TREATMENT OF GONADAL HYPOFUNCTION*

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The disorders of gonad hormone production which have been identified may be considered varieties of reduced function in almost every case. The usual finding in study of any endocrine structure is a group of clinical cases with evidences of deficiency of secretion, another with results attributable to an excess of the hormone, and still other cases with anatomic problems without evidence of any significant deviation from the normal secretory pattern. In the case of the pancreas, diabetes was for many years believed to represent an insulin deficit. The discovery of relatively pure insulin led at an early date to the recognition of a syndrome characteristic of excessive insulin production. In the case of gonadal function the analogy does not yet apply, for we have no clinical conditions which we can be certain represent excessive hormone secretion. Certain neoplasms must remain an exception, but they do not affect this conclusion. Consequently the clinical states subject to examination and treatment in the field of gonad function are endocrine deficiency or hypofunctional syndromes. Employing conventional terms these may be listed as in Table I. It is becoming increas-

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lingly evident that the large number of disorders of menstrual rhythm and of fertility do not represent so many entities, but result from varying relationships among a few biological factors. Attention has been focused on three of these factors that are of predominant significance: production of estrogenic substances by the Graafian follicle, production of progesterone by the corpus luteum, and the maturation and liberation of a mature ovum which normally precedes corpus luteum formation. It will be recognized that the two secretory processes may vary in intensity, duration, or rhythmicality. The biological stimuli necessary for the ovarian cycle have been presented by Evans and Collip in the preceding lectures. Given at least two pituitary gonadotropic factors, two ovarian hormones, and the multitude of incidental biological modifying factors which impinge on this delicately balanced system, it would tax mathematical methods to predict the number of syndromes that might occur with only hypofunction to be considered. It will be profitable to examine in functional terms some of the typical disorders as examples of these generalizations. We know, for example, that we must no longer contrast amenorrhea and menorrhagia as deficiency and excess of ovarian activity, respectively. These are but contrasted types of underactivity of ovaries. Why amenorrhea occurs in one woman or at one time, menorrhagia in another, we do not yet know.
PATHOGENESIS OF HYPOGONADAL CONDITIONS

From the ancient traditions of clinical medicine to the present era we have recognized the interference with reproductive function which is frequently the sequel of chronic infection or debilitating disease. Whether this operates via the anterior pituitary or the gonads is usually not clear. Perhaps the quantitative methods of measuring the functions of these glands will become adequate to enable future clinical investigators to decide these points. Within the endocrine system itself the results upon ovarian function of adrenal or pancreatic deficiency states are recognized, but not explained. The gynecologist has long been saying that his best endocrine tool is thyroid therapy. This must not be understood to mean that thyroid has a specific gonadotropic effect. The key to this question has been provided by the observations of A. E. Severinghaus that the anterior pituitary is morphologically altered in experimental animals by either thyroidectomy or administered thyroid. The clinician correspondingly finds it important to search for slight thyroid disturbances as one of the possible causes for gonad disorders. Even lacking clinically demonstrable hypothyroidism, it occasionally is found that moderate doses of thyroid have provided a stimulus to some part of the pituitary-gonad system, with relief from amenorrhea, menorrhagia, dysmenorrhea, or sterility. Although it is to be hoped that the improving methods for diagnosis will make this non-specific therapeutic approach less important, at present it remains the method most widely relied upon outside the investigative clinics.

Another question with peculiar problems is presented by variable phenomena of adolescence. The growth in stature, which comes to its maximum during this period, is conditioned by the pituitary which seems to act both directly and via the thyroid and parathyroids. The rapid maturing of sex organs and functions depends on pituitary stimulation. These two processes—growth and maturation—are usually nicely adjusted in time and intensity, with the result which we choose to call normal adult types. But the clinician knows that these two pituitary functions can be dissociated, as shown by the occurrence of sexually mature dwarfs and sexually infantile giants, where one pituitary conditioned process greatly outstrips the other. Furthermore, there is an apparent antagonism between these two processes in one way. When sex maturity is well advanced the union of epiphyses occurs in the last
of the long bones, and further gain in height is forestalled. The explanation of this apparent sex effect on bone maturation is not yet at hand. But the clinician is well advised to concentrate attention on skeletal growth before the epiphyses of the femur unite to make further gain in stature impossible. If intensive gonad stimulation is planned, it should wait. This is merely recognizing in a clinical plan the orderly procedures of nature: final growth is achieved during adolescence and before sexual development is complete. An exception may be made for such a brief period of therapy as may be necessary to induce descent of cryptorchid testes.

Failure of gonadal functions in late adolescence or adult life always presents the problem of differentiating between inability of the gonad to respond and understimulation by the anterior pituitary. Removal of gonads by surgery or irradiation has proved that increased production, secretion, and urinary excretion of pituitary gonadotropic hormone occurs after the removal from the body of the gonadal hormones. This has led to the belief in the inhibition of the pituitary by the gonadal secretion. The quantitative aspects of this inhibition need far more exploration than has yet been reported. With our limited information it is easy to construct theoretical explanations for these disorders beyond our present ability to test the theories, much less to prove them. For example, it is common practice (not in experimentally organized clinics, of course) to administer to the same woman pituitary extracts to stimulate her ovaries and follicular extracts to stimulate her uterus. Current criticism of this procedure is based on belief in the inhibition of pituitary activity by the use of such follicular or estrogenic hormones. Recent results from my laboratory make it appear that relatively enormous doses of estrogen are required to accomplish such inhibition. These results, although obtained in human subjects, are limited to the greatly increased pituitary hormone excretion which occurs in the climacteric. Such findings may not be transferred directly and quantitatively to the reproductive period characterized by lower pituitary activity until the approach of the climacteric exaggeration of this process. It is known that the use of estrogenic hormone in women with regularly recurring menstrual cycles may lead to irregularity. This is prima facie evidence of the sensitivity of the mechanism to estrogen. It is theoretically possible that certain doses, given for brief periods, may act to stimulate secretion or release of a pituitary hormone. So much uncertainty attends this
question, that no recommendations can yet be made except this: when it is desired to stimulate the ovary, avoid the administration of ovarian hormone and employ pituitary gonadotropic extract.

Another aspect of the question of ovarian versus pituitary failure is presented in its most extreme form by secondary amenorrhea. Can the ovary no longer respond adequately, or is its stimulation inadequate? This question cannot be answered by history and physical examination, nor by pelvic examination even when amplified with the study of tissue obtained from endometrium or vaginal mucosa. It is stated that assays of blood and urine for estrogen and gonadotropic hormone will add significant data. With methods usually employed even this is doubtful in many cases. The hormone assay methods are being improved, and, even more important, are being evaluated by studies of normal human subjects. But the clinical decision about ovarian or pituitary responsibility for underfunction of the ovaries must usually be determined by a trial of gonadotropic therapy. If the treatment fails to produce increased ovarian activity, in spite of large doses of active pituitary material, it must be concluded that the ovary is for some reason refractory. Treatment, therefore, seems futile. Such a decision, possibly prejudicial to the patient's future, should be made only after the use of known active gonadotropic extracts and with objective criteria for ovarian activity. This leads to a discussion of the diagnostic techniques and the therapeutic materials.

Diagnostic Techniques

Careful inquiry into the details of menstrual rhythm, fertility, and contraceptive practice still needs to be stressed. A casual assertion of regularity of menses cannot be accepted at face value. The varied picture of rhythm in health, in contrast to the usually asserted "every twenty-eight days", is reported by Engle and Shelesnyak and Fluhmann. But even normal regularity is no guarantee of a fertile cycle marked by ovulation, for some cases of proven anovulatory flowing may occur in cycles of essentially four week type. The details of history will often provide a more profitable lead in the study of a gynecological endocrine problem that can be obtained from the physical examination.

In the history, increasing attention is being devoted to the possible origin of the difficulty shortly after a pregnancy. Except for infantilism
and primary amenorrhea at one extreme and the climacteric at the other, any of the syndromes mentioned in Table I may occur soon after a pregnancy. The pathogenesis of this association may be logically considered in connection with the striking morphological changes in the pituitary during pregnancy. These alterations in anterior lobe cells are usually reversible, but at times there may be enduring residuals. Most striking is the report of infarcts in the anterior lobe following a shock-like picture at delivery. In this connection Sheehan\textsuperscript{7} has provided us with human postmortem evidence of glandular alterations which can cause genital failure. It appears probable that less extensive infarcts or other types of damage in this area may be traced with increasing frequency when their possible significance is appreciated. Consequently, we must inquire not only into the time of onset of the gynecological symptoms, but also we must search for other evidences of disturbed anterior pituitary functions and for hypothalamic symptoms. For the latter growing field, reference should be made to the monograph of Ranson.\textsuperscript{8}

In conducting a physical examination the details need not be listed here, but the problems of obesity and skeletal development require some comment. I must confess inability to discriminate with any certainty those types of obesity associated with evident pituitary regional disease as opposed to the ones explainable by overeating and inactivity, or by hypoglycemia with its exaggerated hunger. Increasingly I have been convinced that all these gynecological conditions may occur either with or without obesity. When there is obesity we choose to call the hypo-function a Froehlich syndrome. With the recognition of the obesity as a separate factor in the syndrome has come the admission that it must be treated as a problem for dietary control. So far the only way in which pituitary therapy appears to help reduce obesity has been the stimulation to more adult points of view as secondary sex characters have developed, with consequent improved self control in adhering to dietary restrictions.

More important than obesity from a diagnostic point of view is the matter of skeletal proportions. Relationship of span to height has been associated with control by the pituitary growth factors.\textsuperscript{9} A distortion from approximate equality in these measurements may give correlative evidence for pituitary disease during juvenile or adolescent years. The relatively narrow shoulders and broad pelvic girdle of the female type
do not appear in the male unless there is a lack of androgenic influence. Conversely broad shoulders and narrow pelvis should make us seek masculinizing factors in a female. At present, inspection is more serviceable than accurate measurements in judging the shoulder and pelvic girdles.

Direct examination of the external genitalia, prostatic palpation, and bimanual pelvic examination must be thorough. When these do not eliminate endocrine problems as of etiologic importance, they may serve to give anatomic information about delayed development. The use of curette or endometrial biopsy instrument is increasing, but it should become still more widespread. Obtaining the specimen of endometrium is to be planned with care as to the time in the menstrual cycle. If it is obtained shortly before the appearance of the flow, or during the first hours of the menses, the absence of the typical progestational changes will justify the diagnosis of failure of ovulation or anovulatory flowing. If the tissue is obtained too early in the cycle one can only speculate about ovulation and corpus luteum formation, and secure an approximation about the intensity of follicular hormone activity from the extent of glandular development.

A more quantitative idea of the intensity of estrogenic effect may be secured from the examination of vaginal mucosa, by biopsy or most simply by the study of smears as described by Papanicolaou and Shorr. Although the vaginal tissue does not contribute definite evidence of progestin action, the type of epithelial cells does indicate the estrin effect with sufficient certainty that one may follow increases from day to day whether estrogen is administered, as in the menopause, or the ovaries are stimulated by gonadotropic hormone to produce more estrogen. It is this technique which makes it possible to determine whether a given therapeutic program has promise, for example in treating amenorrhea.

Widespread enthusiasm for assays of estrogenic and gonadotropic hormones in blood and urine has followed the proved dependability of the Aschheim-Zondek and Friedman tests for pregnancy. The demonstrated accuracy of pregnancy-diagnosis methods does not apply to these methods used in the non-pregnant. This enthusiasm for assays is giving way now to disappointment in many quarters, because of the technical difficulties and cost of the assays, and even more because of the uncertainty of interpretation. This lack of dependability of assay results is probably due to three factors: the methods lack specificity for the hor-
mone in question, they are not sufficiently sensitive to detect the normal amount of hormone day by day, or they have not been studied in enough normal subjects to provide a dependable base line for comparisons with the patients we desire to study. For some time to come this approach must remain a method for the research clinic only. Improvements are being produced rapidly. A method recently published\(^\text{13}\) is enabling us to make discriminations between climacteric types and those resulting from pituitary failure. The way in which it can be used will be illustrated.

**Therapeutic Materials**

The first sex hormones to be employed in the clinic were of the estrogenic group. These are useful for replacement therapy, as in the climacteric, or for temporary effects on the vagina, as in juvenile gonorrheal vaginitis. The relative merits of the different estrogens have been described\(^\text{13}\) and will be further discussed by Doctor Shorr.\(^\text{14}\) The employment of estrogens to stimulate the pituitary, and secondarily the ovaries, is a theoretical possibility which has not yet been studied sufficiently to allow any suggestions about its use. The attempt to inhibit pituitary overactivity by estrogen therapy in the menopause is probably futile unless the doses are enormously large as compared with those which secure clinical control of the menopausal symptoms.\(^\text{15}\)

More recently androgens have been secured in pure form. These are analogous to estrogens for substitution therapy in the male climacteric. They have been employed similarly in the female, with some symptomatic benefit. They exert a powerful inhibitory influence on the anterior pituitary, and hence can suppress ovarian activity markedly. These activities have led to treatment of a variety of gynecological disorders with testosterone. Caution seems urgent because even a slight increase in dose above the amount found necessary has not infrequently led to such masculine changes as beard growth and enlargement of the larynx with voice change. Such phenomena are not easily reversible. Since this androgenic therapy does not achieve results which cannot be accomplished otherwise, it seems at present to be of scientific interest rather than clinical importance in the female.

The hormone of the corpus luteum, progesterone, is of indispensable importance in obtaining the progestational changes in endometrium which must precede nidation of the fertilized ovum and must support
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gestation. It is available in several preparations, but the therapeutic effects have been disappointing save in some cases of dysmenorrhea and of repeated abortion. This may be due to inadequate dosage, but it is more probable that mere administration of this hormone to a woman without ovulation and corpus luteum formation is not sufficient to correct the difficulty. The therapy must include gonadotrophic material which can add to the normal stimulation of the ovaries by the patient's own gland.

The first of these gonadotropic substances tried was a concentrate from the urine of pregnant women, chorionic gonadotropin, usually spoken of as anterior pituitary-like hormone, A.P.L. A constantly increasing body of evidence justifies the statement that this hormone has as its normal function the maintenance of the corpus luteum of pregnancy, but that in the non-pregnant woman it causes atresia of the Graafian follicles, and does not stimulate the human ovaries to ovulation and the formation of corpora lutea. A most interesting discovery has been that chorionic gonadotropin will stimulate the descent of cryptorchid testes and this has been applied to human therapy with profit. Thompson and Heckel have discussed the dosage, differential diagnosis, and the risks involved.

The extraction from the anterior pituitary itself of gonadotropic materials which could be used clinically began with Hisaw and Fevold, and Collip has added alternative methods. All the pituitary extracts so far available contain at least two gonadotropic substances, called follicle stimulating (F.S.H.) and luteinizing (L.H.) hormones. These occur in varying proportions. Known methods of assay do not allow quantitative determinations of the two when they occur in mixtures. Consequently, we must work at present with mixtures the composition of which we cannot be told. Shortly it will be possible to have extracts of these two hormones in separate solutions for clinical trials. We may anticipate superior results from more accurate prescription to fit the needs. One further handicap to the use of these pituitary extracts is the presence in all commercial products of proteins which are probably of no therapeutic importance but which cause painful local reactions and occasionally allergic manifestations.

The protein content has been greatly reduced in the gonadotropic preparations made from the serum of pregnant mares. This substance is not identical with either the chorionic gonadotropin of women or the
hormones from the anterior lobe itself. However, its physiological effects most nearly resemble the pituitary hormone, and results to be reported are typical of the way in which this hormone may stimulate the human ovaries to ovulation, corpus luteum formation, with improved fertility. The pregnant mare's serum (P.M.S.) contains either two hormones as does the pituitary extract, or its hormone has both types of action. The low protein content of the commercial preparations has made this material safer for intravenous administration of large doses than is the case with the pituitary extracts.20

Reference has been made to the use of thyroid therapy in gynecological conditions. It must be emphasized that thyroid is marketed in several types. We can ill afford to use anything but standardized thyroid. General insistence on U.S.P. thyroidea sicca as the only thyroid used would serve to eliminate many differences of opinion about the efficacy of thyroid therapy.

**Therapeutic Programs**

Since the gonadotropic materials are water-soluble, act quickly and for brief periods only, it is necessary that we employ frequently repeated doses of small or moderate size rather than occasional large injections. An exception occurs in the case of intravenous injection to produce ovulation, as suggested by Hisaw and Foster.²¹ For this latter purpose it may be advisable to use smaller doses hypodermically before intravenous injection, to lead to adequate follicle development, and small doses after the large one to sustain the secretory activity of the corpus luteum. The injections of gonadotropic material for this supportive therapy of follicle or corpus luteum are to be given hypodermically. There is no evidence that intramuscular injections are better, and animal experiments suggest that the slower absorption under the skin is desirable.

Because the ovarian cycle of women is marked by variations in the amount of pituitary activity, it seems logical to vary the pituitary therapy in cyclic fashion. The complete rationalization of this cyclic therapy must await quantitative data from assays in any given patient. This we hope to make available in due time. Until then we prefer to employ therapy for stimulation of the follicle during the first two weeks of the menstrual cycle only, to avoid the risk of producing cystic follicles. Hisaw has shown that continuous therapy can do this in the
monkey. In the most extensive pituitary failure it may be necessary to continue therapy through the entire cycle, but even here it can be varied in its intensity in a cyclic manner.

The control of the size of dose and its frequency may be based on the study of response to treatment, gauged by vaginal smears, occasional endometrial biopsies, observations of developing secondary sex characteristics, growth of external genitalia or uterus, and by the careful recording in graphic fashion of the duration and interval of the menstrual flows. If large doses of gonadotropic extracts fail to give increased evidence of estrogenic activity in the vaginal mucosa in cases of amenorrhea or infantilism, therapy may as well be abandoned.

Allergic reactions, though occasionally seen, have been infrequent, in spite of the protein content of the gonadotropic extracts. Local inflammatory reactions, when severe, may necessitate a change from pituitary to pregnant-mare serum extracts. The development of antihormones under therapy is a puzzling aspect of this program. Elsewhere, Meyer and Sevrinhaus are reporting this phenomenon but point out that it does not appear to be a limiting factor in securing results. We are inclined to minimize the importance of antihormones in the clinic.

One of the most confusing features in this field is the variation in units employed by the different manufacturers. No two products on the American market are labeled in identical units. There is a movement to make the standardization of chorionic gonadotropin uniform. This may soon be accomplished. Systematization of unitage in the pituitary or pregnant mare serum extracts is handicapped by the presence of at least two hormones in varying proportions. At present all that can be said is that the unit of Gonadogen (Upjohn) is largest, that of Prephysin (Chappel) and Gonadin (Cutter) are smaller and approximately equivalent, and that of Gonadotropic Hormone (Armour, and Ayerst, McKenna and Harrison) are identical and much smaller than the others. With appropriate doses any one of these materials will accomplish the results to be described in the following illustrative cases.

**Clinical Examples—Male Hypogonadism**

Interesting examples of sex infantilism are brothers, E. and J. R. (106361 and 106363), ages twenty-four and twenty-seven, who had five siblings normally developed (Fig. 1). The histories and examinations were not remarkable save for high pitched voices, absence of adolescent
interests, absence of beard growth, the distinctly longer span than height, broad type of pelvic girdle, slight obesity in the older one, and the presence in the scrotum of small, but firm, testes, with almost no hairs in the escutcheon. Both men have a persistent leukocytosis involving myeloid and lymphoid series, without known reason. Therapy, confined to pituitary gonadotropic extract (Prephysin), 25 units daily for over three months, produced a slight gain in size of testes and penis in each man. For another month the dose was increased to 100 units daily with no further development. The next material used was pregnant mare's serum (Gonadogen), 10 units daily for one month, then 20 units daily for six weeks. Prostatic tissue was just palpable at this stage, but no other progress was evident. After six weeks of daily injection of 250 units of pregnant woman's urine extract (Antuitrin-S) there was no more gain.
noted, but after four weeks more of 500 units daily there was a slight
tenderness and enlargement of the prostate, slight increase in size of
testes, and definite increase in the hair growth of the escutcheon. The
older patient began to report frequent erections due to suggestions. A
further two months at this same dose level produced no more response
than a more wrinkled scrotum, larger but still juvenile penis, and still
more frequent erections in both men. At the end of thirteen months
both were eager to continue treatment, with the hope of completing
their masculine development. It appears that the testicular tissue is prob-
ably not capable of much response in these men, for reasons unknown.

**Froehlich Syndrome**

A much commoner variety of hypogonadism is presented by S. H.
(204654), age fourteen, with typical Froehlich syndrome. History was
not unusual except that thyroid therapy did not help control the weight
or delayed development of genitalia. Physical examination showed no
significant findings save those shown in Fig. 2 and the presence of small
scrotal testicles. After ten months of daily therapy with pituitary gon-
adotropic extract (Prephysin), 25 units daily, the penis, testicles, pro-
tate, and pubic hair had all shown gratifying growth. The patient had
gained a total of 2 inches in height and the adolescent voice change was
in evidence. Blood cholesterol of 230 mgs. per 100 cc. confirmed the
diagnosis of hypothyroidism as a complication, and thyroid therapy was
resumed, using 2 grains U.S.P. thyroidea sicca daily. This was not until
he had demonstrated that on a 1200 calorie diet alone he had lost 22
pounds in four months, during which time he grew one inch taller.
Experience here is typical in that weight control depended most upon
dietary cooperation; gonad development responded promptly to gon-
adotropic therapy; thyroid therapy showed results only in its effects on
basal metabolism, blood cholesterol, and the character of the skin.

**Cryptorchidism**

A ten year old boy, W. R. (36115), was seen after he had been
given pituitary extract (Prephysin) 1 to 3 times weekly for five months
without making the testes descend into the scrotum. He was tall and a
bit overweight. The dose was then set at 25 units daily, and after eight
weeks a soft mass in the scrotum was believed to be the right testis. The
dose was increased to 100 units daily, but numerous doses were missed.
After four months, both testes were about 1 cm. in diameter, but in the canals. A change to pregnancy urine extract (Antuitrin-S), 250 units daily, led to descent into the scrotum in about three weeks. Therapy was continued for four weeks longer, at 250 units twice weekly, after which the testes, now nearly 2 cm. in diameter, remained in the scrotum. During the year of treatment the boy had grown 1.5 inches and had gained 5 pounds. The results certainly suggest that although the pituitary gonadotropic material caused development, the pregnancy urine gonadotrope was more effective in bringing about testicular descent, and also it seems to have stimulated rapid growth in size simultaneously with the attainment of the scrotal position.

**Eunuchoidism**

A strikingly tall, narrow shouldered and youthful male, E. P. (105-117), was seen when he was twenty-seven, complaining of absence of testes and of secondary sex characters. The atypical skeletal proportions as well as the juvenile penis are shown in Fig. 3. There was no beard, the voice was boyish, the escutcheon was a scanty feminine type, and neither testes nor prostate could be identified. He stated that testicles had been present until the age of seventeen, although small, after which they disappeared without known cause. The use of a month’s course of daily injections of pregnancy-urine extract at the age of twenty-three had accomplished no change. He was given daily therapy with pituitary extract (Prephysin) for over three months. The injections were made in the thighs, and led to tender and rounded masses in each inguinal region. When these failed to descend after six months, surgical exploration proved one of them to be a lymph node, and no testicular structure could be found in the inguinal region. There were no subjective changes nor alteration in voice or beard. Thereupon he was transferred to the use of testosterone propionate, which promptly caused increased size of the penis and priapism, indicating that doses smaller than 10 mg. were required. This type of treatment brought about sufficient improvement in an otherwise difficult personality so that the patient and his family were glad to continue its use. Apparently the testicular tissue, if ever present, had atrophied completely.

The obvious difficulties of poor reactivity of testicular tissue in some patients, need for long continued treatment with large doses of gonadotropic material, and uncertainty about the presence of testicles when
they are not palpable in the scrotum have their corresponding difficulties in the female. A further handicap in treatment of the male is the lack of any accepted method by which biopsies may be obtained for study, as from endometrium or vaginal mucosa, and absence of spontaneous and objective cycle of events, like the menstrual flow, by which to judge progress. By comparison it may be seen the diagnosis and treatment of female hypogonadism appears more dependable and with a better prognosis in many cases.

**Female Infantilism**

As an example of sexual, emotional, and mental infantilism, the progress of M. H. (102165) is gratifying. When first seen at the age of
twenty-one her complaints were of menses at 1 to 3 month intervals, and slight obesity. Members of her family reported behavior suggesting hebephrenic schizophrenia. Intelligence quotient was reported as 0.83 (Binet-Simon). Pelvic examination revealed a small and retroverted uterus. The endometrium obtained on the forty-eighth day was a normally active proliferative tissue but with no evidence of progestational action. Nevertheless, a flow began the following day, which must be classed as anovulatory. Therapy was undertaken with 10 doses of 25 units each, using Prephysin (Chappel) for a series of months as shown in Fig. 4. Simple dietary restrictions were employed, but no other treatment used. Within three months marked psychological improvement was reported by the family. Soon the girl obtained employment, and has continued to support herself for two years, in addition to which she has entered a teacher's college. She earns her way and has done better than average work. Vaginal epithelium studied by smear technique is approaching the normal estrogenic intensity.

**Primary Amenorrhea**

Partial success in treatment of primary amenorrhea is illustrated by the results achieved with N. S. (94770). She was hospitalized at the age of twenty-five because of personality problems which made her retention in the family home difficult, and employment impossible. Permanent institutional care appeared necessary to the family physician. She refused to allow even a woman physician to make a pelvic examination to determine whether the pelvic organs were present, although the amenorrhea made her fear that she was "turning into a man." The vaginal smear from this case, shown in Fig. 5a, is typical of the castrate type. She was given Prephysin in 100 unit doses daily. The smear showed evidences of estrogenic action within two days, and after 15 doses therapy was interrupted. The vaginal mucosa had changed to the type shown in Fig. 5b. Four days later she experienced her first menstrual flow, which continued for seven days. This sequence proved the presence of ovarian tissue. During almost three years following this time she has received further series of treatments, and has reported a total of four flows. Her mental status improved within the first few months so that her family welcome her presence and help. She has been able to retain employment. She expresses a shy interest in a young man. Studies of the vaginal smear show that some estrogenic activity can be secured when she is given
gonadotropic injections, whether this be Prephysin (Chappel), Gonadotropic Extract (Armour or Ayerst, McKenna and Harrison), or Gonadin (Cutter). Omission of therapy for a few weeks on several occasions has led to beginning of a mental relapse. Even though regular menses have not been established, the personality adjustment achieved appears to justify continued therapy.

Less success has followed a similar attempt to stimulate ovaries in G. F. (201240), who was seen at the age of twenty because of primary amenorrhea. The mental and emotional status was normal. Pelvic examination left it uncertain whether there was ovarian tissue. Vaginal smears were of the castrate type, and under stimulation with either pituitary or pregnant-mare serum gonadotropic extracts, there was only occasionally any evidence of estrogenic response. On one occasion a slight flow occurred for three days. It is evident that although this patient had ovarian tissue it was either scanty in amount, or for some reason refractory to treatment with the most potent gonadotropic materials so far available. The prospect of achieving better results by therapy for more than the nine months trial was so poor that the patient was advised to be resigned to amenorrhea with its implied sterility, to which she is satisfactorily adjusted.

Froehlich Syndrome

Typical of the combination of stubborn obesity and genital underactivity is the case of E. M. (86364), who was first seen at the age of
twenty-three. Her menses began at the age of thirteen and occurred at monthly intervals for about eight years, but she had had amenorrhea for the last two years. She had many of the nervous and emotional symptoms of the climacteric type. Although her basal metabolism was above the average, she continued gaining weight with admitted poor cooperation in dietary limitation. Pelvic examination revealed a small and retroverted uterus and a slightly enlarged left ovary. The endometrium was totally inactive. Therapy was continued for thirty-three monthly series, as shown in the chart, Fig. 6. The obvious improvement manifested by return of menstrual cycles led to a series of further endometrial biopsies. Even the latest, taken a year after concluding thirty-six months of treatment, shows less than normal degree of glandular development. No progestational changes have been seen, indicating that these flows are still anovulatory. The vaginal epithelial smears are still a little below optimal estrogenic response. But the nervous and mental symptoms have remained in abeyance, she has coöperated in dieting, and has recently been married. If the period of observation without therapy is marked by return to infrequent menses, it seems worth returning to a further course of gonadotropic injections.
Amenorrhea was possibly secondary to pulmonary tuberculosis in B. P. (69874), but by the age of twenty-seven she had had two abortions, spontaneous at the age of eighteen, induced at the age of twenty-six, with obviously low fertility between these events; and a year of amenorrhea after the last abortion. She was asthenic, had a number of complaints of climacteric type, but pelvic examination showed nothing unusual. Endometrium was of low activity, but not castrate in type. The use of gonadotropic therapy (Prephysin) was followed by prompt return to regular cycles, and this gain was maintained without therapy. The regularity of cycles, shown in Fig. 7 is surprising. Because of persistent asthenia, hypotension, and the tuberculous history, a mild Addison’s disease was suspected. The use of adrenal cortex extract was symptomatically helpful, although the menses continued about as before, save for a decreased duration of flow. No serious menstrual irregularity has recurred in almost four years since treatment was first undertaken.

Another amenorrheic woman, age, twenty, M. S. (86349), was seen
after a year without flowing. Except for moderate obesity, a basal metabolic rate of minus 14 per cent, and a small, retroverted uterus, there were no unusual findings. Endometrium was obtainable only with a curette, and showed no more activity than in a castrate woman. Therapy was limited to 25 unit doses of Prephysin, given five and later ten times in the first two weeks of menstrual cycles, or at intervals of at least four weeks when amenorrhea recurred. The chart of her flows, Fig. 8, shows how promptly she returned to more frequent flowing, and how regular monthly rhythm was resumed within fifteen months. Later, after a four month period without therapy, she was started on thyroid alone, due to the persistent slight reduction of the basal rate and the continued obesity in spite of dietary efforts. Menstrual rhythm continues satisfactory, weight control is improved, but there has been no test of the completeness of the ovarian or endometrial cycle of activity.

INFREQUENT MENSTRUATION

One of the most trying problems in the field under discussion is presented by the emaciated young woman who either will not or cannot
Treatment of Gonadal Hypofunction

eat an adequate diet, or who cannot maintain a normal weight in spite of an apparently ordinary amount of food intake. Menstrual irregularity of different sorts may appear, but long intervals and scanty flows are common. The term “Simmonds’ Cachexia” comes easily to mind, but usually there are not enough evidences of complete pituitary failure to justify such a diagnosis. Typical of this group is a twenty year old girl, V. G. (205784), who had begun menstruating at the age of fifteen. After a few years of four week type of flowing, irregularity appeared, and she was first examined after twelve months of amenorrhea, at which time she had a small and retroverted uterus. Endometrium was not obtainable, even with a curette, and she complained of most of the nervous and emotional difficulties characteristic of the climacteric. She was hypotensive, asthenic, underweight, unable to eat a generous diet, but by studies of salt restriction she was proved not to have adrenal insufficiency. Therapy was a combination of simple suggestive approach to secure a better food intake, and the use of 100 units of anterior pituitary gonadotropic extract (Prephysin) daily for fifteen days, repeated each month. A three day flow appeared just at the end of the first series of such injections, but amenorrhea recurred during the next six months. Therapy had caused little relief from the asthenia and anorexia. At the close of the third series of injections endometrium was obtainable with a biopsy punch, but it showed only a very few tubular glands, dense stroma, and no evidences of mitotic activity in the cells of the glands. A change was made to 100 units of pregnant mare’s serum (Gonadin) for the fifteen daily doses, with no greater improvement. It is entirely probable that the substances employed in such cases are useless, not because of low potency, but because they do not supply the materials really needed. Study of the urine of this patient revealed an excretion of gonadotropic hormone which is comparable to that in normally menstruating young women, but without the increased excretion seen uniformly after the menopause has begun. The possibility which needs exploration is that there is deficiency of some other fraction of the pituitary in such cases. So far we can only speculate as to which of the several other pituitary extracts might be helpful for such a woman with the combination of amenorrhea, anorexia, asthenia, climacteric nervous symptoms, but without the usual climacteric exaggeration of gonadotropic excretion.
IRREGULAR MENSTRUATION

As an example of irregular and slightly infrequent menstruation, the record of S. R. (S. H. 96791) under therapy is encouraging. She was first seen at the age of nineteen, with a history of six years of totally irregular intervals, varying from one to ten months, usually about two months, with flows decreasing from seven to three days in duration, and with no help from the use of pregnant woman’s urine concentrate or estriol. There were no nervous symptoms. Pelvic examination showed the familiar small and retroverted uterus. A biopsy showed loosely organized endometrium containing a few tubular glands, with very little mitotic activity, in spite of a twenty-five day interval since the last flow. The following day anovulatory bleeding of seven days began. The record of cycles is shown in Fig. 9 where improvement following therapy is evident. The doses were limited to 25 units of Prephysin ten times in the first two weeks of each cycle. After a little less than a year therapy was omitted, and two months later menstrual intervals began to lengthen. The vaginal epithelial smears showed almost no estrogenic activity. Therapy was resumed, and the epithelium showed progressive
improvement to nearly a normal intensity in two cycles. After eight months she was married, and had only one flow before becoming pregnant due to carelessness about contraceptive practice. Results are not always so easily attained.

**Anovulatory Flowing**

Another case record has some similarities to the last one described. This twenty year old student, L. H. (80971), had likewise flowed very irregularly from the age of sixteen, previous to which flows had occurred at about six week intervals. Uterus was small. The chart of her cycles in Fig. 10 shows little progress in improving the rhythm. After several months of treatment with pregnant woman's urine concentrate the use of Prephysin was begun. Following six months of this an endometrial biopsy in the fourth week showed a fairly active follicular hormone effect (Fig. 11a), but the flow which followed within seven days was probably anovulatory—certainly not preceded by a normally active corpus luteum. Therefore, therapy was resumed and after six months a second biopsy showed a well matured progestational endometrium (Fig. 11b). During the previous two years of married life this patient had
become careless of contraceptive technique, for she knew of her under-active ovarian problem. Although she was told that the progress she had made under therapy was toward improved fertility, the irregularity of menses continued, and she was surprised to find herself pregnant. Her baby was born at term with an uneventful pregnancy. During the ensuing two years, with no endocrine therapy, she menstruated at four to five week intervals.

**Menorrhagia**

A slight variation from this type of disturbance is presented by K. M. (91934), who was referred for examination at the age of twenty-nine because of repeated menorrhagia, with intervals essentially of a four week type, but duration of flow from three days to two weeks. She had repeated basal metabolic rates of 23 per cent or more above normal, but too few physical findings to justify a diagnosis of thyrotoxicosis. Thyroid therapy seemed contraindicated. Trials of pregnant woman's urine and of corpus luteum extracts had been of no avail. It is probable that mumps a year earlier had some etiologic importance. Pelvic examination showed an enlarged and retroverted uterus, from which the curette produced tissue with enlarged glands of varying sizes characteristic of the "Swiss cheese" endometrium. The uterus was replaced and supported by a pessary, but the menorrhagia recurred, as shown in Fig. 12. Thereupon she was treated with pituitary gonadotropic extract (experimental

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Fig. 11. Relief from anovulatory flowing by continued treatment. (a) Proliferative endometrium in the fourth week, hypofunction. (b) Progestational endometrium in the fourth week, normal function.
Material from Parke, Davis and Company) with definite improvement, which became evident after a few months. One year after the first examination a biopsy produced endometrium with typical progestational endometrium, demonstrating the normal and complete ovarian cycle. After six more cycles of treatment, the pituitary extract was omitted, but the intermenstrual intervals gradually lengthened, and the menorrhagia returned. When therapy was resumed with a stronger preparation, the Gonadotropic Pituitary Extract (Armour), there was immediate return to regularity. Such results have convinced us that menorrhagia is to be considered as hypofunction of the ovaries if it is due to any endocrine anomaly.

**Sterility**

Although it is apparent that many of the types already presented were, or probably would be sterile, there are some instructive features in the record of S. N. (74900), a thirty-three year old mother of a two year old child, who was disappointed because of her inability to conceive again. After the pregnancy she had noted menses as infrequently as three months, and dysmenorrhea had occurred for many days. Obesity, acne, and many of the climacteric complaints had appeared. The basal metabolic rate was above normal. Pelvic examination revealed a retroverted uterus which was held in place with a pessary. The ovaries were enlarged and cystic. Endometrium obtained at the end of the fourth week showed only a low intensity of estrogentic effect. Flow did not appear
until more than three weeks later, so that it is impossible to determine whether ovulation occurred in that cycle. Therapy was begun, using pregnant mare's serum concentrate (Gonadogen), 10 unit doses as shown in Fig. 13. After only twelve doses, in four cycles, a longer amenorrhea than usual was marked with nausea, and the urine test indicated pregnancy, which went to term. She was given progesterone, without any known need, to reduce the risk of abortion. Pregnancy following such brief treatment is surprising. Such occurrences have been repeated, and serve to indicate that in some women a relatively small amount of pituitary treatment is sufficient to restore a fertile ovarian cycle.

REPEATED ABORTION

Typical case reports of treatment of repeated abortion will not be presented, for they are being separately published by my colleague in this field of investigation, Doctor Ralph E. Campbell. In his series there are thirteen women who have aborted two or more times previously, of which number eleven have now delivered living children at term. The treatment has been based on the use of progesterone, employing preparations made at the University of Wisconsin, and commercial material such as Proluton (Schering) and Progestin (Upjohn). The doses have been 1 to 3 units three times weekly, the maximum dose 5 units, and the duration of treatment usually lasting into the fifth month.

We have no data on the relative merits of progesterone and of choriionic gonadotropic extract. Theoretically the material from the urine of pregnant women should maintain the activity of the gravid woman's
corpus luteum and accomplish the same results. Comparative results are not yet available in the literature.

**Premature Climacteric**

It is admittedly impossible at this time to draw a sharp line between the cases of secondary amenorrhea and other varieties of ovarian failure above described, and those which can be listed as premature climacteric. Attention may be directed to a rather striking type of history illustrated by the case of H.H. (204902), age twenty-four, who had a child born when she was nineteen, after which menstrual irregularity became evident and led to amenorrhea at age twenty-three. In addition to several typical climacteric complaints she noted almost constant breast pain, and she was asthenic and hypotensive, but ate normal amounts of food. The uterus was found to be distinctly small, the endometrium totally inactive, and the vaginal mucosa was atrophic, resembling that in the castrate. The use of 100 units of pituitary gonadotropic extract (Prephysin) daily for ten doses, repeated at four week intervals, led to a minimal estrogenic response in the vaginal mucosa, but no flow ever appeared. It was, therefore, concluded that the only effective therapy was symptomatic relief of climacteric symptoms by the use of estrogenic substances. The use of estrogens for this purpose will be described in a subsequent paper by Doctor Ephraim Shorr, and will, therefore, not be further discussed.

**Dysmenorrhea**

Although the relief of menstrual pain is one of the gynecologist's commonest problems, we confess to no dependable means for relieving this type of discomfort. The fundamental causes are still unidentified. We can be certain that pain may attend either flows preceded by corpus luteum formation or those which are anovulatory. One encouraging observation is typified by the results of treatment of E. B. (94088), a student who was referred at the age of eighteen because of pain, but who flowed at variable intervals of one to nine months. There were no other findings to suggest incomplete development. Endometrium showed progestational changes well developed early in the fourth week. Since the flows occurred so infrequently, she was treated with 100 unit doses of Prephysin ten times in the first two weeks of each cycle. A striking improvement in rhythm occurred, with intervals averaging five weeks,
and the patient had satisfactory relief from pain. Omission of the therapy for more than two cycles was followed by return of the pain. We cannot draw far reaching conclusions from such observations, but we have observed such improvement at times in treating underdeveloped girls. On the other hand, the majority of such patients do not have any serious pain. The mechanism by which pain was relieved may be similar to that involved in relief of dysmenorrhea by estrogens. Again estrogens have been known to exaggerate dysmenorrhea. From the endocrine point of view dysmenorrhea is still a fertile field for exploration. A recent report from two of my colleagues demonstrates the help which may be obtained by the use of thyroid. If time permitted, I might cite examples of relief from dysmenorrhea, menorrhagia, irregular menstruation, pre-menstrual tension states, and other menstrual disorders by thyroid. This type of therapy has been depended upon in cases where the basal metabolic rate, blood cholesterol, and the physical findings made relative hypothyroidism the probable diagnosis. The importance of thyroid disorders must not be lost sight of in our study of the direct relationships of anterior pituitary and ovaries. There are other endocrine and somatic problems which challenge the breadth of view of the diagnostician. But the types of results presented here lead us to the following conclusions:

Conclusions

1. The chief disorders of gonadal endocrine function are to be classified as hypofunction of the gonad, either primary or secondary to that of the anterior pituitary.

2. Gonadal hypofunction may be a consequence of disturbance in thyroid secretion, of other endocrine disorders, or of various systemic diseases.

3. Disorders of gonadotropic secretion by the anterior pituitary are especially frequent in the following circumstances: during the rapidly changing period of adolescence, during and immediately after pregnancy, and at the climacteric, either spontaneous or induced.

4. The frequent association of obesity with menstrual disorders is still unexplained, but it seems probable that the obesity is more a result of disturbances in the hypothalamic region than of the hypofunction of either pituitary or gonads per se.

5. For accurate diagnoses of the types of menstrual disorder and for estimating progress under treatment, the use of properly timed endo-
metrial biopsies, smears of vaginal mucosa, and determinations of urinary pregnandiol output are invaluable. Only the first two are generally available.

6. Assays of hormone content of blood and urine are still used only as research tools.

7. Estrogenic substances are useful chiefly for relief from climacteric symptoms, or from gonorrheal vaginitis in young girls.

8. Progesterone is helpful so far only in preventing repeated abortion.

9. Among gonadotropic materials the chorionic product is helpful in stimulating growth of testes and descent of some cryptorchid organs. It does not stimulate the human ovaries. Anterior pituitary extracts or concentrates from the serum of pregnant mares will accomplish stimulation of testes or ovaries in the human.

10. The optimal therapeutic program with pituitary gonadotropic extracts in the male is based on daily injection of small to moderate doses.

11. Optimal results with females are secured by use of cycles of injections. To stimulate the follicle the doses should be confined to the first two weeks of the menstrual cycle. To initiate ovulation the gonadotropic extract needs to be given intravenously. It is probable that sustained luteal secretion can best be stimulated by hypodermic therapy after ovulation.

12. Favorable results have been reported following the use of Prephisin (Chappel), Gonadogen (Upjohn), Gonadin (Cutter), and Gonadotropic Extract (Armour or Ayerst, McKenna and Harrison). The units of these materials are not interchangeable.

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