'PROGYNON'
AND
'PROLUTON'

Schering

The Hormone Therapy of Disturbances of Menstruation, Climacteric Disorders and other Ovarian Deficiencies

CONTENTS.

	PAGE
'Progynon'	4
'Progynon-B Oleosum'	5
'Proluton'	6
General Observations on Therapy with Ovarian Hormones	7
Climacteric Disorders	10
Amenorrhœa	12
Oligomenorrhœa	14
Polymenorrhœa and Menorrhagia	15
Gynæcological Hæmorrhage	16
Dysmenorrhœa	19
Sterility	22
Habitual Abortion	23
Frigidity	25
Extragenital Disorders due to Ovarian Insufficiency (so-called deficiency phenomena)	26
Pruritus and Kraurosis Vulvæ	26
Eczema and Dermatoses	27
Circulatory Disorders	28
Endocrine Arthritis	28
Psychoses and Neuroses	29
Diseases of the Vagina	29
Vulvo-Vaginitis Gonorrhoica Infantum	29
Vaginitis Senilis Atrophicans	30
Emesis Gravidarum	31
Simple Vomiting of Pregnancy	31
Hyperemesis Gravidarum	31
Eclampsia and Pre-eclampsia	31
Inhibition of Lactation	32
Premature Babies	32
General Health Prescriptions	33
References	35
Packings	38

The Hormone Therapy of Disturbances of Menstruation, Climacteric Disorders and other Ovarian Deficiencies

THE early discoveries of the influence produced on the female organism by the hormones of the sex-glands gave rise to the therapeutic use of animal ovaries or extracts in cases of disordered ovarian functions. The results of this organotherapy were, however, inconclusive and, in very many cases, negative. By means of the exact method of identifying the follicular hormone (Allen-Doisy Test), it is known to-day that ovarian preparations contain only very small amounts of hormones, and that fact is recognised as the cause of the frequent failure of organ extracts.

The ovaries do not store their hormones, but continually secrete them into the blood stream. Only the preparation of the ovarian hormones in a pure state from different initial materials and the subsequent ability to concentrate them to any desired degree and to administer them in exact dosage, has led to ovarian hormone therapy on a scientific basis.

With the hormone preparations 'Progynon' and 'Proluton,' it has been possible, for the first time in the history of medicine, to produce true menstruation in women whose ovaries had been removed by operation and to

produce the full development of the secondary sex characteristics (1). Thus the hopes that had been disappointed by organotherapy found their fulfilment in hormone therapy, by means of which complete substitution for the normal ovarian functions can be obtained.

Apart from the follicular hormone and the corpus luteum hormone, no other hormones have to this day been isolated from the ovaries.

Follicular hormone is produced continuously in all the follicles of the ovaries and cyclically, in larger quantities, in the ripening Graafian follicle; also during pregnancy in the placenta. Corpus luteum hormone is found in the corpus luteum into which the Graafian follicle is transformed after ovulation. The placenta produces corpus luteum hormone during the last two-thirds of pregnancy (2).

'PROGYNON.'

The follicular hormone ('Progynon') is a crystalline body having an empirical formula $C_{18}H_{22}O_2$. It is a sterol derivative prepared for the first time in pure crystalline form by Doisy (3) in America and, at the same time, independently of him by Butenandt (4) in Germany, while the latter also elucidated its structural formula.

'Progynon' is standardised in 'International Units' (I.U.). One international unit is 0·1 γ (0.0000001 gram) of a standard preparation deposited in London and known as *Œstrone*.

The follicular hormone is markedly resistant to acids,

bases, ferments and heat, and is indefinitely stable. In contrast to many other hormones, the follicular hormone is not destroyed by the digestive juices, and is, therefore, also active when administered by mouth.

'PROGYNON-B OLEOSUM.'

Certain chemical transformations of the follicular hormone produce a considerable increase in its biological activity Thus Butenandt (5) has discovered that esterification with benzoic acid considerably prolongs the biological effect of the hormone, a point which is obviously of great value for therapeutic purposes. In the head laboratories of Schering, A. G. Schwenk and Hildebrandt (6) succeeded in increasing the activity of the follicular hormone from five to eight times by its hydrogenation to the so-called **dihydro-follicular hormone.**

Two years after the dihydro-follicular hormone had been prepared by chemical methods, Doisy and his co-workers (7) working on 1,500 kilos of pig's ovaries, were able to show that the follicular hormone is present in the ovaries in that form. Accordingly, the body hitherto known as follicular hormone ($C_{18}H_{22}O_2$) must be looked on as a product of excretion **of the true ovarian follicular hormone ($C_{18}H_{24}O_2$).**

The benzoic ester of the dihydro-follicular hormone will be seen from the foregoing remarks to be the most active form of the follicular hormone for therapeutic purposes. It was put on the market under the name **'Progynon-B Oleosum'** and rapidly gave excellent results

in the therapeutic treatment of severe cases of ovarian deficiency.

The great importance of ' Progynon-B Oleosum ' (dihydro-follicular hormone benzoate) in therapy has been recognised by the creation by the Standardisations Committee of the Permanent Health Commission of the League of Nations, in London, 1935, of a special standard preparation for the dihydro-follicular hormone benzoate in its purest form. 0·1 γ of this substance, known as Œstradiol monobenzoate, is one ' International Benzoate Unit ' (I.B.U.). In the rat, the monkey and clinically in women, the Benzoate Unit has the effect of 5-8 ' International Units ' with a prolonged time of activity.

' Progynon-B Oleosum ' is made in ampoules of 1 mg. (10,000 I.B.U.) and 5 mg. (50,000 I.B.U.). If smaller doses are indicated, the oral administration of ' Progynon ' dragées gives excellent results.

For the easier handling of the injection preparations, the ampoules of 1 mg. (10,000 I.B.U.) have been denoted by ' Progynon-B Oleosum ' and those of 5 mg. (50,000 I.B.U.) by ' Progynon-B Oleosum Forte.'

' PROLUTON.'

According to its constitutional structure, the corpus luteum hormone (' Proluton ') is related to the follicular hormone and has the empirical formula $C_{21}H_{30}O_2$. This hormone, called ' progesterone,' was first produced in crystalline form by Butenandt (8), who also elucidated its structural formula.

The Standardisation Commission of the Hygiene Committee

of the League of Nations has defined one 'International Unit' as 1 mg. of progesterone.

The manufacture of appreciable quantities of corpus luteum hormone remained extremely difficult as long as it was necessary to extract it from ovaries. In order to obtain only 1 gram of corpus luteum hormone, the ovaries of more than 50,000 pigs were required. Not until Butenandt (9) once again had shown us the way to its synthetic production, were we able to prepare the hormone from a vegetable sterol. Experimental and clinical research have clearly shown that 'Proluton' prepared by chemical means corresponds exactly to the naturally occurring product.

In contrast to the follicular hormone, the corpus luteum hormone loses its activity when subjected to the action of acids, and, as yet, its therapeutic administration per os is useless.

GENERAL OBSERVATIONS ON THERAPEUTICS WITH THE OVARIAN HORMONES.

The follicular hormone is the actual female sex hormone which, apart from its effect on the sexual organs, also determines the female habitus and psyche. The corpus luteum hormone's action, on the other hand, is limited to the specific changes in the uterus necessary for the nidation of the fertilised ovum and the maintenance of pregnancy.

Both ovarian hormones are substances naturally occurring in the body and capable of passing into the urine, and even

in very high therapeutic doses* are devoid of harmful effects.

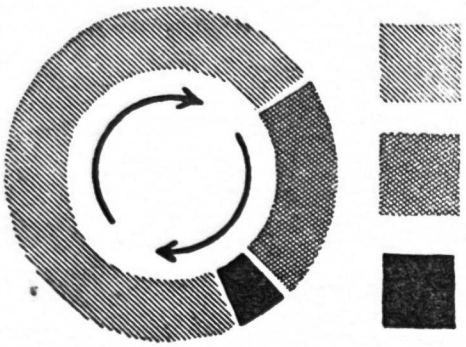
American workers (10) administered large doses of follicular hormone to healthy women for a period of three months during which regular investigations of the weight, metabolic rate, blood pressure, blood picture (hæmoglobin %, red cell count, leucocyte count, coagulation time, etc.) were carried out. In a few of these women there was a slight increase in the size of the mammæ and the 'libido' was rather more marked. No other effects of any kind were observed.

The enormous amounts of follicular hormone which are produced and excreted during pregnancy clearly show that the artificial administration of this hormone can never produce abortion, and this fact has also been confirmed experimentally. In cases of early pregnancy in which the termination of pregnancy was indicated for medical reasons, many millions of units of follicular hormone were injected and in no single case did abortion occur (11). On the other hand, Jeffcoate (12) was able to show that in cases of missed abortion, or intra-uterine death of the fœtus, 'Progynon' brought about satisfactory evacuation of the uterus.

For the successful therapeutic use of 'Progynon' and

* The large figures of the so-called high doses have a confusing effect. Actually, it amounts to much the same thing as expressing the height of a human being in millimetres. The dose does not appear at all high as soon as we express the amount of hormones used in terms of weight. The maximum doses of 'Progynon-B Oleosum Forte' necessary to obtain menstruation, *i.e.*, 250,000 I.B.U., corresponds to an amount of 0.025 grams of 'Progynon-B,' which is distributed over 20 days.

'Proluton,' it is necessary constantly to bear in mind the physiological course of the menstrual cycle in women :—



Follicular hormone phase ('Progynon').
Luteal hormone phase ('Proluton').
Menstruation.

The production of follicular hormone by the Graafian follicle produces intense growth of the uterine endometrium, the so-called 'proliferative phase' of the endometrium. At the end of about 14 days, the process of maturation is complete and the Graafian follicle ruptures. The ovum escapes and is taken up by the Fallopian tube. The empty follicle becomes converted into the corpus luteum. The latter secretes the corpus luteum hormone, which has the task of transforming the proliferated endometrium into the functional stage, which is also known as the 'secretory phase,' and thus of preparing for the nidation of the ovum.

Should the ovum fail to become fertilised, it dies and the corpus luteum degenerates. The highly developed endometrium breaks down and is expelled from the uterus accompanied by hæmorrhage. Menstruation thus occurs. This process takes place in regular 28-day cycles.

The first half of the intermenstruum thus corresponds to the follicular hormone phase and to the stage of proliferation of the endometrium, while the second half is the corpus luteum phase and the secretory stage of the endometrium.

It is of outstanding importance that the therapeutic use of the hormones should be adapted to the physiological conditions, as regards the time they are given and the quantities, *i.e.*, **'Progynon' should be given only during the first half of the intermenstruum and 'Proluton' only during the second half, and their times of administration should never coincide.** This is not, of course, possible with total ovarian extracts.
It is difficult to give a dosage scheme for 'Progynon' and 'Proluton' covering every individual case, but nevertheless the following dosage schemes have been worked out in collaboration with the leading authorities in the field of hormone therapy, and these may offer some guidance.*

CLIMACTERIC DISORDERS.

The normone therapy of climacteric disorders with 'Progynon' is based on the well-known rejuvenation of senile animals by 'Progynon' (13).
The best-known forms of ovarian deficiency in the menopause are the vasomotor disturbances, 'hot flushes,' etc. These complaints, well-known to all doctors, react very favourably to 'Progynon' therapy with 3 to 4 'Progynon' dragées per day. Severe forms in which 20 to 30 and even more flushes occur within 24 hours should be treated with the preparations 'Progynon-B Oleosum' and 'Progynon-B Oleosum Forte,' injected once or twice a week. In order to produce rapid relief of symptoms in cases associated

* *Schering Limited would like to take this opportunity of pointing out that suggestions and comments on the clinical application of their hormone products are always at the disposal of practitioners.*

with severe ovarian deficiency, it is advisable to begin with injections of 'Progynon-B Oleosum Forte' twice weekly combined with 1 dragée 4 times daily by mouth. As soon as the symptoms have been brought under control, the dosage may be reduced by incorporation of 10,000 I.B.U. strength. Relapses are to be anticipated from time to time, however, owing to sudden variations in hormonal level.

The dosage should be adapted to the requirements of the patient. At times no treatment at all will be needed, or only dragées, on the other hand, injections may have to be resumed. Such variations in the hormone level are quite normal and the recourse to treatment will diminish as the organism becomes accustomed to the lack of œstrin. In some women this readjustment takes but a few months, in others even several years. This should be explained to the patient and she should be instructed to return for further treatment directly the slightest symptoms of a relapse are noticed. Menopausal disturbance of recent origin responds much more readily to œstrin treatment than the long-standing cases.

Kaufmann (14), as a result of extensive experience, was able to state that this treatment has proved successful in those cases to which the most diverse forms of therapy had formerly been applied without avail. Similar opinions are expressed by almost all authors who have occupied themselves with the hormone treatment of climacteric disorders (15). 'Progynon' produces marked enhancement of the physical and mental condition in women at the climacteric. Sleep, which is so commonly

deranged at this time of life, becomes normally deep and and refreshing again. Headache, migraine, and psychic disturbances, which are also common symptoms of the menopause, are also relieved by ' Progynon.'

Extending far beyond the aforesaid complaints, which were formerly almost exclusively grouped together as ' climacteric disorders,' many other conditions have in recent years been shown to be symptoms of deficiency in the menopause or of ovarian insufficiency. Kaufmann reported as follows at the Tenth British Gynæcological Congress in Belfast (1936) :—' There is hardly a disturbance of the entire organism which cannot upon occasion arise from deficient hormone secretion.' Particularly impressive is the relief of severe skin conditions of many years' duration, by means of ' Progynon.' Such cases demonstrated for the first time the close connection between the function of the genital glands and the skin.

AMENORRHŒA

The fact that the follicular hormone not only influences the uterus and secondary sex characteristics in woman, **but also affects the function of the ovaries** as a result of its action on the anterior pituitary (16), is of decisive importance in the treatment of amenorrhœa. This explains the resumption of spontaneous menstruations after treatment with ' Progynon.'

Primary Amenorrhœa.

According to our present experience, permanent results are only seldom obtained with ovarian hormone treatment in

true primary amenorrhœa with a high degree of infantilism (hypoplasia of the genital organs). On the other hand, a definite increase in the size of the uterus is often brought about in a few weeks by two injections per week of one ampoule of ' Progynon-B Oleosum Forte.' When adequate increase of the size of the uterus is attained or if there is in the first place no marked hypoplasia of the uterus, it is possible to produce artificial menstruation by cyclic treatment. The cyclic treatment is carried out in the following manner:—Five injections of ' Progynon-B Oleosum Forte,' distributed over 20 days, are given, supplemented by the oral administration of 1 dragée four times daily over a similar period, and thereupon from the 21st to the 25th day 5 mg. of ' Proluton ' are administered each day. At the beginning rhythmic treatment with ' Progynon ' alone is recommended until the uterus has developed to almost normal size. Extragenital signs of deficiency, which frequently accompany amenorrhœa, are almost always eliminated by the hormone therapy.

Secondary Amenorrhœa.

Far more common than the above are disturbances in the follicle ripening process in women who have already menstruated regularly for a longer or shorter period. The secondary amenorrhœa resulting in such cases is usually overcome by the administration of ' Progynon.' On the basis of considerable experience it is possible to say that in at least 25 per cent. of cases, spontaneous menstruation persists after the cessation of treatment.

Not infrequently treatment is given up as unsuccessful too early, after perhaps 4 to 6 months ; but even then it has

been reported that many months later menstruation has begun spontaneously. It seems, therefore, that even in amenorrhœa there is still a cycle present which does not come to bleeding; if, however, the pendulum is pushed sufficiently it will swing again later of its own accord (17).
The treatment of secondary amenorrhœa is in many cases successful when 'Progynon' alone is administered. In this case, 5 ampoules of 'Progynon-B Oleosum Forte' (likewise distributed over 20 days) and supplemented by dragées orally as mentioned above, are given, followed by an interval of 10 days; during such intervals menstruation often occurs. Sometimes success is only obtained by much higher single doses as shown by Foss (17).
Frequently, the injection of 'Progynon-B Oleosum' is sufficient—or in some cases even the taking of 'Progynon' dragées alone—particularly in the case of secondary amenorrhœa of only a few months' standing. In very obstinate cases persisting over many years, combined 'Progynon-Proluton' treatment, as described for the therapy of primary amenorrhœa, is nevertheless advisable, but should be preceded by three or four courses of rhythmic treatment with 'Progynon B Oleosum Forte' alone.
Patients not infrequently cease to menstruate for a few months after treatment, but without further treatment they resume spontaneous menstruation a few months later and remain regular.

OLIGOMENORRHŒA.

In this condition, where the menstrual loss is scanty, it is important to remember that there is nevertheless a definite

cycle present and that, therefore, smaller quantities of follicular hormone should be employed than in complete amenorrhœa (18). As a rule, it is sufficient to give 1 or 2 injections of ' Progynon-B Oleosum ' during the first half of the cycle, supplemented by 2 or 3 dragées daily for the same time.

POLYMENORRHŒA AND MENORRHAGIA.

The term polymenorrhœa is used to designate the occurrence of bleeding at too frequent intervals. In these cases, menstrual bleeding is also often excessive (menorrhagia). Both of these symptoms are due to too early onset of the corpus luteum phase (premature ovulation). The appearance of menstruation can, therefore, be deferred by means of substitution therapy with ' Proluton.'

The daily injection of 2-mg. ' Proluton ' on 3 or 4 days preceding menstruation is, in most cases, sufficient to delay the flow a few days.

In many cases of polymenorrhœa, it is also possible to prolong the cycle by giving 1 to 2 injections of ' Progynon-B Oleosum ' during the first few days of the intermenstruum (19).

The prolongation of the corpus luteum phase by means of follicular hormone is explained by the experimental researches of Hohlweg (20), who showed that by reason of its action on the hypophysis, the follicular hormone promotes the formation of the corpus luteum.

For those cases presenting difficulty under this treatment see ' Testoviron ' literature.

GYNÆCOLOGICAL HÆMORRHAGE.

Irregular uterine hæmorrhages are particularly common in young girls at the time of the menarche and in women at the climacteric, but can occur at any time during the existence of the female cycle, and even sometimes after the menopause.

To determine the cause of any uterine bleeding, it is strongly advisable first of all to have an endometrial biopsy performed in order to exclude tumour formation, particularly of a malignant nature, and any possible causes other than those of hormonal origin.

If the hæmorrhage is hormonal in origin, then especially in juvenile and climacteric bleeding, one will generally find glandulo-cystic hyperplasia of the endometrium (metropathia hæmorrhagica). There are, however, other cases of metrorrhagia in which the cause may be an atrophic endometrium or an endometrium which is not able to build up a full proliferation phase. A third possibility is for the proliferation phase to be only partly or not fully developed into the secretory phase. It cannot be too strongly emphasised how important it is to determine the underlying cause before treatment is instituted, otherwise one must risk failure in treatment. Endometrial biopsy should be performed wherever possible, and the day before the onset of menstruation is the optimum time at which to do this. A guide to the interpretation of endometrial material is given in (21).

Treatment.

In all cases of metropathia hæmorrhagica (glandulo-cystic hyperplasia of the endometrium) a persistent follicle

which has not ruptured and not become transformed into a corpus luteum, is the source of the trouble. Due to this persistence, huge quantities of follicular hormone are produced and these lead to hyperproliferation of the uterine mucosa, from which bleeding takes place irregularly, more or less severely. The logical treatment is to bring about transformation of the hyperproliferation phase into a fully developed secretory phase by means of the luteal hormone and this can be done usually with 8 to 10 injections of 'Proluton' 5 mg. on consecutive days. Sometimes it is necessary to give 'Proluton' for a longer time and even double dosage (10 mg.) per injection, but at least 8 to 10 injections should be given, even if bleeding ceases after the second or third day.

Several days after ceasing 'Proluton' treatment, bleeding may commence and this must be regarded as true menstruation, the hyper-proliferated mucosa having been transformed under the influence of luteal hormone into a normal secretory phase. After withdrawal of 'Proluton' physiological disintegration of the endometrium takes place.

This treatment produces very satisfactory results, especially in juveniles (22), but it is not always so successful in metropathia hæmorrhagica of the climacteric. Hamblen (23) comes to the conclusion that previous follicular hormone administration sensitises the endometrium to the action of luteal hormone. He finds that in these cases where luteal hormone alone is not satisfactory, he obtains excellent results if the patients are previously treated with follicular hormone. The technique he suggests is an

injection every fourth day of 'Progynon-B Oleosum Forte' 50,000 I.B.U. for 5 injections in all. During this period, 1 dragée 4 times daily should also be given; then 3 days' interval is allowed, after which an injection of 'Proluton' 5 mg. is given each day for the following 5 days.

Latest clinical research work (24) has shown that excellent and permanent results can be obtained with 'Testoviron' treatment. 'Testoviron' is testosterone propionate,*a male hormone which is very closely related chemically to the luteal hormone (25).

Castration should never be performed for bleeding in young women before hormone treatment has been given a thorough trial, and many a woman will be grateful if she can be spared surgical or X-ray treatment. (See 'Testoviron' brochure.)

In cases of bleeding from an atrophic endometrium or where there is an insufficiently developed proliferation phase, treatment has first to be given with dihydrofollicular hormone benzoate. If the endometrium is atrophic, at least 5 injections of 'Progynon-B Oleosum Forte,' 1 twice weekly, supplemented by dragées 4 times daily over a similar period, have to be given. This alone may in some cases be sufficient, but in other cases before bleeding can be checked and stopped it may be necessary to follow up with 5 injections of luteal hormone, 'Proluton.' In cases where there is only a partly developed or under-

*Korenchevsky even goes so far as to call it a 'bisexual' hormone. Parkes considers 'ambi-sexual' a better term.

developed proliferation phase, the dosage might not necessarily need to be so high.

For the third type of endometrial state, where the endometrium is only partly or insufficiently transformed into the secretory phase, the treatment suggested is as follows :—If a cycle can be distinguished, an injection should be given on the 5th day and 8th day of the cycle of 10,000 I.B.U. ' Progynon-B Oleosum,' and on the 12th day, 1 of 50,000 I.B.U. (a special stimulus for the rupture of the follicle). From the 5th to 18th day 1 ' Progynon ' dragée should be prescribed, 3 times daily. Then on the 23rd, 24th, 25th, 26th and 27th days, 1 injection of ' Proluton ' 5-mg. should be administered daily. This, for instance, can only be given as an idea of the rhythm and dosage. It depends on individual cases which strength should be chosen; in certain cases, ' Proluton ' 2-mg. might be sufficient. In cases where no cycle is recognisable, cyclic treatment must, nevertheless, be given, in an attempt to produce a definite rhythm in the patient.

DYSMENORRHŒA.

Experience shows that true cases of dysmenorrhœa are relieved to a very considerable extent with endocrine therapy (26), but it must be stressed at the outset that it is only cases of **true** dysmenorrhœa which will be influenced, and not all cases of pain associated with the menstrual flow, for example, pelvic diseases such as uterine polypi, stenosis, post-operative conditions and adhesions following pelvic inflammation, must be distinguished (27). Of cases of dysmenorrhœa which respond to hormonal treatment we can distinguish the congestive and spasmodic types.

The congestive type (generally characterised by pain before the onset of the period, which improves as the flow becomes free). Sometimes, an acutely anteflexed uterus with a hard body and elongated cervix is found ; sometimes the uterus is more or less markedly under-developed. In such cases, the follicular hormone, ' Progynon,' is indicated, but since considerable time is required for the uterine muscle to become developed and strengthened for its task, it is advisable, at least during the first 3 to 4 months of treatment to follow up the follicular hormone with luteal hormone (in order to obtain regularity of the uterine contractions).

The spasmodic type (generally characterised by irregular and cramp-like pain during menstruation). The genital organs often appear entirely normal and sufficiently developed. In these cases, the luteal hormone, ' Proluton,' is indicated, since it has been demonstrated that the corpus luteum hormone regularises contractions of the uterine musculature (28) ' Proluton ' treatment must naturally be given immediately before menstruation should occur.

It seems, however, that sensitising of the uterus to the effect of luteal hormone is obtained by previous administration of follicular hormone (29). Even in the spasmodic type, therefore, it is better to combine follicular and luteal hormone treatment.

For two entirely different reasons, therefore, the following method of treatment is recommended for the congestive as well as the spasmodic types :—Counting the 1st day of the last menstrual period as Day 1, an injection of ' Progynon-B Oleosum ' 10,000 I.B.U. should be given on

the 5th and 12th days of the cycle. (If 3 injections seem advisable, give these on the 5th, 8th and 12th days.) The injection on the 12th day may be of 50,000 I.B.U., particularly if a special stimulus for ovulation is desired. In women who do not menstruate in a 28-day cycle, this last injection should be timed for the day before that on which ovulation may be assumed to take place. The first injection on the 5th day of the cycle should be given, even if the menstrual flow still continues. Then, an injection of 'Proluton' 2-mg. should be given on the 5th, 4th, 3rd and 2nd days before the expected onset of menstruation. (If necessary, 5 injections of 2-mg. from the 6th to 2nd days before the period may be given, or the dosage even increased to 5 mg. per injection.)

In cases where the patient does not menstruate in a 28-day cycle, the injections of 'Proluton' must be adapted accordingly, but later during treatment an attempt should be made to train the patients gradually to a 28-day rhythm. It is fairly certain that it will be necessary to train the cycle for at least 5 or 6 months before an attempt to lower the dosage is made. In cases of dysmenorrhœa of several years' standing, it may even be necessary to continue treatment for about one year, before it can be hoped that the cycle has been "regulated," and that patients will continue to menstruate satisfactorily of their own accord. This especially refers to the spasmodic type of dysmenorrhœa. In the congestive type with under-development of the sex organs, treatment will have to be given without interruption, at least until the organs have developed to normal size, before an attempt is made to find out if the

dysmenorrhœa will recur when treatment is discontinued. In view of the lengthy treatment required and that the patient has to attend for injections on definite days, great interest has been shown in the paper by Desmarest and Capitain (30) on the treatment of dysmenorrhœa with 'Testoviron.' (See 'Testoviron' literature.)

STERILITY.

The hormone treatment of sterility, according to the experiences of the Univ. Frauenklinik der Charité, Berlin often leads to success (31). The indication is present when there are associated irregularities of menstruation, such as amenorrhœa, dysmenorrhœa or oligomenorrhœa. But even when no outward signs of the ovarian origin of the condition are present, it is not uncommon to find, despite normal menstruation and a regular cycle, minor degrees of genital hypoplasia, such as a long, pointed cervix and acute anteflexion, which suggest the administration of 'Progynon' (32). Here again 2 to 3 ampoules of 'Progynon-B Oleosum' are given during the first 14 days following menstruation.

In cases of sterility with normal pelvic findings Buschbeck employed the following technique:—He injected 1 ampoule 'Progynon-B Oleosum Forte' on the day before that on which it is believed the follicle ruptures, *i.e.*, in a 28-day cycle the 12th or 13th day. This technique might also be applied in the treatment of anovular menstruation where patients are for this reason sterile.

If no signs of follicular hormone deficiency are present, it may be that the sterility is due to the loss of a fertilised

ovum with the menstrual flow, the failure of the ovum to nidate being due to insufficient development of the decidua as a result of deficient corpus luteum hormone secretion. Such cases are really a borderline type of habitual abortion. Here again the diagnosis is greatly facilitated by a biopsy test to determine whether or not the endometrium develops a complete secretory phase. If one begins with the daily injections of 2 mg. 'Proluton' from the 5th to 2nd day before the expected onset of menstruation, it is possible to obtain better development of the pregravid endometrium and hence to secure better conditions for the nidation of the ovum.

It is obvious that, in every case, the institution of hormone therapy should be preceded by the careful exclusion of organic changes such as occlusion of the tubes, retroflection of the uterus, mechanical obstacles to conception in the vagina (scars, etc.), and that the male partner of the marriage should be carefully examined beforehand.

HABITUAL ABORTION.

Deficient secretion of corpus luteum hormone during pregnancy results in abortion. Habitual abortion is best treated prophylactically with 'Proluton' (33), but it is even possible to secure the persistence of pregnancy after hæmorrhage has commenced.

It should be mentioned that all children that have to date been brought into the world—thanks to 'Proluton' therapy—are completely healthy and that, therefore, it is wrong to express the view that habitual abortion is a natural selective process for the prevention of monsters. The

cause of habitual abortion seems to lie not in the ovum but rather in hormone insufficiency alone.

Women who have frequently had abortions at intervals of less than one year should be warned not to become pregnant for a further year, so that a better chance of preserving pregnancy later on may be given.

During the waiting period it is advisable to give treatment on the following lines:—10,000 I.B.U. 'Progynon B. Oleosum' on the 5th and 12th days of the cycle together with one dragée three times daily from the 5th to 18th day. This is followed by 4 to 5 injections of 2 mg. 'Proluton' from the 7th to 2nd days preceding menstruation, thus creating a better nidation place.

After pregnancy has been established the safest method is to give an injection of 'Proluton' 2 mg. twice weekly, and always 24 hours before the day on which the menstrual period would have commenced if the patient were not pregnant, 1 injection of 'Proluton' 5 mg. If the 2 mg. injection is due near to the date of the menstrual period the injection of 5 mg. of course then replaces this.

It is very strongly recommended to keep at hand ready for emergency a box of five ampoules 'Proluton' 5 mg. so that if, in spite of all precautions bleeding should commence, an injection of this may be given on five consecutive days. Even if the hæmorrhage ceases after the 2nd or 3rd injection, the full course of five should be administered. If bleeding does not lessen considerably or cease within 12 to 24 hours, treatment must be intensified to 10 mg. 'Proluton' daily given either in one or two injections.

If the patient cannot afford treatment along these lines for

the whole pregnancy, the next best thing would be to give it for six weeks, three before and three after the time when abortion has occurred previously and if economically possible, also, 24 hours before every menstrual date, an injection of 5 mg.

Some further prescriptions are advisable: the patient should be kept in bed for the time when her menstrual period would have been present, preferably one day previous to and after these days. During pregnancy only mild laxatives should be used, and at the dangerous times (as calculated from previous menstrual dates) even these should be avoided if possible.

The patient should be kept in bed for as long as possible at the times when abortion has taken place previously. Food rich in vitamins is recommended (fresh fruits, salads, raw vegetables) especially including Vitamins C and E (wheat germ oil). Calcium treatment during the whole pregnancy, and sometimes small doses of thyroid are helpful.

It must be borne in mind that ' Proluton ' should not be given longer than the 9th month of pregnancy in order not to retard labour and make the birth more difficult on account of the growth of the child.

There seems to be evidence that once the spell of habitual abortion is broken with ' Proluton,' following pregnancies go on normally without further treatment.

FRIGIDITY.

Frigidity is in so large a degree a psychological condition that the prospects of hormone therapy in such cases can

only be estimated after a detailed psychological examination of the patient. If other signs of ovarian dysfunction are also present, the employment of hormone therapy is more readily justified.

EXTRA-GENITAL DISORDERS (SO-CALLED DEFICIENCY SYMPTOMS) IN OVARIAN INSUFFICIENCY.

In the treatment of general symptons due to ovarian deficiency it is important to differentiate between :—

(1) Younger patients in whom it is necessary to restore a normal menstrual cycle ; and
(2) Older women at the menopause, in whom only the generalised physical and mental disturbances have to be dealt with.

In the first type of case, treatment should be carried out cyclically on the same lines as that described for amenorrhœa. In the second class, treatment may be given continuously until the symptoms disappear.

Pruritus and Kraurosis Vulvæ.

Very remarkable and permanent results can be obtained with ' Progynon ' in pruritus of the external genitalia, a condition which causes great distress to many women at the climacterium (34). In severe cases, in which the skin of the external genitalia undergoes kraurotic changes, relatively large doses (twice or three times weekly 1 injection of ' Progynon-B Oleosum Forte ' 50,000 and even up to 250,000 I.B.U.) combined with dragées 1 four times daily are often necessary. As soon as the condition of the vulva

and vagina is sufficiently improved to permit of absorption, 'Progynon' vaginal suppositories should also be employed twice daily, thereby enabling the 'Progynon' to exert a more local action. The dosage recommended is 1 suppository twice daily inserted high into the vagina, combined with the usual injections. The fact that in some cases kraurosis vulvæ leads to carcinoma of the vulva adds further significance to the possibility of curing this disease by hormone therapy.

Eczema, Alopecia, Acne Rosacea, Dermatitis Herpetiformis.

These conditions are also frequently the expression of deficient ovarian secretion at the menopause. In cases of secondary amenorrhœa and also in minor degrees of disturbances in menstruation, Kaufmann was able to cure very severe cases of papillomatous eczema and ulceration of the mucous membranes as well as periodically recurring forms of dermatitis by the simple administration of 'Progynon' without recourse to any form of local treatment whatsoever. It is noteworthy that skin conditions due to ovarian deficiency are not confined to the genital and anal regions, but may also be localised on the face, the buttocks and the extremities.

'Progynon' has also been successfully employed in cases of **Psoriasis** associated with menstrual anomalies.
If the women suffering from skin conditions of an endocrine origin are of an age where menstruation can occur, the treatment must be carried out cyclically. In the case of women in the menopause, on the other hand, 1 ampoule

of 'Progynon-B Oleosum' or 'Progynon-B Oleosum Forte' is injected twice or three times a week supplemented by dragées 1 three times daily and vaginal suppositories if the vulva is affected, until the symptoms disappear. It has been found that the skin conditions often require larger doses (up to 50,000 to 250,000 I.B.U. of 'Progynon-B Oleosum' three times a week) than other symptoms of deficiency.

Circulatory Disorders.

The observation that patients suffering from cold extremities experienced a sensation of warmth several hours after injections of 'Progynon' led Teitge (35) to investigate the hormone treatment of poor peripheral circulation such as acrocyanosis, endangiitis obliterans, etc.

Although no influence was noted in gangrene either in Raynaud's disease or diabetes, good results were recorded in endangiitis and ulcus cruris. In general the patient received an injection of 10,000 I.B.U. 'Progynon-B Oleosum' on alternate days. In ulcus cruris higher doses were needed in several cases. A weekly injection of 10,000 I.B.U. 'Progynon-B Oleosum' was given for a period to prevent relapse. The treatment was successful in both male and female cases.

Investigations are being undertaken regarding the therapeutic value in chilblains.

Endocrine Arthritis.

Joint disease is very common in women at the climacterium. Leading physicians, such as v. Bergmann(36), Marañon(37),

G. A. Wagner (38) *et al.*, have described the cure of obstinate chronic disease of the joints by means of ' Progynon-B Oleosum.'

Endocrine arthritis has clinically a certain resemblance to gout, particularly in its tendency to begin in the finger-joints and the comparatively late involvement of the large joints, of which the knee joints are affected with special frequence. As a rule 2 to 3 injections of ' Progynon-B Oleosum ' per week, supplemented by 1 dragée three times daily, are sufficient to eliminate arthritic disorders of hormone origin.

Psychoses and Neuroses.

It is only recently that neurologists have taken up the question of the hormone origin of psychiatric diseases. **Depressive psychoses** of the menopause react best to ' Progynon ' therapy, but a number of reports have been received of good results in **epilepsy** of ovarian origin and in early cases of **schizophrenia** (39). **Organ neuroses,** particularly disorders of the heart and alimentary tract in the climacterium, frequently subside rapidly under ' Progynon ' treatment.

DISEASES OF THE VAGINA.

Vulvo-Vaginitis Gonorrhoica Infantum.

It is a matter of experience that the delicate vaginal mucosa of children reacts far more severely to gonococcal infection than the mucosa of adult women. For this reason an attempt has been made to utilise the proliferative effect

of the follicular hormone in gonococcal infections of the vagina in children. Many reports have been published testifying to the fact that by the injection of 1 ampoule of 'Progynon-B Oleosum' per week, supplemented by one dragée four times daily, it is possible to influence favourably the course of the disease (40).

As soon as the severe inflammation of the genital sphere has subsided in the child under 'Progynon-B Oleosum' injection treatment, one should introduce into the vulva one 'Progynon' vaginal capsule twice daily. This local treatment is highly successful and free from the secondary effects which injections of oestrogens sometimes produce, for instance, congestion in the lower pelvis and swelling and tenderness of the breasts, these symptoms, of course, disappear as soon as treatment is discontinued.

Vaginitis Senilis Atrophicans.

The atrophic, senile vaginal mucosa of women in the menopause is also easily subject to infection. Without resorting to tedious treatment with caustics, antiseptics, etc., it is possible to cure the vaginitis with 'Progynon' by stimulating the atrophic epithelium of the vaginal mucosa to resume normal proliferation (41). Success is obtained by the injection of 2 ampoules of 'Progynon-B Oleosum Forte' per week combined with dragées orally, 1 four times daily. As soon as relief has been obtained with injections, 1 'Progynon' vaginal suppository should be given twice daily for some weeks in order to prevent relapse. The suppositories then replace the dragée treatment per os.

EMESIS, HYPEREMESIS GRAVIDARUM ECLAMPSIA AND PRE-ECLAMPTIC STATES.

Simple Vomiting of Pregnancy.

This is quite frequent during the first months of pregnancy and may be controlled by injections of 'Progynon-B Oleosum' 10,000 I.B.U. given every other day, if necessary increasing for some time to daily injections, or going up to 50,000 I.B.U. until vomiting has been completely controlled for two or three days. In order to avoid relapses, it is advisable to continue with 'Progynon' dragée treatment (one, two or three times daily).

Hyperemesis Gravidarum.

This is much more rare and may be considered as a toxicosis or pre-eclamptic condition. During the first few months of pregnancy, we suggest 'Progynon-B Oleosum' treatment as for emesis gravidarum, but after the fourth month of pregnancy, 'Proluton' treatment every day (2-5 mg.) until complete cessation of vomiting. It is advisable to continue with 'Proluton' treatment, but gradually to lengthen the intervals at which it is given and to lower the dosage.

Pre-Eclamptic Symptoms and Eclampsia.

'Proluton' 5 mg. three-hourly until the subjective and objective symptoms have disappeared. Here it is also advisable to continue treatment for some time, but gradually to lengthen the intervals and decrease the dosage (42). 'Proluton' treatment should not be continued

beyond full term of pregnancy otherwise growth of child may complicate delivery.

INHIBITION OF LACTATION.

Only after the fall of the follicular hormone level in the blood after the completion of birth or premature birth, does the milk secretion in the mammary gland commence, probably under the influence of a specific hormone from the pituitary (lactation hormone, prolactin). If large amounts of follicular hormone (1 or 2 ampoules of 'Progynon-B Oleosum Forte' per day) be administered to a patient lying-in, the milk secretion dries up again in a few days, without any symptoms of blocking in the breast. 'Progynon' has also proved a useful remedy in puerperal mastitis or in milk fistulas after incision of mammary abscess. Mayor (43) has obtained in every case excellent results with 'Progynon' in 47 cases of women where inhibition of lactation was indicated owing to the death of the child. Jeffcoate (44) has recently reported that lower dosage with dragée treatment is also often successful in inhibiting lactation.

PREMATURE BABIES.

Œstrin administered orally to premature babies directly after birth has been shown not only to arrest the initial loss but also to bring about a satisfactory increase in weight. Furthermore, the general condition of the infant is greatly improved, feeds are taken more readily and there is less cause for anxiety. The rate of mortality in prematurely born infants is high, and it is interesting to note that the

report from one hospital states that not a single death has occurred since œstrin treatment was instituted (45). In general the dosage is 5 to 10 drops of 'Progynon-B' solution twice daily morning and evening, according to the weight of the child. Treatment should be commenced early following birth. Some authors state on the first day, others on the second or third day. The administration of 'Progynon' should be continued until the infant has adapted itself to its ex-uterine environment. It is generally recommended that treatment be carried out until the baby has reached normal birth-weight (6 to 8 lbs.).

GENERAL HEALTH PRESCRIPTIONS.

In all the fore-mentioned indications it is advisable to combine the hormone treatment with general health prescriptions because it is necessary to establish as satisfactory a condition of general health as possible. Simple, healthy and regular habits should be cultivated and an adequate and regular diet maintained. Food should be rich in vitamins—plenty of salads, vegetables and raw fruit and not too much meat, but avoid slimming cures. Fresh tomato, lemon or orange juice, should be taken in preference to other beverages and an excess of tea and coffee avoided.

Sleep should be sufficient and regular, beginning before midnight, and open-air exercise, without over-doing sport should be carried out as a routine. In cases of dysmenorrhœa, scanty menstruation, and sterility, special exercises to improve the circulation and strengthen the musculature of the pelvis are advisable.

Alcohol and—especially—nicotine abuse should be avoided, as also should the administration of aperient drugs, intestinal regularity being brought about as far as possible by food and exercise.

Where there is a likelihood of deficiency of calcium or thyroid, concomitant treatment with either or both of these may be safely undertaken, often with very great benefit.

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ORIGINAL PACKINGS.

'Progynon' Dragées :

Bottles of 30, 60 and 250 dragées containing 1,000 International Units per dragée.

'Progynon' Vaginal Capsules :

Boxes of 20 capsules containing 0.25 mg.

'Progynon' Vaginal Suppositories :

Boxes of 20 suppositories containing 0.36 mg.

'Progynon-B Oleosum' :

Boxes of 5 amouples of 1 c.c containing 1 mg. œstradiol benzoate corresponding to 10,000 International Benzoate Units per ampoule.

'Progynon-B Oleosum Forte' :

Boxes of 1 ampoule of 1 cc. containing 5 mg. œstradiol benzoate, corresponding to 50,000 International Benzoate Units.

Boxes of 5 ampoules of 1 cc.

'Progynon-B' Solution :

10 cc. aqueous alcoholic solution containing 1 mg. œstradiol. (The relatively small content of alcohol is in no way injurious to the child.)

'Proluton' :

Boxes of 3 × 1 cc. ampoules each	2 mg.
Boxes of 3 × 1 cc. ampoules each	5 mg.
Boxes of 3 × 1 cc. ampoules each	10 mg.

1 mg. 'Proluton'=1 International Unit.

1 International Unit is the equivalent of 4 Clinical Units or approx. 2 Rabbit Units (Clauberg).

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