
THE PRESENT STATUS OF GYNECOLOGIC ENDOCRINE THERAPY

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GYNECOLOGIC endocrine therapy has enjoyed an extraordinary development in the last few years. It is only a decade since the only available endocrine products from the ovary or anterior pituitary were desiccated extracts, now regarded as quite inert, but which the gynecologist optimistically made use of. Since then, glandular preparations of three or four major types, each in several forms with varying indications, have become available. Yet it is almost universally recognized that the rapid expansion in the clinical use of these substances has been accomplished at some sacrifice of soundness and sincerity.

The reasons for the vogue which endocrine therapy is enjoying are not hard to find. First, there is the undoubted need for a scientific therapy of the many functional disorders of the female reproductive system. Furthermore, the so-called sex hormones are apparently relatively safe, more or less regardless of dosage, and no accidents have occurred, such as attended the introduction of insulin, thyroid extract or pituitrin. That a certain artificial demand has been created by an advertising campaign to the physician is also probable.

Yet the most important reason for the acceptance of the new products is the brilliance of the basic scientific work which preceded their appearance in the clinical field, for whatever may be said against the new endocrine therapy, it can never be said that it is entirely empirical. The soundness of the reasoning which leads to the prescription of certain gland products is often so good as to make the physician biased in the evaluation of his results. To this sound physiologic background must be added the helpful but misleading fact that gynecologic endocrine dysfunction has a great tendency to spontaneous improvement. A series of optimistic reports has, as a result, led to a rapid approval of the endocrines for many conditions for which more critical judgment may eventually question their value. Any attempt at present to delimit the field of gynecologic endocrine therapy is bound to be tentative and to lead to conclusions which will be unacceptable to many. Nevertheless

such provisional accounting may occasionally be useful.

In the following pages, the subject of gynecologic endocrine therapy will be considered under the following heads:

(1) The endocrine agents now available for affecting the female pelvic function and their physiologic action.

(2) The diagnostic methods available to determine the physiologic nature of the disturbance underlying the patient's clinical symptoms.

(3) A classification of the conditions for which the so-called sex hormones have been advised into categories of relatively proven usefulness.

I. THE AVAILABLE AGENTS

The agents available for affecting the endocrine status of the female reproductive tract fall into several groups. First are those which in a measure reproduce the function of the ovary itself by acting upon the secondary organs, the uterus, vagina and breasts. This group includes the various estrogenic substances and the specific hormone of the corpus luteum. Second are the substances which affect the ovary and are therefore classed as gonadotropic. They are a somewhat miscellaneous group, both as regards their origin and action. Third, there is the hormone of the thyroid gland whose action on the pelvis is not definitely understood, but whose clinical effectiveness for some conditions seems established. Finally, there is radiation therapy, which as a rule has the opposite action from that of most of the hormones, namely, to reduce rather than increase function.

A. THE ESTROGENIC HORMONE

Estrogenic substances are available for therapeutic use in several forms. The substance most widely employed is probably estrone or ketohydroxyestrin, known to the profession by the terms theelin, folliculin, amniotin, menformon and others. A closely related substance is estriol or trihydroxyestrin, sometimes called theelol. This latter product is somewhat less active than estrone, but has been believed to be more efficient as a preparation to be given orally. A material intermediate in chemical formula between estrone and estriol is estradiol or dihydroxyestrin. This substance has been combined with benzoic acid to form estradiol benzoate, marketed under the commercial names, progynon B or oestroform B. This compound has the property of being more slowly broken up in the body than are the simpler estrogens, and has there-

fore the advantage of a more prolonged effect. A fourth estrogenic substance is the one commonly known as emmenin (Collip¹), and thought to be estriol in a combined form, probably estriol glucuronide (Cohen²). It is much less active than are the "free estrogens", perhaps especially in the absence of an ovary, the site of its supposed transformation to a more potent form. It is recommended, however, as a substance especially available for oral administration.

Great confusion has resulted from the fact that the clinician has been subject to a constantly changing nomenclature of dosage, namely mouse units, rat units, and now, unexpectedly, international units. The present unit, accepted by a committee of the League of Nations, is perhaps relatively permanent. This "international unit" is the equivalent of one ten-thousandth of a milligram (0.1 gamma) of a crystalline preparation of estrone. The relation of the animal units to this gravimetric unit is actually quite variable, depending on the method of bio-assay, but a mouse unit is usually accepted as about equal to one international unit, a rat unit to five international units.

Although the use of estrogenic substance has a certain rationale, the dosage for most of its indications is largely empirical. This is obvious when it is remembered that except in the case of the menopause, the degree of ovarian deficiency which must be compensated for by therapy, is unknown. A start toward the development of a rational dosage has been made chiefly in reference to the menopause. Kaufmann³ in 1932 showed that artificial menstruation could be produced by a dosage of 210,000 mouse units of progynon benzoate followed by 35 rabbit units of corpus luteum. This is apparently the basic requirement for the building up of an endometrium sufficient to cause bleeding. Such a result, however, is unnecessary in usual therapy and the goal is more generally simply the suppression of the excessive anterior pituitary activity which is associated with hot flashes. Frank, Goldberger and Salmon⁴ have reported the disappearance of the gonadotropic factor from the urine, the alteration of the vaginal spreads and the disappearance of menopause symptoms when 4,000 rat units are given every other day for two weeks. Thus their figure for the suppression of gonadotropic activity in a woman without ovarian tissue is 120,000 international units of estradiol benzoate in two weeks time. Papanicolaou and Shorr⁵ had found that it took from 250 to 300 rat units daily to induce complete changes in the vaginal smear, and with oral administration fifteen to twenty times this dose.

Other workers (Werner⁶) have, however, placed the figures somewhat lower and have noted stimulation of the breasts, endometrium and vagina with as little as 5,000 to 10,000 international units. Using a different method of study, that of following urinary excretion of the estrogens, Mazer and Israel⁷ noted that an injection of 1,000 rat units in castrated women produced normal levels for four days. Larger amounts, such as 5,000 to 10,000 rat units, produced a temporary hyperestrinism which fell to a normal level by the fourth to fifth day.

The use of estrogenic substance for any purpose in women who have sufficient ovarian function to menstruate does not give dependable results. Since the basic ovarian function which the menstruating patient possesses is difficult or impossible to gauge, the additional estrogenic substance which must be added to raise the theoretically low level to a theoretical normal is the purest guess work.

The functions of the estrogenic hormone which are invoked to support its use in therapy are briefly the following:

(1) To stimulate proliferation of the mucosa of the uterus, vagina and mammary glands and to a certain extent the muscular walls and supporting stroma of these organs. This function is the basis of the treatment of amenorrhea and hypomenorrhea due to deficient development of the endometrium, of dysmenorrhea supposedly due to deficiency of the myometrium, and of senile and juvenile vaginitis.

(2) To increase the sensitivity of the uterine musculature. This function has given rise to little definite therapy, although the estrogens have been suggested in the therapy of missed abortion and postmaturity in obstetrics.

(3) To suppress excessive activity of the anterior pituitary gland. Continuous small doses of estrin have apparently found a definite place in the therapy of the menopause. A somewhat paradoxical effect may, however, be produced when very large doses of an estrogen are given and, instead of a suppression, a temporary increase in gonadotropic activity, especially in its luteinizing function, may result. This reaction may be at the basis of successful therapy of amenorrhea with large doses of estrin.

The dangers of estrogen therapy are, like its uses, somewhat theoretical. The experience of research in mammary gland cancer in mice, where the ovarian hormone undoubtedly is a factor in bringing out latent tendencies to cancer in susceptible strains, leads to some anxiety

as to the effects of the too indiscriminate use of this agent. Mammary carcinoma developing during or after estrogen therapy is sometimes heard of, but such a coincidence must of necessity occasionally occur in view of the frequency of spontaneous breast cancer. Depression of the pituitary, and indirectly of the ovary, by long-continued injections is theoretically possible (Clauberg and Breipohl⁸). Immediate reactions associated with swelling of hands, face and eyes have been noted (Klaften⁹) and unexpected uterine bleeding is not unusual.

B. CORPUS LUTEUM HORMONE

Desiccated tablets of corpus luteum gland have been in use for a long time, but it is only a few years since active preparations have been available. The names under which the hormone passes include progestin, progesterone, corporin, proluton, lipolutein and many others.

The question of units is again a confusing one. Two biologic units have been tried, one based on the use of an adult, the other on an immature female rabbit. The former gives the American or Corner-Allen unit, which is about twice the size of the Clauberg or European unit (Young¹⁰). More recently an international unit has been introduced, which is the equivalent of one milligram of pure crystalline progesterone. This unit is a little larger than the Clauberg rabbit unit, considerably smaller than the Corner-Allen unit. It is well to remember that an international unit of corpus luteum is one milligram, an international unit of estrone one ten-thousandth of a milligram, for otherwise the respective doses of the two substances seem completely out of harmony.

The dosage of corpus luteum hormone is again largely empirical. In castrated women Kaufmann³ found that from 35 to 90 rabbit units (Clauberg) needed to be added to change a proliferative phase produced by estrogenic substance to a truly secretory endometrium. On the other hand clinical results have been reported in dysmenorrhea with dosages varying from 2/25 to one rabbit unit.

The functions of the corpus luteum hormone upon which therapy is based are the following:

- (1) The transformation of a proliferative to a secretory type of endometrium. This effect leads to the use of the hormone in cases of bleeding due to a hyperplasia of the endometrium, and perhaps also in sterility when theoretically due to a deficient corpus luteum preparation of the endometrium.

(2) The control of nidation of the ovum. This function is bound up with the one just mentioned, for the protective effect of the corpus luteum on early pregnancy is in all likelihood the stimulation of early decidual development. The loss of the corpus luteum early in pregnancy is well known to result in abortion, and the hormone has accordingly been given in threatened or habitual abortion on the theory that a natural deficiency in the patient is to be remedied.

(3) Reductions in sensitivity of uterine musculature. Repeated observations and experiments have indicated that under the influence of progestin the uterine musculature becomes less responsive to certain stimuli, such as pituitrin, and that the uterus of certain animals is less active during times when corpora lutea are present. In this respect the effect of progestin is antagonistic to that of estrin. This function has been used to build up a corpus luteum therapy of dysmenorrhea. The same rationale can be found for its use in after pains following labor.

In general, progestin has been available until very recently in amounts too small for its wide trial in physiologically effective doses. No deleterious effects are yet recognized, beyond possibly a disturbance in menstrual rhythm or in the amount of flow.

C. THE GONADOTROPIC HORMONES

There are certainly several substances which affect the ovary and the testis and it is of primary importance to recognize the essential differences in their actions. Two effects on the ovary are of possible clinical importance, the stimulation of follicle growth itself and the luteinization of follicles already present. The former function is, in general, predominant in substances derived from the urine of women in the menopause and from the pituitary gland itself, the latter in products derived from the urine of pregnancy and from the placenta.

(1) The true anterior pituitary hormone is essentially follicle-stimulating. This or related substances have been variously styled FSH (follicle-stimulating hormone), maturity factor, prephysin and gonadogen and prolan A. Even substances within this group undoubtedly differ from each other in their physiologic effects, depending upon their source.

The units of measurement of the follicle-stimulating hormone depend upon the production of mature follicles in the ovary of an infantile rat or mouse or upon an accepted percentage increase in the weight of the ovary or of the uterus. The clinical dosage is quite undetermined, and

it is possible on account of the scarcity and expense of the material that practically all recommended or reported doses have been insufficient to produce true clinical effects.

The use of the follicle-stimulating hormone is based on its known effect in causing development of the ovary and follicle formation. On account of this it may logically be used in any condition of known hypoovarianism and its secondary genital underdevelopment. It is perhaps especially indicated in sterility due to failure of normal ovulation.

(2) The gonadotropic substances derived from pregnancy urine have been called APL (anterior-pituitary-like), prolan B, antuitrin S, antophysin and follutein. The standard on which this substance is measured is based upon the production of corpora lutea in immature rats or sometimes in mice.

The dosage here is again still on an empirical basis but the supply of this hormone is sufficiently great to have permitted the trial of a wide range of dosage. Novak and Hurd¹¹ reported success with 200 rat units daily in cases of functional bleeding. Kurzrok¹² advises 750 rat units daily in cases of severe bleeding. On the other hand, Hamblen¹³ failed to find evidence from endometrial biopsy that ovulation or corpus luteum formation had occurred after total doses of 6,000 to 24,250 rat units in daily amounts of 400 to 8,000 units.

On account of its known luteinizing effect on the immature ovaries of mice, the luteinizing hormone is recommended clinically whenever the corpus luteum is theoretically deficient. Thus it is advised especially in cases of dysmenorrhea and functional uterine bleeding. For the latter, a direct effect on the endometrium itself has also been claimed. The substance is likewise used, although probably without a sound theoretical basis, for various types of ovarian underfunction.

(3) A third hormone of the anterior pituitary is thought to stimulate secretion of the mammary gland. The substance is measured in so-called bird units, depending upon its effect on the crop glands of pigeons. It has been available as prolactin and has been used to stimulate the secretion of milk in the postpartum period (Kurzrok, Bates, Riddle and Miller¹⁴) and in chronic mastitis (Lewis and Geschickter¹⁵).

The dangers of the use of the gonadotropic substances are not known, and are probably not great. On account of the fact that these are complex molecules and are not yet available as pure products, local and general reactions sometimes occur. The luteinizing substance is not be-

lieved to have a simple physiologic effect on human ovaries, and abnormal cystic follicles may be produced (Geist¹⁶). Certain defects produced in the offspring of mice injected with this material have led at least two observers to suggest that anterior pituitary hormone should not be given during the child-bearing period (Wolff¹⁷). The contraindications based on animal experimentation have probably about the validity of indications on the same basis.

D. RADIATION OF THE OVARY

It is perhaps unconventional to include radiation under the heading of endocrine therapy, but this is actually a most precise and effective method of influencing ovarian function. The small dosage of radiation usually employed in gynecologic work shows that it is the ovarian effect which is depended upon in practically all indications, except in the control of malignant tumors.

It is possible to produce certain different effects upon the ovary by varying the radiation dosage. A large dose will permanently suppress the ovarian function by destroying all the follicles, while one which is somewhat smaller, 28 per cent of a skin erythema according to Wintz¹⁸, will cause a temporary amenorrhea by injuring only those approaching maturity. That a still smaller dose has a "stimulating" effect is a possibility raised by certain reported successes in the treatment of amenorrhea and sterility.

The disadvantages of radiation therapy are well known. The disappearance of the original symptoms almost always coincides with the appearance of the symptoms of the menopause. Where a temporary amenorrhea is attempted, the chance of it becoming permanent must be accepted. The possibility of damage to the germ plasm, on the other hand, must be thought of when conception occurs after a temporary amenorrhea. In spite of these objections the place of radiation of the pelvis in the endocrinologic field is assured. The invariable control of functional uterine bleeding in women approaching the menopause is alone a more brilliant endocrine success than anything attained by the injection of hormone substances.

Radiation of the pituitary either to diminish or stimulate function has a much less recognized position. The doubt which usually exists as to the actual relationship of the pituitary to the symptoms, the uncertainty as to dosage, the unknown effect on brain structure, and the not

infrequent loss of hair, combine to make this an unacceptable procedure except in research clinics.

E. THYROID EXTRACT

Thyroid extract must be mentioned in any list of endocrine agents affecting the pelvis. The exact nature of its action on the genital organs is unknown, but the clinical fact of disturbances in the reproductive functions in association with thyroid disease is well established. The frequent reports of thyroid extract successfully used to control pelvic dysfunction, especially in patients who have a low basal metabolism or who are overweight, demands its early consideration in all such cases.

II. DIAGNOSTIC PROCEDURE IN GYNECOLOGIC ENDOCRINE THERAPY

It would be an enormous aid to intelligent therapy if there were satisfactory means of measuring the activity of the ovary and pituitary gland and actually determining the type and degree of dysfunction from which a patient with given symptoms is suffering. Actually, although such terms as "hypopituitarism" and "hyperestrinism" are rather commonly used, they are based largely upon supposition.

Certain tests to measure the function of the ovary and anterior pituitary have, it is true, been in use for some time and are constantly being improved. They represent a thoroughly sound approach to the problem, but one which has as yet limited practical applications. The tests are apt to be overlooked by the majority and perhaps overestimated by the remainder of the profession. A simple attention to details of the history and physical examination will in many cases give as much information as can be obtained. Under certain circumstances, however, a few additional procedures may be of great value.

A. THE HISTORY

Here the patient's age, the evidence of fertility as derived from the dates of her pregnancies and the use of contraceptives, as well as changes in weight, are of fundamental importance. The menstrual history, however, deserves the greatest consideration. It is well to remember that the changes in the timing of the periods must always be ascribed to a deviation from the normal ovarian function in the form of delays or accelerations of the development of the follicle or corpus luteum. Changes in the amount and duration of the flow, especially if this be in

the form of an increase, are much more apt to be due to local causes in the uterus than to a glandular disturbance.

B. THE PHYSICAL EXAMINATION

The physical examination is also of obvious value. The state of the patient's nutrition, especially if there has been a recent pronounced increase or decrease in weight, has a great bearing on pelvic glandular function. Peculiar distributions of fat and hair, although written and talked of considerably, appear to be of little importance unless the degree of deviation from the normal is very marked. A rough gauge of the patient's constitutional degree of reproductive development may be obtained from noting the size of the breast and nipples, as well as the external genitalia, vagina, and uterus. In contrast to this, some idea of existent ovarian function may be obtained by noting the degree of congestion or ischemia of the vaginal and cervical mucous membranes. The palpation of the ovaries may be important, especially if enlarged, and hence probably cystic organs are detected.

C. ENDOMETRIAL BIOPSY

The patient's own endometrium is decidedly the best test object to determine qualitatively, at least, the presence of ovarian and corpus luteum hormones. Fragments of the endometrium are readily obtained without anesthesia by various types of curettes devised for the purpose (Klingler and Burch,¹⁹ Novak,²⁰ Hoffmann,²¹ Rock and Bartlett,²² Campbell, Lendrum and Sevringhaus²³). By correlation of histologic sections with the time in the cycle at which the biopsy is taken, the presence and relative durations of the follicular and corpus luteum phases may be determined. The method may be of special value in the classification of amenorrhea and in the detection of a non-ovulatory cycle as the cause of sterility.

D. VAGINAL SMEARS

It has been shown by Papanicolaou and Shorr⁵ that smears of the vagina from women in the menopause are made up of leukocytes and of compact, round or oval cells with well preserved nuclei from the deeper layers of the squamous epithelium. The follicular phase of the menstruating woman and the vaginal secretions of a menopause patient adequately treated with estrin are characterized by an absence of leuko-

cytes and of the oval nucleated cells, while in their place are found flat, enlarged cells with small pyknotic nuclei. Numerous intermediate types of smears occur, corresponding perhaps to various degrees of vaginal atrophy. The study of the vaginal smears is of some practical use in determining whether an adequate amount of estrin has been given for the treatment of menopause symptoms, and perhaps for the separation of the so-called hyperhormonal amenorrhea from the common type due to ovarian underfunction.

E. BASAL METABOLISM

A basal metabolism determination is of enormous importance in gynecologic endocrinology. It is one of the few tests which are roughly quantitative, and if abnormal readings are obtained, adequate agents are at hand for their correction. A basal metabolism test is particularly indicated where sterility is present with obesity or abnormal bleeding occurs unassociated with a hyperplastic pattern of the endometrium.

F. BIO-ASSAY OF ESTROGENIC SUBSTANCE IN THE BLOOD AND URINE

This procedure is one of the most interesting of the methods of clinical study of reproductive physiology. Many clinicians feel that the ultimate has been done for the patient with a genital dysfunction when she is referred for "hormone studies." Few realize that the procedure is still largely in the research stage and that unless the tests are performed with exactness and enormous labor and expense, they are of absolutely no value.

The assay of a single specimen of urine for estrin involves several chemical steps and the use of perhaps twenty castrated mice or rats. It must also be remembered that the excretion of estrin is quite variable throughout the menstrual cycle, and that a report on a single specimen may give a quite erroneous idea of the patient's ovarian function. Even four specimens taken at weekly intervals may accidentally strike only the peaks or the depressions in the irregular curve of estrin excretion. It is scarcely possible to avoid, then, some system of continuous study, such as the assay of consecutive 72-hour specimens, throughout the cycle. Such a routine is confining to the patient and the actual cost of the test to the laboratory cannot be less than a hundred dollars. Tests made upon the blood are even less satisfactory, for a mouse unit is rarely present in less than 40 cc. The amount of blood that would be required

practically precludes repeated tests or a quantitative assay.

The indications for such an assay of the estrogenic hormones in practice are at present few. If a patient menstruates, it may be assumed that a definite amount of estrogenic substance is being excreted. Furthermore, enough data have not yet accumulated upon urinary assays to define the range which should be considered normal. Only if very large or very small amounts are excreted can the figure be given much significance. In amenorrhea, the test may be of use in determining prognosis and possibly in avoiding the mistake of treating a rare case of hyperhormonal amenorrhea with estrogenic substance.

G. BIO-ASSAY OF GONADOTROPIC SUBSTANCE

The study of anterior pituitary hormone excretion is often attempted in association with estrogenic assays. It must be remembered, however, that except during pregnancy and in pronounced degrees of ovarian underfunction, the gonadotropic hormones are present in the urine in amounts too small for accurate measurement. Various workers, it is true, have reported gonadotropic hormone in the urine of normal women especially at or near the time of ovulation (Zondek;²⁴ Katzman and Doisy;²⁵ Kurzrok *et al*;²⁶ Frank and Salmon²⁷). The results of different workers have varied so much from each other, however, that the test must be regarded as having as yet little value in routine clinical procedures. Certainly the number of units of gonadotropic hormone reported from a laboratory has no absolute significance, and the validity of the entire report depends entirely upon the accuracy and sincerity of the laboratory doing the assay. The field for the tests for gonadotropic hormone in the non-pregnant woman is certainly at present very small. Possibly it may give an indication of the type and prognosis of certain forms of amenorrhea. Other uses for the test may develop with refinement of methods.

H. CORPUS LUTEUM

Corpus luteum hormone cannot be detected in the blood or urine of the non-pregnant patient. For this reason, until very recently, the endometrial biopsy taken shortly before menstruation has been the only way of determining whether a corpus luteum has been produced. The recent discovery that corpus luteum was excreted in the form of sodium pregnanediol glucuronidate (Venning and Browne²⁸), and that this substance could be extracted from the urine and measured, points perhaps

to the development of the most practical of all the tests for the sex hormones. At present the test is merely awaiting its application to suitable series of cases for its clinical value to be determined.

III. THE CLINICAL INDICATIONS FOR THE USE OF HORMONE THERAPY IN GYNECOLOGY

The value of therapy with the ovarian and anterior pituitary hormones has been established to a varying degree for different clinical conditions. For one or two it is to be regarded as almost specific and certainly the first method of therapy to be considered. For another group favorable reports by a number of reputable workers seem to justify its clinical uses, but only after other investigations and procedures have been carried out. Finally, there is a third group represented by a long list of conditions for which endocrine treatment has been tried, often empirically, with occasional successes, often uncritically reported. Hormone therapy for the latter group should probably be restricted to series of cases under scientific study or resorted to in the individual patient only after all other therapeutic measures have failed.

A. CONDITIONS FOR WHICH HORMONE THERAPY IS A MORE OR LESS SPECIFIC THERAPY

1. *The menopause*

For the vasomotor symptoms of the menopause, gynecologists are agreed that estrogenic hormones are the therapy of choice. Many successful series have recently been reported (Albright,²⁹ Houghton and Neville,³⁰ Frank and Salmon,²⁷ Papanicolaou and Shorr⁵). A single recent study (Pratt and Thomas³¹) noted very little difference in the rate of improvement of cases treated by theelin and by other agents. The relatively small dosage employed by these workers is perhaps the explanation of their failure to get better results.

Theoretical estrin requirements in the complete absence of ovarian function have already been discussed. Review of various reports indicates, however, a vast difference in the recommended practical dosage in the menopause. Most workers seem to approve a plan of a relatively large initial dosage with a gradual reduction. The attempt should not be made permanently to maintain the patient at premenopausal levels of estrin blood concentration, but to make the usual abrupt onset of the menopause a gradual one. A convenient plan is to give by intramuscular injection

10,000 international units of estrone or estradiol benzoate twice a week for two or three weeks; then once a week for three weeks with at the same time about 500 to 1,000 units of estriol or some other preparation by mouth; then a period when the substance is given by mouth alone; with finally a period of gradual reduction of the oral preparation. The responsiveness of different patients varies greatly and a few may require as much as 50,000 units twice weekly at the start. Finally, it cannot be too strongly emphasized that a woman entering the menopause with few, if any symptoms, should not be subjected to any attempts at therapy.

2. *Vaginitis*

The demonstration of definite histologic alterations in the vaginal mucosa and changes in the pH of the vaginal secretions gives support to the belief that the estrogenic hormone is also a more or less specific agent for the treatment of certain vaginal conditions, notably gonorrhoeal vaginitis in children and atrophic vaginitis after the menopause. The reports on the treatments of these conditions are only a little less favorable than those for the menopause.

a. Infantile and juvenile gonorrhoeal vaginitis

The first report on the successful therapy of gonorrhoeal vaginitis in children was by Lewis³² in 1933. Since then there have been many corroborative studies (Te Linde and Brawner,³³ Miller³⁴). While some success may be obtained by hypodermic injections of 1,000 to 2,000 international units daily, Lewis and Adler³⁵ now recommend vaginal suppositories of 1,000 units each daily. They obtained 30 negative smears out of 33 cases treated on an average of 20.7 days. Although there seems little doubt of the real effectiveness of this treatment, relapses are prone to occur. It is at least possible that sulphanilamide will supersede the estrogens as the first therapeutic agent to be tried for this disease. No permanent ill effects are believed to result from the premature estrogenic stimulation of the reproductive tract, and although temporary hypertrophy of the breasts and uterus sometimes occurs, these changes disappear after the cessation of treatment.

b. Senile vaginitis and pruritus vulvae can be treated on a rationale similar to that for the cases of juvenile vaginitis. The proliferation of the epithelium and the disappearance of signs of inflammation after estrogen therapy has been begun have been demonstrated in a series of histologic sections from patients before, during, and after treatment (Davis³⁶).

Many reports on this type of therapy have been favorable, both for vaginitis (Davis,³⁶ Jacoby and Rabbiner³⁷) and for vulvitis with pruritus (Rust,³⁸ Klawften,⁹ Wetterwald,³⁹ Schockaert,⁴⁰ Béclère⁴¹).

In the treatment of senile vaginitis care should of course be taken to exclude specific organisms, such as the *Trichomonas vaginalis*, but after such causes have been excluded, estrogenic therapy appears to offer the best chance of success. As regards dosage, the widest possible range has been recommended. Davis³⁶ reported success with 100 rat units subcutaneously, three times a week, the average treatment lasting six weeks, and alleviation of symptoms being usually noted in ten days. Several writers recommend doses as high as 50,000 international unit equivalents of estradiol benzoate once or twice a week for periods of two months. Estrin in ointment (Klawften⁹) or a suppository has been given successfully. On the whole, it seems advisable to give a dosage similar to that employed for the vasomotor symptoms of the menopause, beginning with a dose of 10,000 international units twice a week and gradually reducing it, with a reservation of the dose of 50,000 units for the cases of failure with the smaller amount.

B. CONDITIONS FOR WHICH ENDOCRINE AGENTS MAY WITH JUSTIFICATION BE TRIED AFTER OR IN ASSOCIATION WITH OTHER THERAPEUTIC MEASURES

In this group of cases the value of endocrine agents is still a matter of dispute. Custom has somewhat justified their use. Nevertheless, success is not sufficiently consistent, nor is the rationale always clear enough to permit any of the hormones to be termed specific. No practitioner is justified in beginning and ending his therapy with their use, and heavy responsibility rests upon him if he fails to search for other than endocrine causes for the symptoms.

1. *Amenorrhoea*

In approaching the therapy of amenorrhoea in a younger woman, one must remember that the physiologic basis of the condition is quite different from that of the absent menstruation of the menopause. Complex disturbances in gland relationship, little understood, are present and the simple addition of the ovarian hormone is not necessarily the correct way to relieve the symptoms. Certain diagnostic procedures always must be carried out before sex hormone therapy can be con-

sidered. Constitutional disease, particularly tuberculosis, should be excluded and nutritional disturbances with marked abnormalities in weight attended to. Finally, the basal metabolism must be determined and, if abnormal, correct treatment instituted.

If therapy with one of the sex hormones is to be given a trial, a classification of the amenorrhea should be attempted. There are certainly several types: one, with absent or low ovarian function; one, much less common, with a high or normal ovarian function, the so-called polyhormonal amenorrhea (Zondek²⁴). The differential diagnosis may perhaps be made by observing the condition of the pelvic mucous membranes; more definitely by endometrial biopsy or assay of the estrogenic or gonadotropic excretion in the urine. Many of these cases are probably instances of a primary pituitary disturbance, so that an anterior pituitary hormone is theoretically indicated. The luteinizing hormone of pregnancy urine is not, however, correct from a physiological standpoint, nor has it given satisfactory results. The follicle-stimulating hormone has perhaps not been given sufficient trial in adequate dosage to have its value known, but failures have been reported (Frank *et al*⁴²).

There remains the estrogenic substance which in sufficiently large dosage will often produce some uterine bleeding. Its disadvantage is that usually the only period that occurs is that immediately following a course of therapy. This is to be expected since the drug is essentially substitutional. It is probable, however, that in some cases, 20 per cent according to Mazer and Israel,⁷ the menstrual cycle is successfully "started up" after the first period, perhaps through some effect of the massive dosage on the pituitary. An occasional conception has also been reported following such therapy.

The dosage required to produce a menstrual period in an amenorrheic woman is more variable than in a surgical castrate or a woman in the menopause. Rock used an average of 50,000 rat units of "folliculin" and 50 rabbit units of corporin over a three-week period. Mazer and Israel,⁷ although reporting a high percentage of temporary successes, had one failure in a patient receiving a total of 675,000 rat units. Frank and his associates,⁴² using doses from 80,000 to 3,450,000 international units noted no responses below 1,000,000 international units, and a failure was recorded with the highest dose given. It appears clear, as these workers point out, that other factors besides ovarian deficiency are responsible for amenorrhea.

Amenorrhea in itself is probably not harmful and only in an occasional case will it appear justifiable to give injections of estrogenic hormone. When this agent is employed, short courses with relatively high dosage, possibly 50,000 international units every other day for two weeks, should be given with intervals of a week or two of rest in between. Corpus luteum hormone given in doses of one to five units every day for three or four days at the end of the course of estrogenic therapy may serve to make the bleeding, if it occurs, histologically more realistic, but it is questionable whether it contributes anything toward a permanent cure (Elden,⁴³ Rock⁴⁴). Such treatments, as outlined, are very expensive and the chance of lasting improvement is small.

In most exceptional cases, presumably in those of polyhormonal amenorrhea with cystic ovaries, two other methods of approach may be of help. One is the use of so-called stimulating x-ray to the ovaries, for which considerable success has been reported (Kaplan⁴⁵). The other is a surgical operation with removal of a part of each cystic ovary (Robinson⁴⁶).

2. Abnormal Uterine Bleeding

A careful exclusion or correction of organic causes of uterine bleeding is essential before any endocrine therapy is to be thought of. Systematic physical examination will disclose the majority of these organic lesions, but the possibilities of an endometrial polyp, submucous fibroid or retained placental fragment, even of endometrial carcinoma, will remain. Before the age of forty the frequency of the last cause is so small as to justify some delay in the performance of a diagnostic curettage, but in older patients the physician accepts considerable responsibility in attempting a hormone therapy without first exploring the uterine cavity.

The plan of treatment adopted for abnormal uterine bleeding will therefore differ markedly according to the patient's age. Before the fortieth year endocrine therapy—thyroid extract in cases with a low basal metabolism or either the luteinizing or the corpus luteum hormone itself—may justifiably be tried. After the age of forty, if bleeding recurs following curettage, the best plan is probably to resort at once to some form of radiation therapy with the aim of suppressing completely the ovarian function. Whether, following curettage, hormone therapy is of value to prevent return of the bleeding, is at present unknown and will

be difficult to prove.

The use of the luteinizing hormone of pregnancy urine has already had a number of years of trial. Novak and Hurd¹¹ in 1931 reported improvement in all but seven of fifty-one cases and recommended a dose of 200 rat units, to be repeated one to six times. Wilson and Kurzrok⁴⁷ stated in 1936 that practically every case of functional uterine bleeding could be controlled with pregnancy urine extract if adequate dosage were employed. Their recommended average dose during periods of active bleeding was 200 to 750 rat units daily, followed when the bleeding ceased by 200 rat units once or twice a week for several weeks or months. In contrast to the optimism of these reports is a growing scepticism among many gynecologists, as well as a few definite reports (Keene and Payne⁴⁸, Jeffcoate⁴⁹) which indicate that the brilliant claims of the early investigators are not being substantiated. Opinion is crystallizing that this hormone justifies a trial in bleeding during early and middle life, but that failure frequently follows its use even in these years, and other methods must often be resorted to (Meigs,⁵⁰ Smith and Rock⁵¹).

Corpus luteum hormone has also been advocated for menorrhagia and metrorrhagia (Wilson and Elden,⁵² Stemmer,⁵³ Preissecker⁵⁴) with the object of luteinizing the endometrium which in certain forms of functional bleeding is characterized by a morphology believed to be estrogen-produced. Although Wilson and Elden⁵² have written of successes with small fractions of a rabbit unit, such dosages seem inconsistent with the amounts needed to produce a progestational change in the castrate uterus. Few clinical reports are available, but it would appear that if this form of therapy is to be tried, a dose of at least one rabbit unit daily should be given for several days before the expected excessive period is due, or during intervals of abnormal bleeding.

3. Dysmenorrhea

The theories offered to explain the so-called primary or essential dysmenorrhea are sufficiently varied to furnish grounds for almost any type of endocrine therapy. If the disease is due to the myometrial insufficiency of an underdeveloped uterus, one may with reason recommend an estrogenic substance, while if it is due to a hypersensitivity of the musculature from excessive estrin, then a corpus luteum hormone is to be advised. On the other hand, adherents of a mechanical theory still exist who feel that a dilatation of the cervix or a straightening of the

canal by a stem pessary is the only direct approach to the problem. With the cause of the symptom still unknown, some empirical but systematic plan must be adopted which will start with the simplest measures and work up slowly through the more complicated, in the hope that a means to give relief may be found without the necessity of resort to surgery.

It is again essential that secondary dysmenorrhea due to organic lesions be carefully excluded before the endocrines are thought of. When the pain appears only after several years of normal periods, one must search especially for such conditions as inflammatory disease, a myoma or adenomyoma, or a congested pelvis with uterine malposition.

If no organic basis is found, the next step is to review the possibilities of excessive fatigue, nervous stress, constipation, and other factors capable of affecting the autonomic nerves and the vascular system of the pelvis. An adjustment of the patient's daily activities and the improvement of her general health will yield the largest fraction of the cures to be obtained by the entire list of therapeutic procedures.

If general measures fail, endocrine therapy may be tried, because it is simpler than any form of surgical approach. Two hormones may be considered, estrogenic for the hypoplastic uterus, and corpus luteum for the hypercontractile one (Cannon⁵⁵). Both conditions are admittedly somewhat theoretical entities, especially the latter. In general the patient with a uterus of normal size is most logically treated by progesterone, and with this therapy some successes have been noted (Elden and Wilson;⁵⁶ Lackner, Krohn and Soskin;⁵⁷ Kotz and Parker⁵⁸). Although smaller doses have been reported as effective, a rabbit unit given every other day during the fourteen days preceding menstruation would appear to be a minimum reasonable dosage. Instead of the corpus luteum itself, the luteinizing factor from pregnancy urine has been advised (Novak and Reynolds,⁵⁹ Browne⁶⁰). On the other hand, in patients with very small uteri, estrogenic substance usually administered during the first half of the cycle may be given, either alone or preceding the progesterone injections of the latter half of the month.

It must finally be re-emphasized that no one has yet proved that dysmenorrhea is an endocrine disease, to say nothing of demonstrating the type of glandular dysfunction present. Endocrine therapy of the present types may be counted upon to give frequent failures. The passage of time, marriage and conception are still the factors which determine

the final cure for most women. On account of the occasional necessity for immediate relief, there is still a place for dilatation of the cervix, rarely the suspension of a retroverted uterus, exceptionally perhaps the resection of a presacral nerve.

4. Sterility

An imposing list of diagnostic procedures must be carried out in cases of sterility before a position is reached where hormone therapy is permissible. The male must be examined and the semen studied. Gross lesions in the female pelvis must be excluded, the patency of the tubes determined and any minor infection of the cervix cleared up. The diet should be considered and gross nutritional defects corrected. In the majority of cases a cause for the sterility will be found during these procedures.

If the endocrine field is to be explored, the determination of the basal metabolism is undoubtedly the first step. Cases of hypothyroidism treated with thyroid extract are generally agreed to give the most favorable results in this difficult group. Beyond this is uncertain ground. If the uterus is underdeveloped, relatively small doses of estrogenic substance may be given during the first half of the menstrual cycle over several months time. Kurzrok's¹² recommendation of not more than 75,000 to 100,000 international units, parenterally, or five times that amount by mouth during any one cycle, seems a logical one. In a certain proportion of cases endometrial biopsies, taken shortly before menstruation, may give an indication of the degree of corpus luteum activity and perhaps show the absence of ovulation. In these cases corpus luteum hormone or a follicle-stimulating hormone to induce ovulation may be tried. Finally, when other methods have failed, success may sometimes be obtained by "stimulating" doses of x-ray to the ovaries (Rubin,⁶¹ Kaplan⁴⁵). Even resection of the enlarged cystic ovaries has been recommended, but is not now often resorted to. Surgical procedures should only be undertaken when the patient's desire or need of a child is very great, and she should not be deceived as to the probable chances of success.

5. Habitual and threatened abortion

The causes of abortion are far from understood and it is probable that many are rooted in primary defects of the ova or spermatozoa.

Nevertheless it is tempting to believe that a corpus luteum deficiency, acting either to cause a defective decidua or an overactive myometrium, may play a part in abortion. Providing that other causes are carefully considered, such as hypothyroidism, dietary deficiencies, and organic disease in the pelvis, it is permissible to add corpus luteum as a part of a plan of treatment. Numerous clinical reports are available to indicate its value. Falls, Lackner and Krohn⁶² in 1936 reported success in all but seven of forty-one cases of so-called habitual and threatened abortion. They recommended one rabbit unit twice a day in cases of threatened abortion until the symptoms had subsided and in cases of habitual abortion one rabbit unit prophylactically twice each week until the thirty-second week of pregnancy. That Kane⁶³ in the same year obtained equally good results from treatments with only $1/25$ of a unit is another example of the uncertainty of dosage with these substances. Furthermore if, as appears probable, the smaller dosage was physiologically insignificant, the series of Kane may serve as a control to show what is to be expected in cases of repeated abortion when they are given simply the best of general attention without specific treatment.

6. *Chronic cystic mastitis*

For a number of years certain diseases of the breast, notably that associated with a painful nodularity, have been treated with estrogenic substances. The reported results have been equally good whether the therapy has been by the undoubtedly inert tablets of ovarian residue of 1931 (Cutler⁶⁴) or the potent preparations of 1937 (Lewis and Geschickter¹⁵). Indeed, with the current belief in the estrogenic *cause* of many breast lesions, to find a rationale for an estrogenic *therapy* requires a dextrous rearranging of the physiologic diagrams of endocrine interrelationships.

The above is a personal opinion and it must at once be conceded that many clinical reports do indicate a favorable effect when estrogenic hormone is given to cases of chronic mastitis. In cases in which the possibility of a malignant neoplasm has been unquestionably excluded and the symptoms are severe enough to merit any therapy, estrogenic hormone may be tried. The plan of therapy advocated by Lewis and Geschickter¹⁵ is to give 10,000 international units at each injection, twice a week for six doses the first month; once a week for three doses the next month; twice the third month; and once during the premenstrual

weeks of the fourth, fifth and sixth months of therapy.

In a rare case of marked painful congestion of the breasts in patients near the menopause, radiation of the ovaries will offer a successful means of endocrine therapy. The dramatic relief which follows a reduction in the ovarian function more than compensates for a slightly premature menopause in exceptional cases of this type.

IV. CONDITIONS FOR WHICH ENDOCRINE AGENTS ARE ON TOO UNTRIED A BASIS FOR GENERAL USE

There is, finally, a long list of conditions for which the sex hormones have occasionally been tried, but for which the conscientious physician should resort to endocrine therapy with considerable hesitation. The conditions placed in this group have been so classed for several reasons. First, the indications may be relatively rare and sufficient cases have not yet accumulated to afford material for adequate trial. Second, the original reports of success may have remained relatively uncorroborated and the silence of other physicians be suggestive of disappointment. Finally, the general nature of the condition, as we now know it, may be such as to make the sex hormones appear too remotely related to promise an effective influence. It is conceded that arguments could easily be brought to transfer certain of the conditions listed in group III to group II and vice versa. Certainly it is probable that the next few years will see many changes in classification. In general, however, a case may be made for the statement that the endocrine treatment of the diseases to be listed in group III has neither the support of proved efficiency, of established rationale, or even of accepted practice.

The conditions which might be placed under group III are too numerous for more than an incomplete list.

A. ESTROGENIC HORMONE

1. Hypertension (Schaefer;⁶⁸ Wallis;⁶⁶ Fellner⁶⁷).
2. Involutional melancholia (Schube and associates,⁶⁵ Sevringhaus,⁶⁹ Werner⁷⁰).
3. Migraine (Glass;⁷¹ Blakie and Hossack;⁷² Thomson⁷³).
4. Frigidity.
5. Epilepsy (Schaefer and Brosius⁷⁴).
6. Eclampsia (Shute⁷⁵).
7. Vomiting of pregnancy (Hawkinson⁷⁶).
8. Postmaturity and missed abortion.
9. Uterine inertia (Robinson⁷⁷).
10. Menopausal arthritis.
11. Urinary incontinence (Hoffmann⁷⁸).
12. To delay menstruation (Foss⁷⁹).
13. Hemophilia (White,⁸⁰ Kimm and Van Allen,⁸¹ Birch⁸²).
14. Atrophic

rhinitis (Mortimer, Wright and Collip⁸³). 15. The Cushing syndrome (Dunn⁸⁴).

B. GONADOTROPIC HORMONE

1. Migraine (Moffat⁸⁵). 2. Acne vulgaris (Lawrence⁸⁶).

C. PROLACTIN

1. Deficient lactation (Kurzrok, Bates, Riddle and Miller¹⁴).

D. CORPUS LUTEUM HORMONE

1. After pains (Lubin and Clarke⁸⁷). 2. Pernicious vomiting. 3. Premature labor.

CONCLUSION

The present status of gynecologic endocrine therapy places the physician in a dilemma. He cannot forswear these substances completely, because his patients will demand them. He cannot use them too frequently without appearing something of a charlatan to his more sceptical colleagues.

A year or so ago an editorial in the *Journal of the American Medical Association* (October 24, 1936) urged that only those physicians with facilities for critical study be encouraged to administer the new preparations and that other physicians should "cease their indiscriminate injections of unknown substances into unsuspecting patients." This advice cannot and should not be taken too literally. The physician with facilities for critical study has produced too many studies far from critical. Furthermore, a report of a percentage of successes with a new plan of therapy from a large clinic is only the beginning of its trial.

A new endocrine preparation, after one or two series of cases have been published, must be subjected to the test of its use in practice. Its final adoption will depend not upon whether a certain per cent of a series of fifty women are benefited, but whether it is sufficiently dependable to be used on a special case in whom an individual practitioner is individually interested. That the final test rests, therefore, with the general profession gives justification for the present cautious administration of these substances.

The use of the so-called sex hormones, however, involves certain

responsibilities. He who prescribes them must be certain of at least three things: (1) that conditions other than an endocrine disturbance have been excluded as the cause of the symptoms; (2) that experienced authorities regard the new material as safe; (3) that there is a rational basis and at least some expert testimony to the efficacy of the substance in treating the disease for which it is to be given.

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