the approved formula.

The specimens of urine covered two consecutive days' output, and assays were made throughout two cycles in four patients and one cycle in another patient. An interval of either two or three days elapsed between the collection of each specimen. In no case was pregnanediol found in the urine during the first half of the cycle; the days on which it was recovered in the urine are indicated in the fourth column of Table I, and the amounts for twenty-four hours are shown in Column 2.

TABLE I.—*Pregnanediol in the Menstrual Cycle*

Case No.	Amount of Pregl. in 24 hrs. (mg.)	Estimated Amount Pregl. in Cycle (mg.)	Days on which Pregl. Recovered	Length of Cycle Days	Remarks
P1	4.8 } Cycle 1 6.2 } 6.9 } 6.2 } Cycle 2 6.0 }	22 + ? 15 = 37	{ 26, 27 29, 30 23, 24 26, 27 30, 31	32 35	Almost normal luteal function Normal luteal function
P2	5.1 } Cycle 1 3.2 } 6.2 } Cycle 2 3.3 }	16.6 + ? 12 = 38	{ 25, 26 28, 29 24, 25 27, 28	29 30	Excretion too low and luteal phase short
P3	3.0 } Cycle 1 3.4 } 10.5 } 2.1 } 2.2 } Cycle 2 3.0 }	38 + ? 22 = 60	{ 17, 18 21, 22 24, 25 28, 29 15, 16 25, 26	31 27	Normal luteal function ?
P4	Nil } Cycle 1 3.6 } 1.5 } Cycle 2	Nil ?	{ Nil 17, 18 20, 21	28 24	Deficient ovarian activity
P5	Cycle 1 not done 3.3 } 7.0 } Cycle 2 5.5 }	Not done 31.6 + ? 15 = 46	{ Not done 19, 20 23, 24 26, 27	30 29	? Normal luteal activity

For the purpose of gauging whether the cases investigated fell within the range of normality as given by Venning and Browne—namely, 40 to 60 mg.—an estimated total was arrived at by calculating the likely output on days between specimens. Such figures are preceded by a question mark in Column 3 of Table I, and from the totals thus reached it is possible to put forward the tentative interpretation given in the last column.

Biopsies.—By the aid of a special tubular curette small portions of endometrium were removed (by E. M. R.) from each patient for histological examination at the various stages of the cycle indicated on Chart 1 by an asterisk. The histological findings given in Table II, when correlated with the figures for pregnanediol, are

CHART 1.—Showing excretion of pregnanediol per day during menstrual cycles of five women. X, Menstruation begun. * Endometrial biopsy made.

TABLE II.—*Endometrial Biopsies in the Menstrual Cycle*

Case No.	Stage of Cycle	Histological Report	Phase of Cycle	Pregnanediol Excretion (per diem)
P1	15th day	Well-marked proliferative	Proliferative	Nil
P2	6th day	Not typical of one or other. Early secretory; endometrium thick and profuse	Late menstruating	Nil
P3	10th day 17th " 24th " 26th " (2nd cycle)	Poor specimen; no report Poor specimen: probably early proliferative Late proliferative, stroma and glands Secretory	Proliferative Early secretory Secretory Secretory	Nil 3 mg. 10.5 mg. 3 mg. (Menstruation next day)
P4	8th day 18th " (2nd cycle)	Perfect proliferative phase Well-advanced secretory phase. Vessels congested and ruptured, oedema	Proliferative Secretory	Nil 3.6 mg.
P5	28th day (1st cycle) 5th day 12th " 19th " 26th "	Well-marked late secretory Commencing secretory or else menstruation Late proliferative or early secretory Late proliferative or commencing secretory (definite diagnosis) Secretory (poor specimen)	Late secretory Menstruation Late proliferative Early secretory Secretory(late)	Not done Nil Nil 3.3 mg. 5.5 mg.

of special interest. In only one case is there any divergence between the histological and excretion findings—namely, in P3 on the twenty-fourth day a pregnanediol output of 10.5 mg. is associated with an endometrial

CHART 2.—Showing excretion of pregnanediol plotted against the days of the menstrual cycle.

picture which is not secretory. The clinical value of an output of such dimensions is easily recognized in face of the histological report.

When the excretion of pregnanediol in the five women investigated is plotted against the days of its occurrence (Chart 2), it is seen that the period covered is from the fifteenth to the thirtieth day of the cycle, the peak being about the twenty-third and twenty-fourth days. In studying individual cases, however, attention must be paid to the length of cycle normal to that person if it is desired to investigate the whole of the luteal phase. The data confirm Venning and Browne's conclusions.

Summary

The excretion of pregnanediol was correlated with endometrial biopsies in five women during the menstrual cycle.

No pregnanediol was excreted during the proliferative phase—that is, the early part of the cycle.

Pregnanediol excretion was found in all cases having a secretory endometrium.

On the basis of Venning and Browne's findings estimates were made as to the normality of ovarian function.

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TREATMENT OF GONORRHOEA BY M & B 693

BY

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In May, 1938, I began to treat a series of cases of gonorrhoea with the preparation which is now known as M & B 693. In this series 152 consecutive cases come under review; from these are excluded thirteen early defaulters and irregular attenders. Failures—cases which showed no material improvement after approximately two to three weeks' administration of the drug—numbered five. It should be noted here, however, that those "failures" cleared rapidly when irrigation was instituted after the drug had been withdrawn. Relapses occurred in eleven cases: six under fourteen days and five between twenty-one and forty-two days, all in alcoholics. Re-exposures numbered five, and the defaulter rate was about 30 per cent.

The following represents the detailed results in 134 cases. I began these investigations by using a dosage of two tablets three times a day. I excluded adjuvant irrigation therapy, as I had had a long-standing suspicion that the high incidence of complications which occurred during treatment at all the Glasgow centres—somewhere in the region of between 30 and 40 per cent.—was due to the act of irrigation, and also because I wished to see what the drug could do unaided. I began, therefore, with a dosage of two tablets thrice daily, later increasing it to two tablets four times daily to obtain a more even concentration during waking hours. Precautions with regard to sulphur intake were emphasized. As the results with two tablets four times a day were more encouraging I was emboldened to try three tablets four times a day; but my first case produced a rash with temperature, and I did not feel justified in proceeding further with this dosage.

Later, to find if a smaller dosage given in the same way would have as much benefit and, I hoped, with lessened toxic effects, I instituted a daily dosage of one tablet four times a day, and until recently this has been my routine treatment. The tablets were given until the discharge had completely ceased, and maintained for a period varying from one to two weeks thereafter. Following this there was a rest from treatment for three or four days, followed by a week's treatment, and then

two weeks' rest; after which a prostatic smear was taken, and, if this was satisfactory, a week later a urethoscopic examination was carried out and the urethra dilated, with a subsequent examination and blood Kahn test. Throughout the course of treatment the patients were so far as possible seen daily, but this quite often proved impossible, so that "dry" readings were more numerous than "G.C.-negative" ones. Thus it may safely be assumed that the figures obtained represent periods longer than would be got by exact findings under "indoor" supervision.

Table I shows the results obtained with varying dosage, and the extraordinary fact emerges that one tablet four times a day produced my best results, surpassing those with double that amount.

TABLE I

Dosage	Urethral Smear G.C.-negative		Urethra Dry	
	No. of Cases	Average in Days	No. of Cases	Average in Days
2 tablets 3 times daily ..	9	3.33	22	5.73
2 .. 4	12	3.00	17	3.80
1 tablet 4	40	1.92	33	3.37
3 tablets 4	1	2.00		
Total	62	2.33	72	4.19

Thus it will be seen that sixty-two cases were gonococcus-negative in an average of 2.33 days, and if we read "dry" as "G.C.-negative" we get an average of 3.33 days for the total 134 cases.

As cases may be gonococcus-negative but not dry I have extracted my total "dry" observations.

105 cases were dry in 7 days or under, averaging 4.21
 16 " " " 14 " " " 10.7
 5 " " " 21 " " " 16.9
 1 case was dry in 26 days.

Taking detailed dosage the following results were got:

29 cases with 2 tablets thrice daily were dry in average 7.2 days
 29 " " " four times daily, " " " 5.62
 69 " " 1 tablet " " " " " 4.86

The remaining seven cases were gonococcus-negative but not dry before defaulting.

Complications.—No complications were encountered during treatment, and where complications were noted before treatment these cleared up rapidly.

Intolerance.—This was observed in fifty-two cases, or approximately 39 per cent. Table II reveals the frequency of each toxic symptom noted and its average time incidence in days. In some cases more than one symptom occurred.

TABLE II.—Intolerance

Symptom	No. of Cases	Average Day Incidence
Vomiting	3	3.5
Nausea	30	3.7
Headache	26	4.0
Vertigo	6	4.3
Migraine	1	5.0
Temperature	5	6.2
Rash	3	6.6
Constipation	2	7.0

No case of breathlessness or cyanosis was found. With the dosage of one tablet four times a day the symptoms