of the opinion that these active principles are the specific products of placental tissue functioning, and are actively related to the condition of pregnancy. The functional interrelationship which must exist between the pituitary sex hormones and those of the placenta can in the light of our present knowledge only be conjectured. Much more research must be done in this field before the data now available can be satisfactorily correlated.

It is a great pleasure for me to state that through the kindness of the Medical Research Council and the

National Institute for Medical Research I have recently been given facilities to repeat much of the work outlined above in Dr. H. H. Dale's laboratory at Hampstead.

REFERENCES.

- ¹ Aschheim, S.: *Zeit. Geb. Gynäk.*, 1929, xcv, 371.
- ² Collip, J. B.: *Canadian Med. Assoc. Journ.*, 1930, xxii, 761.
- ³ Crow, F. A. E.: Presidential Address, Second International Sex Congress, London, August, 1930.
- ⁴ Ehrhardt: *Klin. Woch.*, 1929, viii, 178.
- ⁵ Wiesner, B. P.: *Edin. Med. Journ.*, 1930, xxii, 761.
- ⁶ Zondek, B.: *Klin. Woch.*, 1930, ix, 245, 293.
- ⁷ Idem: *Deut. med. Woch.*, 1930, lvi, 300.

NOTES ON THE CLINICAL USE OF CERTAIN PLACENTAL EXTRACTS.*

BY

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THE process of menstruation in the normal state occurs every twenty-eight days from puberty to the menopause, except as interrupted by pregnancy and lactation. Variations in the length of the interval, the duration of the epoch, or in the amount of blood lost or endometrial tissue shed may not necessarily be considered pathological so long as such variations represent individual peculiarities. The conception that physiological changes in the endometrium leading to menstruation are dependent upon chronological ovarian changes is now generally accepted. Similarly, deviations from normal menstrual cycles, whether amenor-

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rhoea, polymenorrhoea, or haemorrhage resulting from non-malignant lesions of the endometrium, may likewise be considered as secondary to deranged ovarian function.

Since Knauer¹ in 1896 first demonstrated the effect on the endometrium of ovarian transplants, scores of workers have used various products of glandular origin with a view to correcting menstrual disorders. The demonstration that alcoholic extracts of the human placenta can be separated into three definite fractions, each having distinctive physiological properties, as described in the previous paper, suggests that a clinical trial of each of these fractions should be made. The observations which are herein reported deal in the main with the possible therapeutic value of the 85 per cent. alcohol-soluble fraction (menmenin). A few clinical experiments with the so-called anterior pituitary-like fraction of the placental extract (85 per cent. alcohol precipitate) are also included. As yet similar experiments involving the oestrin-containing fraction have not been carried out. One hundred and twenty-three cases of deranged ovarian function as judged clinically have been treated and observed for periods

FIG. 1.—Five characteristic cases. Note in Case A decreasing intermenstrual periods, and in Case R slight lengthening of interval and period, cycle being established in both cases at twenty-eight days. Case G stopped her extract two days before the period on one occasion, and only had partial relief. With proper administration complete relief was obtained. The fifth case was a problem; even with varying dosage she received no benefit.

FIG. 2.—A purely diagrammatic chart to illustrate the non-effect of emmenin and the apparent effect of the anterior pituitary-like substance of the human placenta in the treatment of metrorrhagia. Injections of this latter extract are shown as X. $1\frac{1}{2}$ to 2 c.cm. were administered, each cubic centimetre representing 25 grams of placenta, or approximately ten rat units. In both La 39 and Le 40 the condition was aggravated with emmenin, but, as in the other cases, relief was obtained with the second principle.

varying from three to nine months. The general results are shown in the accompanying table. All the patients investigated were apparently normal individuals, and pelvic examination revealed no gross or obvious pathological conditions, either in the conformation and size of

Summary of Clinical Cases Treated with Emmen'n.

	Number of Cases.	
	Treated.	Improved.
Amenorrhoea:		
Primary	8	1
Secondary:		
Oligomenorrhoea	20	18
Oligomenorrhoea (with lapses) ...	14	12
Regular (with lapse)	19	11
Polymenorrhoea	8	7
Dysmenorrhoea	35	25
Menopausal symptoms	18	14

the uterus or of its adnexa. From a study of such a comparatively small group of cases for a limited time, we are not justified in drawing final conclusions as to the possible therapeutic value of the agent employed. However, our impressions are as follows.

AMENORRHOEA.

Primary Amenorrhoea.—The results in this group have not been encouraging. Out of eight cases in this group only one apparent success was obtained.

Secondary Amenorrhoea.—The cases of secondary amenorrhoea which have been studied have been arbitrarily placed in one of these groups, according to their histories.

1. *Oligomenorrhoea*: individuals with a diminished or scanty flow, and with periods occurring at irregular intervals of five to eight weeks.
2. Cases similar to No. 1, but having intervals of amenorrhoea of a duration of four months or more.
3. Those with normal menstrual cycles, but with periods of amenorrhoea of upwards of four months' duration.

Encouraging results have been obtained in cases in each of these groups. The duration of the amenorrhoea proved to be of great importance, for no results were obtained where the condition had lasted for more than two and a half years.

We realize that, taken individually, any apparent success might be fortuitous. The apparent response to treatment of cases in this class occurred after an average period of twenty-three days.

POLYMENORRHOEA.

Eight cases with intervals varying from eighteen to twenty-four days were treated. The intermenstrual period was increased in seven cases by four to eight days. A favourable effect on intermenstrual pain was also noted.

MENORRHAGIA AND METRORRHAGIA.

No evidence was obtained which would indicate that the emmenin fraction of human placental extract is of any value in treatment of menorrhagia or metrorrhagia occurring either at puberty or in adult life.

DYSMENORRHOEA.

It is possible that this condition is in some manner related to the lutein phase of ovarian activity. If the

luteal phase were absent during the earlier cycles of the human female (as it is known to be in a certain number of instances in the rat), a simple explanation might be had for the rarity of cases of dysmenorrhoea dating from the first menstrual cycle. Thirty-six cases of dysmenorrhoea have been studied, and only two of these gave a history of the condition dating from the first cycle. Relief was obtained in twenty-six cases of this group.

MENOPAUSE.

Observations of this type of case lead one to conclude that the duration of this symptom-complex is of prime importance, since no relief was obtained in cases of long standing, whereas the symptoms were relieved for a time at least in certain cases where the condition was of recent origin—that is, less than one year since the last menstrual flow.

DOSAGE.

A dose corresponding to 75 grams of placenta daily, given in divided doses in water or orange juice before meals, has been used in the majority of cases. There are individuals who do not tolerate the extract well. The cause of this we do not know; but in any case in which untoward symptoms, such as nausea or vertigo, have been observed, the dose has been temporarily reduced until tolerance was acquired. According to our experience, the use of emmenin does not seem to have any untoward effect on impregnation and gestation. It is worthy of note that four patients became pregnant while under treatment with emmenin for ovarian dysfunction. Thirty-six to forty-eight hours after the institution of therapy, some patients volunteered that they experienced a feeling of general well-being and of mental alertness. No effect on libido was reported. As controls, ten cases with normal menstrual cycles were submitted to treatment for three months without any alteration being noted either in the length of the interval or in the duration of the epoch.

The dosage used in cases of dysmenorrhoea was, as a rule, the equivalent of 25 grams of placenta administered daily for approximately seventeen days, beginning with the cessation of a menstrual period. During the week preceding menstruation (twentieth to twenty-eighth day) the dose was raised to 75 grams daily, and treatment was continued until the onset of the flow, then stopped for a period of about a week. Other individuals with normal cycles obtained relief when treated for seven days preceding the anticipated period.

The second principle (85 per cent. alcohol precipitate, or the anterior pituitary-like substance of placenta) was employed in metrorrhagia. The results in this small group of cases have been most encouraging (Fig. 2), and will be discussed in detail in a later communication. The extract used in these cases contained approximately ten rat units per cubic centimetre, and was administered subcutaneously. No enlargement of breasts or milk secretion occurred with the administration of this hormone. It should be noted here that the diagnosis is essential, and that uterine exploration should *always* precede the treatment. Carcinoma as a cause of metrorrhagia, even in the young, must never be lost sight of.

Of 123 patients observed in this preliminary study, basal metabolism determinations were carried out in practically all instances; 60 were detained in hospital for more detailed and special investigation according to the clinical indications; the sella turcica was x-rayed in 35 cases, sugar tolerance curves were taken in 27 instances, and blood cholesterol was estimated in 20 cases. The Wassermann reaction was carried out in all hospital cases, and this was negative in all cases treated. In three cases in which the basal rate was elevated, normal values followed treatment with emmenin. In another case, one of the oligomenorrhoea group, a mild diabetic condition was detected. No significant changes in blood chemistry have been noted as yet, either before or after treatment, in any of the patients examined. Four cases which manifested the clinical signs of anterior lobe insufficiency were quite unaffected by treatment.

SUMMARY.

1. Emmenin does not alter normal menstrual cycles.
2. Its effect in dysmenorrhoea has been particularly encouraging.
3. It appears to correct certain types of amenorrhoea of recent origin.
4. It definitely lengthens cycles in polymenorrhoea.
5. It relieves menopausal symptoms of recent origin, but does not relieve symptoms in castrates.
6. An anterior pituitary-like principle from the placenta arrests certain forms of metrorrhagia.
7. In the treatment of altered ovarian function the importance of a searching and accurate menstrual history, a detailed medical investigation, and, in addition, a scrutinizing pelvic examination, cannot be overestimated.

We wish to thank Drs. I. M. Rabinowitch and E. H. Mason for their kind co-operation in the study of cases which were treated in the Montreal General and Royal Victoria Hospitals. We are also especially indebted to Drs. Chipman, Fraser, and Little for their advice and helpful criticism, and for the facilities which they have afforded to further this investigation.

REFERENCE.

¹Knauer: *Centralbl. f. Gynäk.*, No. 20, p. 524.

Memoranda: MEDICAL, SURGICAL, OBSTETRICAL.

DEVELOPMENTAL MIXED TUMOUR OF THE KIDNEY IN A PATIENT AGED 80.

THE following case is an example of a rare tumour of the kidney occurring during the eightieth year.

History.—Mrs. S., while walking in the street after completing a morning's shopping, experienced a sudden and unbearable pain in the right side. When examined by Dr. Armstrong Atkinson, shortly after the onset of the attack, a large tender mass, about seven inches in diameter, could be felt in the position of the right kidney. There were no urinary symptoms, and the urine was quite clear, although it contained a trace of albumin.

Examination.—When I examined the patient she was in great agony, but spoke of having been troubled many years previously by a movable kidney, which she was always able to replace by manipulation. The mass in the right kidney area felt like a large acute hydronephrosis, and the patient assured me that it had come with the attack of pain. The condition set up was so distressing that it was necessary at once to look and see what could be done to relieve the pain, rather than to await the result of an x-ray and ureter catheter examination.

Operation.—The same evening Dr. Armstrong Atkinson gave her an anaesthetic, and I exposed the tumour by the oblique incision for the exposure of the kidney. The tumour was dark red in colour, and was continuous at its upper and back part with the right kidney. The kidney therefore, together with the growth, was removed. There appeared to be no shock. The patient made a good recovery. After removal of the tumour and the kidney, the tumour was found to spring from the pelvis of the kidney, extending to the kidney substance. The microscopical report from the pathological department of the College of Medicine, Newcastle-upon-Tyne, was that the condition was a developmental mixed tumour of the kidney of varied structure, and referred to as embryonal myosarcoma, non-striped muscle being a prominent feature in the case, conforming to the condition described by Wilms.

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OVARIAN CYST WITH TWISTED PEDICLE IN A CHILD.

CASES of ovarian cyst with twisted pedicle are very uncommon in the literature. Kincaid and Andrews, in the *American Journal of Obstetrics and Gynecology* (February, 1928), describe a case in a girl, 5 years old, differing only in that they report a palpable mass in the left lumbar region. The authors emphasize the difficulty of differentiating the condition from appendicitis. J. Morris (*British Medical Journal*, 1926, i, 944) records a case in a girl aged 4½ years, successfully treated by operation. J. Leveuf (*Semaine d'Hép. de Paris*, June 30th, 1927)