theory that dysmenorrhoea was due to parasympathetic over-activity. Favourable reports have been published.

Ephedrine is also employed in enuresis. Its effectiveness—if it is indeed effective—might be explained in the same way, but it is more likely that the action is on the central nervous system. Perhaps I should add that, like so many drugs, ephedrine has been recommended as a cure for sea-sickness.

The toxic effects ascribed to overdosage are general nervousness and insomnia and tremor, vomiting and sweating, palpitations, urinary retention, and skin eruptions. When large doses are given to rabbits over a long period they cause enlargement of the heart with pronounced degenerative changes (Rühl, 1929).

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The psychological reactions of thirty "problem" children who received benzedrine sulphate for one week are recorded by C. Bradley (*Amer. J. Psychiat.*, November, 1937, p. 577). In fifteen there was spectacular improvement. Many became much less emotional, without, however, losing interest in their surroundings; they also experienced a sense of well-being. In this group were some children who had previously expressed their irritability in group activities by noisy, aggressive, and dominating behaviour; these became more placid and easy-going under the influence of benzedrine. No significant changes were detected in the blood or body weight, but in six cases the onset of sleep was delayed for the first night or so. Loss of appetite and nausea were shown by a few children only. The behaviour changes reached their maximum during the second and third hours after the administration of the drug, and there was a gradual reversion to the state normal for the particular child during the following six to twelve hours. In all cases the full effects became manifest on the first day of administration, continued daily through the week, and disappeared as soon as the drug was discontinued. The optimum dose was found to be 20 mg. In eight cases gastro-intestinal symptoms were provoked; these eight children were given subsequently daily doses of 10 mg. for a week; two derived no benefit, suggesting that the lowest dose which they could tolerate was therapeutically ineffective. No relationship was established between the children's ages or weights and their reactions to benzedrine. The author advises that this drug should be further tested experimentally before being recommended for the treatment of behaviour-problem children; he suggests that its action might be explained on the lines that it rectifies the impaired control activity which has given rise to disorders of behaviour.

AMENORRHOEA: ITS AETIOLOGY AND TREATMENT*

BY

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The data accruing from the present-day intensive study of sex physiology are at times bewildering and often overwhelming in their complexity. Nevertheless, from the conflicting mass of scientific evidence new facts are emerging which are furthering our knowledge of the processes associated with menstrual and reproductive function, and new therapeutic agents are gradually being added to the armamentarium of the clinician. These new therapeutic agents have been enthusiastically accepted and applied in the treatment of all gynaecological conditions that might be associated with underlying endocrinal disturbances. In some such conditions they are eminently successful—for example, in many post-menopausal disorders—but endocrine therapy has not fulfilled the early promise predicted. Disappointing response to treatment, however, may not be due to faulty or ineffective preparations but rather to their indiscriminate application. Without some knowledge of the therapeutic action of the various sex hormones and their relation to the mechanism of menstrual periodicity therapy must in the main be conjectural. In this paper I am dealing with a study of ninety-seven cases of amenorrhoea, most of which have been investigated as fully as present-day methods permit.

Methods of Investigation

1. *History*.—A full anamnesis is of great importance. Special attention should be directed to the state of previous health and to the occurrence of any unusual circumstances present immediately before or at the time of cessation of menstruation. Frequently a history of change of occupation, domestic worry, grief, or social estrangement is obtained which has an important bearing in regard not only to aetiology but also to prognosis and treatment. Details of previous menstrual rhythm and loss should be elicited. The presence or absence of menstrual moulins may also be important as regards prognosis; their presence is rather more favourable than otherwise. Information should be obtained as to any increase or loss of weight and its association with the onset of the amenorrhoea.

2. *Detailed Examination of the Reproductive Tract*.—Whilst the whole reproductive tract must pass under review, the size of the uterus requires special attention, as in many cases this gives an approximate index of ovarian function. It is important, where possible, to examine the endometrium histologically—first, to exclude tuberculosis, and, secondly, to obtain information regarding ovarian activity.

3. *Radiographs of the Sella Turcica*.—Though pathological changes of the sella are rarely found, we may discover in some cases distortion of the sella pointing to gross pituitary disease. Occasionally amenorrhoea is one of the initial features in pituitary lesions, and it is on account of the cessation of menstruation that the patient may seek medical advice.

4. *Estimation of the Basal Metabolic Rate*.—This is the only available method of forming an approximate estimation of thyroid function. As the function of the

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thyroid gland is controlled by a specific hormone of the anterior pituitary some knowledge of its activity may provide an index of pituitary function. However, although a hypophysis is functioning in a normal manner in regard to its thyrotropic secretion, this does not necessarily imply that it is also active in respect of its gonad-stimulating hormone.

5. *Determination of Sugar Tolerance.*—As pancreatic function is controlled by a specific hormone of the anterior pituitary this test may sometimes be of value as an index of pituitary activity. Occasionally, however, amenorrhoea is the only symptom in early cases of diabetes mellitus, and unless the sugar tolerance is determined the condition may be entirely overlooked until it has reached a more positive phase.

6. *Determination of the Hormone Excretion.*—Estimation of the urinary excretion of the gonadotropic and the follicular hormone affords presumptive evidence of anterior pituitary and ovarian function. As these glands are intimately concerned with the control of the menstrual cycle some knowledge of their activity is of the greatest importance.

In the series of cases under review analysis of the total twenty-four-hour output of urine was carried out, according to the technique already described (MacGregor, 1936), at weekly intervals over a period of one month or longer, and, considered in conjunction with other data, this has in many cases been of value in formulating a basis of treatment. Low values for oestrin excretion show that ovarian function is subnormal, and therefore a reactivating therapy in the form of hypophyseal preparations is indicated.

Functional Amenorrhoea

The causes of functional amenorrhoea may be classified broadly into (a) psychogenic influences, and (b) general hormonal disturbances.

(a) PSYCHOGENIC INFLUENCES

The underlying cause of the endocrine dysfunction is not clear. The onset of amenorrhoea, however, so often follows a mental trauma as to suggest that the motive factor may in some cases be psychogenic. Further, the data obtained from an analysis of the hormone excretion suggest that the hypophysis is primarily influenced by a psychological factor operating either via the higher centres or directly through its autonomic nervous control. The effect of the psychogenic disturbance varies in degree, depending on individual susceptibilities, from amenorrhoea of short duration to a more marked constitutional upset. In the initial stages of this investigation the importance of a possible psychological factor was not realized, and accordingly definite figures regarding its incidence are not available. In a proportion amounting to 60 per cent., however, this factor was present. As illustrating the influence of minor upsets such as environmental and occupational changes on the menstrual cycle, the menstrual histories of thirty-eight nurses may be cited. It was found that during the first year of their training 29 per cent. had amenorrhoea varying in duration from one to ten months.

There are thirteen cases in this series in which the outstanding feature was the constitutional disturbance present. They all had in common loss of weight—compared with normal standards for height and age the pro-

Table showing the Investigation Findings in Thirteen Cases of Anorexia Nervosa

Case No.	Age	Duration of Amenorrhoea (years)	Weight	Corrected Percentage Weight	B.M.R.	Blood-sugar Tolerance					Sella Turcica	Utero-cervical Canal	Endometrium	Gonadotropic Hormone	Oestrin
						F. S.	Hours								
							$\frac{1}{2}$	1	1 $\frac{1}{2}$	2					
1	18	3	st. 6 7	$\frac{\%}{-26}$	$\frac{\%}{-18}$	100	150	140	128	102	Normal	2"	Fibrotic	—	—
16	20	2	5 9 $\frac{1}{2}$	-28	-28	90	120	150	140	110	"	2"	V. scanty	—	—
20	22	2 $\frac{1}{2}$	6 7	-31	-21	85	137	106			"	2"	" "		
21	26	3	7 0	-25	+ 2	104	121	118	99		"	2 $\frac{1}{2}$ "	Resting	—	+
26	20	4	6 7	-29	+18	88	100	94	90	90		2 $\frac{1}{2}$ "		+	—
27	15 $\frac{1}{2}$	1/4	5 13	-25	-27	91	119	100	90	88		2"	V. scanty		—
33	29	4	6 10	-28		94	116	147	99	83		2"	" "	—	—
46	21	4	5 9 $\frac{1}{2}$	-37	-21						Normal	2 $\frac{1}{2}$ "		—	—
54	22	1 $\frac{1}{2}$	5 11 $\frac{1}{2}$	-33	-19						"	2"	V. scanty	—	—
55	24	1/2	7 4 $\frac{1}{2}$	-15	- 1	98	112	100	90		"	2"		—	—
81	23	1/2	7 4	-26	-10						"	2 $\frac{1}{2}$ "			
85	18	7/12	6 7 $\frac{1}{2}$												
86	39	1/4	5 7		-19	82	146	189	216	190		2"			

Classification of Material

Investigation carried out on the above lines showed that in twenty out of a total of ninety-seven cases examined the amenorrhoea was due to a recognizable pathology in the pituitary, ovaries, or uterus, and in a few cases was associated with systemic disease. These will be the subject of a later article. In seventy-seven cases, although no obvious pathological condition was observed, laboratory findings disclosed a disturbance of function, particularly of the ductless glands closely concerned with the menstrual process. These cases are therefore described as "functional."

portion of those under weight varied from -15 to -37 per cent.—distaste for food, amenorrhoea, and, with two exceptions, uterine hypoplasia (see Table). These features are characteristic of anorexia nervosa. Sheldon (1937) lays "emphasis on physical aspects of anorexia nervosa which suggest that in some cases there is an underlying hypofunction of the anterior pituitary." He says: "In the chain of events which leads to amenorrhoea the pituitary is involved." While this is undoubtedly true, it may be suggested that in all probability there is an underlying psychological cause in these cases and that the pituitary hypofunction is a secondary phenomenon. As, however, many individuals sustain a similar mental shock

without any resulting sequelae it is presumed that in those patients who display the syndrome of anorexia nervosa there is an inherent psychological maladjustment which cannot withstand mental trauma.

(b) GENERAL HORMONAL DISTURBANCES

In approximately 40 per cent. of the cases no history was obtained of an abnormal psychological stimulus preceding the amenorrhoea: in these it has been presumed that a general hormonal imbalance was the cause of the menstrual disorder. The investigation of these patients showed, however, that dysfunction of the pituitary was present. Whether this was a primary or a secondary phenomenon it was impossible to ascertain.

Treatment of Functional Amenorrhoea

After each case had been investigated as outlined the resulting data were studied. Those cases exhibiting deviations from the normal were treated appropriately. For example, where the basal metabolic rate was low, thyroid medication was given; where anaemia was found, iron was administered. Such treatment was not followed by a return of menstruation in any one case. Those who were over weight, excluding diabetics, were put on a strict anti-obesity regime until their weight was within normal limits. With this treatment alone six patients menstruated spontaneously. It is not clear whether the obesity in such cases is due to a temporary slowing of the general metabolic processes consequent on anterior pituitary hypofunction or is directly associated with derangement of the fat-regulating centre in the hypothalamus arising from the same nervous factor as is responsible for the amenorrhoea. Whatever the cause of the obesity or its relation to amenorrhoea, a suitable regime to counteract it meets with a favourable result in some cases. It is a clinical impression that a strict anti-obesity regime is more efficacious in such cases than thyroid therapy.

The treatment of anorexia nervosa is admittedly difficult. Psychotherapy may be beneficial, but the one patient in the series who was treated in this way, although improved in general health, remained amenorrhoeic. In my opinion improvement of the patient's general health should be the first consideration, and as this is difficult to carry out in domiciliary environment a hospital or nursing-home regime is essential. After a satisfactory response has been obtained from treatment along general lines endocrine therapy should be instituted.

Of the thirteen cases of anorexia nervosa one patient has died as a result of her condition. Seven have had an irregular response to treatment in that one or two uterine bleedings have occurred. The following is the history of one of the cases treated.

Case No. 85.—This patient, aged 18, started to menstruate at 13, and her periods were regular 5/28. Her weight at Christmas, 1936, was 9 st. 7 lb. She had influenza in January, 1937, and was operated on during the same month for appendicitis. After operation her weight was 8 st. 13 lb. On return to school she became very worried at not being able to keep pace with her companions. She gradually went off food, and in February, 1937, her periods stopped. She slowly lost weight, and there was a complete loss of appetite and an apparent inability to eat. She also had attacks of biliousness. When seen on July 23, 1937, her weight was down to 6 st. 7½ lb. and her blood pressure was 90/70. On examination no physical defect was found. She was an alert girl, always on the move. Her condition was diagnosed as one of anorexia nervosa, and complete rest in bed in a home was advised. After a few days of this treatment she began to take an interest in food, became relaxed, and generally felt better. After seventeen days of this negative regime her appetite

became normal and there was a tendency to increase in weight. It was now considered that more rapid improvement might follow if menstruation could be re-established. In deference to the parents' wishes examination of the reproductive tract was not carried out. It was presumed, however, from the findings obtained in similar cases that there was a certain degree of uterine hypoplasia. On this assumption, and despite the knowledge that the hypofunction of the pituitary might be aggravated, oestradiol benzoate therapy was instituted. She was given a daily injection of 5 mg. of dimenformon for six days, and after a few days a further daily injection of 5 mg. for seven days—that is, a total dosage of 65 mg. of dimenformon. On September 10, ten days after her last injection, a slight show was seen. Thereafter she was given 100 mouse units of antostab (serum gonadotropic hormone) intramuscularly at three-day to four-day intervals for five injections, and after an interval of ten days a further course of five injections, each consisting of 100 M.U. of antostab plus 100 M.U. of physostab (urine gonadotropic hormone) over a period of fifteen days. She had a slight loss on November 10, and a further course of five injections of antostab plus physostab was instituted after bleeding ceased. Uterine bleeding followed on December 8, lasting three days. Her weight had increased to 8 st. on December 9. She is taking her food well and is now anxious to resume her studies.

Endocrine Therapy

(a) OVARIAN PREPARATIONS

The role of oestrogenic therapy in the treatment of amenorrhoea is in my opinion a subsidiary one. There are few cases in which it succeeds when given alone. Such therapy is unnecessary if the uterus is of normal size, as this indicates that there is enough hormone in the circulation to stimulate full development of the uterine musculature, but not an adequate amount for endometrial growth. When the uterus is in a hypoplastic condition oestrogenic therapy is called for in order to promote full uterine growth and increased tonicity, so that the organ may be receptive to the stimulation of the normal secretions of the ovaries when these have been reactivated by anterior pituitary preparations. Should it not be possible to measure the uterus after such treatment the production of uterine bleeding, it is suggested, may be taken as a rough index of full development of the uterine musculature. The other indication for oestrogenic therapy is the finding of an excess of gonadotropic hormone excretion. In such cases it may be postulated that sustained overstimulation of the ovaries, resulting primarily from a temporary hyperactivity of the anterior pituitary, may result in a condition of ovarian hypofunction or fatigue. Direct inhibition of the pituitary or inactivation of its secretion as a result of oestrogenic therapy permits the ovary to elaborate its own hormones at a normal concentration. In this way oestrogenic therapy may be curative, in some cases manifesting an excessive excretion of gonadotropic hormone. The importance of urinary hormone analysis prior to treatment is obvious.

Before anterior pituitary preparations were available the oestrogens alone, or combined with corpus luteum hormone, were the form of therapy most favoured. The general scheme of treatment with the oestrogenic hormones was the intramuscular injection of 5 mg. of oestradiol benzoate every three to four days for five injections. If no result was obtained at the end of ten days after the last injection similar courses were repeated, always with ten to fourteen days intervening. Thirty cases were treated by oestrogenic substances. Twelve of these, including a few who had intensive therapy, failed to respond to treatment. Sixteen responded irregularly in that uterine bleeding was provoked as a result of the treatment, but there was no continuation of a cycle on its

cessation. In two cases exhibiting excessive excretion of gonadotropic hormone menstruation became regular, and in one it has continued regularly for twelve months; the other, however, relapsed after three cycles. Analysis of the urine during the relapse showed that the excretion of gonadotropic hormone had again become excessive; after further treatment, however, there have been two periods.

(b) ANTERIOR PITUITARY THERAPY

The preparations available for therapeutic use are the anterior pituitary gland products, the anterior-pituitary-like or chorionic hormone prepared from pregnancy urine, and the gonadotropic hormone prepared from the serum of pregnant mares. The rationale of this form of treatment is ovarian stimulation, but it must be emphasized that it is a substitutive therapy. I believe that a temporary or, in some cases, a sustained anterior pituitary hypofunction resulting from a psychological disturbance may so vitiate the general hormonal balance that the disorganization may be perpetuated after a normal psychological status has been established. The stimulation of the ovary by anterior pituitary preparations permits it to elaborate its own hormones, which, in turn, stimulate the uterus. The restoration of normal ovarian activity promotes an adjustment of the general endocrinal imbalance.

Four cases were treated with anterior pituitary gland extract (gonadotraphon). In three there was no response, whilst in the fourth case uterine bleeding has been produced during the past five months; a course of therapy, however, was given each month during that time. Many cases were treated with anterior pituitary extract containing thyrotropic hormone (ambinon) alone or combined with urine gonadotropic hormone (pregnyl), but no continuous response was obtained with this therapy.

The predominant effect produced by the chorionic hormones in the experimental animal is luteinization of follicles. These hormones have been shown to have no effect on the ovaries of monkeys (Johnson, 1935). In amenorrhoea, therefore, where ovarian function is presumably subnormal or in abeyance and the secretion of oestrin is at a minimum, there are no ripening follicles capable of being luteinized. Highly luteinized ovaries, with the elaboration of progesterone, would only rarely bring about a secretory phase in the endometrium owing to the absence of the prior action of oestrin. Support was obtained for this view in that curettage in these cases seldom disclosed an endometrium stimulated to such a degree as to be capable of being changed to a secretory phase. Sixteen cases were treated with chorionic or urine gonadotropic hormone, with very disappointing results. Only two responded satisfactorily.

(c) SERUM GONADOTROPIC HORMONE

This hormone is capable of stimulating ovarian growth and function in monkeys (Engle and Hamburger, 1935), and has a gonad-stimulating effect in the hypophysectomized experimental animal. In this respect its biological action is similar to that of the anterior pituitary gland. At the present time, therefore, this preparation seems to be the one which is likely to be most beneficial in cases where ovarian stimulation is required. Engle and Hamburger have shown that it has the same effect on the ovaries of monkeys as the anterior pituitary hormone found in castrate urine. This hormone, believed by many to have a follicle-stimulating action only, has been demonstrated by Frank, Salmon, and Friedman (1935) and Lipschütz (1935) also to produce luteinization, provided a sufficiently high concentration is given. Since there is no conclusive evidence that more than one anterior

pituitary sex hormone is secreted, this postulate has been used as the basis for therapy. It is considered that the difference between the hormone present in pregnant serum and that in urine may be due to chemical interactions. In this series of cases, therefore, both hormones have been given together.

The scheme of treatment adopted was as follows: When the uterus was found to be hypoplastic, as indicated by the length of the utero-cervical canal, oestradiol benzoate therapy was administered until the uterus was fully developed. If the uterus was of normal size initially, this preliminary treatment was omitted. Thereafter 100 M.U. of serum gonadotropic hormone and 100 M.U. of urine gonadotropic hormone were given intramuscularly combined as one injection every three to four days for five injections. If no uterine reaction resulted after an interval of ten to fourteen days a further five injections were given as previously, and again after an interval of ten to fourteen days another five injections were given. It is advisable, if there is no response to three courses of injections, to defer further treatment for a period of from two to three months. In a few cases response to the first or second course of therapy was immediately followed by a further course of injections in order to supplement pituitary function and cause full reactivation of the ovaries.

Thirty cases were treated in this way with serum and urine gonadotropic hormones. Of these, ten responded satisfactorily to therapy. In three cases, however, after several months of regular menstruation a period was missed; a further course of serum plus urine gonadotropic hormone was then given, resulting in a return of the normal cycle. Twelve responded irregularly in that one or two periods occurred after treatment. Eight failed to respond after one or more courses of therapy. Included in the irregular responses are a number of cases in which treatment has only recently been instituted, and it is possible that several of these may continue to menstruate normally.

The following is a résumé of the history and treatment of three of the patients in this group treated by serum and urine gonadotropic hormone.

Case No. 80.—This patient, aged 26, had never menstruated. Her basal metabolic rate was +19 per cent. Blood-sugar tolerance: fasting blood sugar, 123 mg. per 100 c.cm.; at half-hourly intervals after 50 grammes of glucose, 180, 140, 125 mg. per 100 c.cm. The utero-cervical canal was 2½ inches in length. The endometrium was scanty and not sufficient for histological examination. The sella turcica was normal. With regard to analysis for hormones, the twenty-four-hour output of urine was examined for the gonadotropic hormone and oestrin on five consecutive occasions at weekly intervals; and 40 c.cm. of blood were also tested for oestrin on four consecutive occasions at weekly intervals. No oestrin was found in the blood by the methods used. The urine gonadotropic hormone on every occasion was negative. The amount of oestrin excreted in the twenty-four-hour output of urine was: (1) 19–36 M.U.; (2) 10–20 M.U.; (3) less than 11 M.U.; (4) 22–44 M.U.; (5) 22–44 M.U. On account of the increased metabolic rate, treatment with Lugol's iodine was given until the basal metabolic rate was within normal limits. Thereafter hormone preparations were administered over a period of fourteen months in various courses of therapy. The patient was given a total dosage of 16,000 R.U. of pregnyl, 145 gonadotropic units of ambion, and 126 mg. of dimenformon. As a result, several uterine bleedings occurred at irregular intervals, but there was no continuation of menstruation on cessation of this treatment. The patient was then given two courses of 200 M.U. of serum gonadotropic hormone plus 200 M.U. of urine gonadotropic hormone, combined as one injection at three-day to four-day intervals, ten days

intervening between each course, making up a total of twelve injections. As a result of this therapy the patient had five uterine bleedings at regular monthly intervals. The rhythm was not maintained, however, and a further course of five injections of serum gonadotropic hormone plus urine gonadotropic hormone was given in May, 1937. Since this last course of treatment menstruation has continued regularly at monthly intervals.

Case No. 65.—This patient, a girl aged 17, had never menstruated. Her twin sister menstruated at 14 and has regular periods. On investigation her weight was 7 st. 12 lb. and her height 5 ft. 5 in. Secondary sex characteristics were normal. The basal metabolic rate was -10 per cent. The sella turcica was smaller than normal. Blood-sugar tolerance: fasting sugar, 87 mg. per 100 c.cm.; at half-hourly intervals after 50 grammes of glucose, 180, 150, 120, 89 mg. per 100 c.cm. The external genitals were normal, the cervix healthy, and the uterus in good position; the utero-cervical canal measured 2½ inches by the sound. The endometrium was so scanty as to be insufficient for examination. The urine was examined for hormone content on two occasions. Urine gonadotropic hormone was negative and urine oestrin less than 10 M.U. per twenty-four-hour output. The patient was treated with Collip's maturity factors over a period of two months without effect. In October, 1936, a course of therapy with 200 M.U. of serum gonadotropic hormone combined with 200 M.U. of urine gonadotropic hormone was given at three-day to four-day intervals for five injections. There was no result from this course of treatment, and it was repeated in November, 1936. Ten days after the last injection uterine bleeding occurred for three days; since then menstruation has been regular every twenty-eight days—that is, over a period of thirteen months.

Case No. 35.—This patient, a woman aged 24, first came under observation in August, 1933. Menstruation began at 13 and had been regular (4/28) until January, 1933. Her father died in November, 1932. Before any investigation was carried out the patient was put on progynon by injection and dragees orally, and between August 21 and November 22, 1933, 71,300 M.U. of progynon were injected and 7,800 M.U. given by mouth. Uterine bleeding started on December 3 and lasted five days. A further total course of 50,000 M.U. was then given by injection and 1,650 M.U. by mouth in the form of progynon. A uterine bleeding occurred from January 3 to 4, 1934. Thereafter another course of 40,000 M.U. of progynon oleosum given by injection was followed by uterine bleeding on February 25. She then had, by injection, 80,000 M.U. progynon oleosum and 120,000 M.U. oestrogen, without effect. The patient was admitted to hospital for investigation. Her weight was 7 st. 10½ lb. and her height 5 ft. 4 in. The basal metabolic rate was +7 per cent. The sella turcica was normal, and x-ray examination of the chest proved negative. Blood-sugar tolerance: fasting sugar, 100 mg. per 100 c.cm.; at half-hourly intervals after 50 grammes of glucose, 150, 126, 100, 98 mg. per 100 c.cm. Fields of vision were normal. The utero-cervical canal measured 2½ inches; the endometrium was very scanty. The twenty-four-hour output of urine was examined for hormones on five occasions at weekly intervals. No gonadotropic hormone or oestrin was demonstrated in the urine but a positive blood oestrin was once obtained.

Between November 18, 1934, and May 20, 1936, the patient had, divided in various courses of therapy, 95 mg. of dimenformon, 9,100 R.U. of pregnyl, and 90 gonadotropic units of ambinon in conjunction with 1,800 R.U. pregnyl. During that time the patient saw traces of blood on five occasions. The last bleeding was on March 22, 1936. From May 31 to August 23, 1936, she was given two courses of serum gonadotropic hormone along with urine gonadotropic hormone. The total amounts of the two courses were 2,000 M.U. of each preparation. Menstruation started on August 19, the bleeding lasting four days; since then—that is, during sixteen months—it has been regular 4-5/28-day type.

It is not likely that menstruation will proceed spontaneously in every case of amenorrhoea responding to

this therapy: cognizance must be taken of the motive factor producing the amenorrhoea. It is, however, probable that menstruation will follow regularly if, by periodic supplementing of the anterior pituitary gonadotropic hormone when it is necessary, the menses can be kept going long enough. It is not improbable that the dosage of the gonadotropic hormones given in this series was inadequate in many cases, but the amounts available at the present time preclude the administration of a much higher dosage.

Spontaneous Onset of Menstruation

It is difficult to assess the results from any one line of treatment in amenorrhoea, as the possibility of the spontaneous onset of menstruation must always be considered. This applies particularly to indiscriminate treatment without prior investigation. Sometimes, from an analysis of the urine for hormone content carried out at weekly intervals, it can be predicted that menstruation is likely to ensue spontaneously.

In eleven out of seventy-seven cases of functional amenorrhoea menstruation recommenced spontaneously. The period of amenorrhoea varied, the longest period of secondary amenorrhoea being five years, whilst one patient with primary amenorrhoea started menstruating at the age of 25. This latter case is of interest in that treatment had been instituted over a period of six months, and during that time, in various courses of therapy, the patient had had a total dosage of 4,600 R.U. of pregnyl, 200 mg. of dimenformon, and 45 mg. of progestin. One of these courses was carried out on the lines indicated by Kaufmann (1934). No uterine bleeding was produced as a result of the treatment. It must be added that marriage was advised when that question arose with this patient, and after eleven months of conjugal life menstruation ensued. This is the only case of primary amenorrhoea in the series which has menstruated spontaneously.

Discussion

The factor or factors responsible for the cessation of menstrual rhythm are rarely apparent. It is therefore necessary that every avenue of approach in the investigation of each case be explored in an attempt to elucidate the underlying cause or causes. An investigation such as suggested reveals in some cases a pathological cause of the amenorrhoea, but in the majority of cases only disturbances of function are found. Further, the investigation is of value in that it often yields presumptive evidence of the degree and nature of the disorder. Rational therapy formulated on this basis is obviously more likely to meet with success than that which is largely empirical.

It has been suggested that the aetiological factor in the majority of cases of functional amenorrhoea is a psychological one; yet in many cases it is undoubtedly not only a suggestion but a true statement of fact. Just as an abnormal psychological stimulus may result in amenorrhoea, so also may a similar factor result in a return of menstruation in an amenorrhoeic patient. This may explain why in some cases menstruation recommences spontaneously after months or years of amenorrhoea.

Although in a few cases of amenorrhoea the oestrogens are of value, in many they are contraindicated, as they may produce a further inhibition of an already under-functioning hypophysis. The results obtained in the present series, and those of many other investigators, indicate that the chorionic hormones *per se* have, for the reasons already stated, very little place in the treatment of amenorrhoea. Until reliable anterior pituitary gland

preparations are available, when a true substitutive therapy can be carried out, the most hopeful preparation seems to be the serum gonadotropic hormone alone or combined with the urinary gonadotropic hormone.

No differentiation has been made between primary and secondary amenorrhoea, as it has been found that when congenital defects are excluded the findings are comparable in both types, and therefore the treatment is similar. The prognosis is just as favourable in primary as in secondary amenorrhoea.

Summary

1. The investigation required in a case of amenorrhoea is detailed, and some consideration is given to the value of each procedure.

2. The primary and secondary factors responsible for the inhibition of menstruation are discussed.

3. The results of treatment based on the investigation findings are presented.

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D. Whyte and R. O'Regan (*N. Zealand med. J.*, December, 1937, p. 381) refer to a previous paper published in February, 1937, in which they stated that the treatment of complete prolapse of the rectum by Gabriel's injection technique was "safe, painless, and effective." They now wish to qualify this statement, as a case has been seen in which the patient's life was in serious danger for some weeks from sloughing of the rectal wall and secondary haemorrhage, although the final result was satisfactory. The patient, a man of 55, was suffering from intractable prolapse of the rectum with continued mucous discharge. Seven submucous injections were given, each of 2 c.cm. of 5 per cent. carbolic acid in almond oil, and three perirectal injections of saline solution. Vomiting and headache persisted for a week, and on the eleventh day after operation a sudden copious haemorrhage from the rectum occurred. Examination under anaesthesia was carried out, and a large sloughing area was found on the posterior wall of the rectum extending into the pararectal tissues, the sacrum being palpable through a mass of blood clot. An acriflavine gauze pack was inserted, and was replaced two days later by a small flavine-vaseline pack. Nineteen days after the original operation a left inguinal colostomy was done. Six blood transfusions had been given during this period, and repacking had been carried out several times on account of bleeding. At the end of two and a half months proctoscopy showed the rectum to be healed and firmly fixed in the sacral hollow, and at the end of a further month the colostomy was closed and the patient made a good recovery.

RATE OF SEDIMENTATION OF RED BLOOD CELLS AS A CLINICAL TEST IN GENERAL PRACTICE

BY

E. SCOTT, B.A., D.M., B.Ch.

This investigation was undertaken two years ago to determine the value of the blood sedimentation rate (B.S.R.) as a test for the general practitioner. From my material I have chosen the experiments which are most likely to be of use. For the test to be practical it must conform to certain conditions. It must be quick, easy of application, and independent of elaborate apparatus. These conditions are satisfied. The blood can be collected and the tube filled in the time it would take to spread a blood film, and the reading, which takes place an hour later, can be jotted down by any educated person. The work has been done in three places—Ashford Hospital, my surgery, and the patient's home. As regards the last-mentioned, to avoid the dangers of transport with a filled tube it is a good plan to leave the tube to be read by the patient at the required time or marked with a strip of stamp paper. Attention to minute differences in end-results is undesirable and may be misleading. The B.S.R. is altered in a variety of pathological conditions that affect the body as a whole. It is thus, within limits, an indication of the existence of organic disease, particularly of an inflammatory nature, and a guide in the assessment of recovery. In theory it runs parallel to the temperature chart, but it covers a wider field, is slower to rise and decline, and can indicate infection in the absence of pyrexia. It affords a closer comparison with the Arneth count. It is the extent and scope of the test which constitute its strength and weakness and render its investigation difficult. The test has become a routine one in hospital practice in many parts of the Continent, particularly Germany, Scandinavia, and Switzerland. It is rapidly becoming popular in England, where it is used as a standard control in the treatment of tuberculosis and chronic rheumatism. Individual readings are not very instructive. I have, in consequence, endeavoured to gain information by choosing cases of known disease and compiling charts with B.S.R. readings as far as possible from inception to cure. In most cases these are correlated with temperature readings.

Technique

There is a somewhat wide choice of tubes, but I have found that Linzemeier's answers all requirements. This tube is marked at the level reached by 1 c.cm. of fluid, and is graduated in millimetres downwards to 24. The reading is particularly easy, and it is noteworthy that if these graduations are extended they divide the c.cm. into 48, so that figure 1 on Linzemeier's tube represents roughly a B.S.R. of 2 per cent. This affords a useful method of comparison with other apparatus. With a hypodermic syringe and needle a solution of 3.8 per cent. sodium citrate is drawn to the 0.2 c.cm. mark and blood is collected from a vein until the 1 c.cm. point is reached. The piston is then withdrawn slightly and the syringe contents are thoroughly mixed by repeated inversion. The citrated blood is injected into the sedimentation tube up to the top mark (1 c.cm.). The tube is placed vertically in a stand and the height of the supernatant clear fluid read off in an hour's time. These tubes are made by Hawksley and Sons, and I have obtained them from