

## OVARIAN THERAPY

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It is a matter of keen disappointment to clinicians that the new knowledge gained by science of the function and properties of the female sex hormone has not led to a more effective therapy. But as Novak<sup>1</sup> well points out, the clinician expects some brilliant specific panacea that will cure every functional disorder to which the complex female pelvic mechanism is heir.

There are numerous reasons why ovarian substance, at least in its present therapeutic form, should be comparatively nonpotent. In the first place the incretory power of the ovary in the normal adult woman is directed chiefly to the pelvic organs for purposes of reproduction, and has little to do with the other functions of her general organism. This is shown by the comparatively small harm that is done by the removal of the secretion. The ovary is not an organ of the same vital significance as the suprarenals, the hypophysis and the thyroid, nor are its extracts as toxic as those of other ductless glands. Not only do ovarian preparations have little influence on the general organism but even in their proper field of the genital system they are comparatively inert. One should not, as a matter of fact, expect too much of a substance which in the performance of its natural function leads such a constantly changing existence. As Fraenkel<sup>2</sup> says, the ovary, in contrast to the other endocrine glands, all of which exercise a stable function, is in a continual state of transformation. In one phase it stimulates hyperplasia and bleeding while at another time in the month its action may be quite the contrary. Commercial extracts, therefore, prepared from many ovaries in different phases must necessarily possess complex and varying potencies, a fact that is sufficiently well demonstrated by the familiar inconstancy of their therapeutic action.

As the chemical composition of the hormone is only partially known and has not been isolated in its pure state, the processes of extraction have necessarily not been perfected. Frank<sup>3</sup> criticizes the commercial preparations on the ground that most of them are "degreased" or "defatted," thus depriving them of those lipoid elements with which the hormone is closely combined. Moreover, it must be remembered that whereas in the body the ovarian secretion passes directly into the circulation, ovarian therapy when administered orally requires that the substance pass through the digestive apparatus, so that a chemical disturbance in the secretion, amounting possibly to destruction, is inevitable. Novak<sup>1</sup> also calls attention to the inefficacy of the watery extracts dispensed in ampules and ascribes their popularity either to a psychic element or to the presence of protein factors that stimulate glandular structures generally.

For the foregoing and doubtless many other reasons, ovarian organotherapy has made but little advance in the many years during which it has been employed. The subject is at present in a state of confusion and flat contradictions. Some competent observers go so far as to deny that the commercial preparations of the

1. Novak, Emil: The Pharmacology of Ovarian Preparations, J. A. M. A. 83: 2016 (Dec. 20) 1924.

2. Fraenkel, L.: Biologie und Pathologie des Weibes, 1923, part 4, p. 588.

3. Frank, R. T.: The Ovary and the Endocrinologist, J. A. M. A. 78: 181 (Jan. 21) 1922.

ovary have any appreciable therapeutic value whatever. Many clinicians, on the other hand, who have long employed them, such as Novak,<sup>1</sup> Fraenkel<sup>2</sup> and Lissner,<sup>4</sup> and many others among whom I include myself, agree that in the treatment of the vasomotor disturbances of the menopause, ovarian substances are distinctively though not constantly efficacious. I agree with Lissner<sup>4</sup> that the word "gland" has a magic effect on the imagination of women of the modern feminist school, but after discounting the psychic effect which undoubtedly plays a part in some cases, the foregoing statement is supported by clinical evidence that cannot well be disregarded. If ovarian substance is proved to be of marked value only in the single instance of treating menopausal symptoms—and in my experience it acts in this respect almost as a specific—ovarian organotherapy hardly deserves the ridicule that has been heaped on it.

Lissner<sup>4</sup> conveniently classifies glandular preparations in three groups according to their practical usefulness. In class A he includes "those endocrine extracts which are standardized, strongly potent, uniformly reliable and specific, and which, when properly administered under appropriate circumstances, will yield consistent and convincing results." Inclusion in this class postulates that the extract shall supply specifically the deficiency of the normal increment. The only glandular extracts with class A honors are thyrotoxin for myxedema and insulin for diabetes mellitus. The admission of solution of pituitary to this class hangs on the decision as to the pituitary origin of diabetes insipidus.

Ovarian preparations have obviously not won a place in class A, but Lissner justly assigns them to class B on account of their near-specificity in the treatment of menopausal symptoms. Class B is described as including "those endocrine substances which in the hands of trustworthy clinicians have produced remarkable improvement in specific deficiency syndromes, where the favorable response to the gland administered seems incontrovertible; but where such satisfactory results have not occurred with sufficient dependability or consistency to justify placing the extracts in class A."

But ovarian substances have been called on for service in many fields other than that of the menopause, and in these fields they have either shown only questionable usefulness or have signally failed. For this reason ovarian therapy has suffered greatly in reputation. Of the many conditions other than the menopause for which it is employed, I shall mention only those which have a more or less logical basis for its use. They are: deficiencies of menstruation, sterility, abnormal uterine hemorrhage, and dysmenorrhea. Other indications are so haphazard and far fetched in their rationale that they may be safely ignored.

In estimating the therapeutic results of a drug like ovarian substance it must be recognized that conclusions are based purely on clinical empiricism, which is in no sense an exact scientific method of research. It is open to innumerable sources of error when there are no laboratory tests by which the course of the disease may be accurately measured, as in diabetes and myxedema. Thus, in judging the results of ovarian therapy on subjective symptoms such as those of the menopause, one must consider not only the psyche of the patient but that of the physician, especially if he is of

an enthusiastic temperament. The possibility of spontaneous improvement irrespective of the drug, and the influence of other factors, inherent and environmental, many of which are more potent than the medication itself, must be taken into account. In cases in which the results sought are objective, as in sterility and menstrual disorders, coincidence and extraneous influences lead to many false conclusions. Bearing these sources of error in mind, I shall discuss briefly the other indications for ovarian therapy which in my opinion have some logical basis.

#### MENSTRUAL DEFICIENCIES

Defective menstruation is commonly classified as (1) amenorrhea (absence of menstruation), (2) hypomenorrhea (scanty flow), and (3) oligomenorrhea (delayed or infrequent menses).

Permanent amenorrhea may be due to certain systemic diseases, such as tuberculosis or grave anemia. Most commonly it is a manifestation of a genital hypoplasia or regression and is associated with other changes suggestive of a pituitary origin, such as adiposogenital dystrophy. In these cases the counteracting influence is obviously something deeper seated and more powerful than a simple ovarian deficiency, and the failure of so feeble a drug as the present commercial ovarian preparations is a foregone conclusion. In the temporary functional amenorrheas, oligomenorrheas and hypomenorrheas, especially if there is no marked genital hypoplasia, it is quite reasonable to expect benefit from ovarian treatment. The effect that extracts of the female sex hormone have in reproducing the normal estrual changes in the vagina and uterus of spayed animals, an effect so distinctive and constant that it is used as a laboratory test for the presence of the hormone,<sup>5</sup> leads one to suppose that similar reactions should be evoked in human organs. As a matter of fact, many of us who have used ovarian drugs extensively have frequently noted successful results after ovarian therapy in these cases for which, after discounting the possible errors, we are convinced that the ovarian substance was responsible. These results hardly warrant us in placing the ovarian substance when used for menstrual deficiency in class B, but we do feel that we are not stretching our conscience in awarding it a grade of B minus or perhaps a C plus in Lissner's marking system.

#### ABNORMAL UTERINE BLEEDING (FUNCTIONAL)

In dealing with abnormal uterine bleeding, the logical indication of ovarian therapy is much less clear. The exhibition of extracts from one and the same organ for two such opposing conditions as amenorrhea and menorrhagia has to the uninitiated always been a puzzle. It has long been assumed that the ovarian hormone influences ovulation and precipitates menstruation. On the other hand, Fraenkel and his school teach us that the corpus luteum inhibits menstruation and ovulation. They say that when impregnation occurs the corpus luteum persists in order to prevent menstruation and to preserve the endometrial soil for the nesting of the egg. If impregnation does not occur, the inhibiting influence of the corpus luteum is released and the flood-

4. Lissner, Hans: *Organotherapy: Present Achievements and Future Prospects*, Endocrinology 9: 1 (Jan.-Feb.) 1925.

5. Frank, R. T., and others: The Occurrence and Present Chemical Status of the Female Sex Hormone, *Endocrinology* 10: 260 (May-June) 1926. Frank, R. T.: Function of the Ovary: A Résumé, *Am. J. Obst. & Gynec.* 12: 585 (Oct.) 1926. Allen, Edgar, and Doisy, E. A.: An Ovarian Hormone, *J. A. M. A.* 81: 819 (Sept. 8) 1923. Allen, Edgar, and Doisy, E. A., and others: The Extraction and Some Properties of an Ovarian Hormone, *J. Biol. Chem.* 61: 711 (Oct.) 1924.

gates of menstruation are let loose. An attempt has been made to show that the ovary manufactures at least two hormones, one of which stimulates the growth of the genitalia and increases menstruation, the other being inhibitory. Experimental evidence to support this view is not convincing. The theory of a dual or triple ovarian hormone has been discredited to a great extent by the work of Frank<sup>5</sup> and his collaborators, Allen and Doisy,<sup>6</sup> Zondek and Aschheim,<sup>6</sup> and others. They have demonstrated the presence of the female sex hormone in the follicles, corpus luteum, circulating blood, menstrual blood and the placenta, and have shown that the hormones extracted from these localities are identical in their properties. Zondek<sup>6</sup> sums up his observations on the subject by saying: "There is only one ovarian hormone that embraces all the hormonal functions" (Es giebt nur ein Ovarialhormon, das alle hormonalen Functionen auslöst).

Wintz<sup>7</sup> and Seitz and Fingerhut have compared the hormone activities of the fresh and matured corpus luteum. From the fresh organ they have extracted a substance, lipamin, which stimulates menstruation, while from the full-blown corpus luteum they find a substance, luteolipoid, which inhibits menstruation. The apparent reverse action of the hormone in the young and the old corpus luteum is explained by Wintz not as a specific change in the hormone itself but by the fact that in the luteolipoid preparation there are split protein products which exert the luteolipoid action. All these conflicting theories leave us very much in the dark as to the specific action of the corpus luteum hormone, and until the question can be settled we must fall back on clinical experience as our guide. We have never been successful in treating uterine hemorrhages with glandular preparations and have long since discarded them. Abnormal uterine bleeding demands immediate diagnosis by biopsy, and as a rule, even if it is functional, more radical treatment than that of drugs.

#### DYSMENORRHEA

What has been said about the relationship of ovarian therapy to deficient menstruation applies to dysmenorrhea. Essential dysmenorrhea is for the most part a manifestation of defective development. There is usually an obvious underdevelopment in the uterus itself. If the proper evolution of the pelvic organs is due to the integrity of an ovarian secretion, the defect in the uterine structure would naturally suggest a defect in the ovarian apparatus; but this is by no means always the case. Normal ovaries may be found in association with extreme hypoplasia of the müllerian tract, even one amounting to rudimentary traces. Since ovarian treatment is incapable of altering the development of the genitals of a matured woman, it is not to be expected that it will have much effect on the dysmenorrheic pain of a hypoplastic uterus. The pain of essential dysmenorrhea is located in the uterus, probably at the internal os, which is usually anteflexed and is the result of the spasmodic contractions of an abnormally formed or placed muscular structure.

I have had in my practice, however, numerous cases of essential dysmenorrhea in which pain is consistently relieved after the administration of ovarian therapy. Most of these patients have been girls between 18 and 25 years of age, usually of nervous type, in whom there

have been but slight signs of uterine hypoplasia. It is impossible to tell whether the effect of treatment in these cases is psychic or coincidental, or whether there are certain particularly favorable cases of essential dysmenorrhea which the drug actually does influence in some beneficial but unknown way. The fact that many of these patients return repeatedly for more of the substance over long periods of time is suggestive but not conclusive evidence of a specific benefit.

Dysmenorrhea in its broader sense means difficult menstruation. Essential dysmenorrhea relates to the purely functional disturbance and excludes those acquired pathologic conditions, the pain of which appears or is accentuated at the period of menstrual congestion. Essential dysmenorrhea usually implies spasmodic, cramplike pains emanating from the uterus. But, strictly speaking, it includes certain other moliminal symptoms that may be associated with the typical pain or that may occur independently with little or no uterine pain. These other manifestations consist of general abdominal discomfort, indigestion, nausea with or without vomiting, headaches, nervousness, dizziness and flashes, all suggestive of an analogy to menopausal symptoms. For these symptoms I have for many years prescribed ovarian substance with sufficient apparent success to persist in the treatment as a routine measure. The effects following treatment for these conditions approach but do not equal those attained in the treatment of the menopause. My observations, unpublished, have received encouraging support in the report of Sharlit, Corscaden and Lyle.<sup>8</sup>

#### STERILITY

The causes for sterility are legion, most of them being of a mechanical or pathologic nature. But there are undoubtedly cases in which sterility is due to functionally defective ovulation. Just what is the nature of the *vis a tergo* which precipitates the rupture of the wall of the matured follicle and the discharge of the egg is a matter of speculation, but it is generally believed that the ovarian hormone plays at least a part in stimulating the process. It is therefore reasonable enough to suppose that in certain cases in which the inherent function of the ovary is inadequate to overcome the resistance of the follicle wall the aid of an artificial supply of hormone may be sufficient to accomplish the result. Reports in the literature of the successful use of ovarian therapy for sterility are few. It will be found, however, that those who use it extensively not infrequently observe a following pregnancy that strongly suggests a causal effect on the part of the extract. If these cases were collected, they would probably make an impressive showing. The chances of drawing wrong conclusions are so great, however, that no one is justified in making a didactic statement on the subject. It is safe enough to say that there is a possibility that in some cases ovarian therapy cures sterility, and that the evidence in favor of this possibility is stronger than that which denies it.

It should be added that some clinicians (Sajous,<sup>9</sup> Solomons,<sup>10</sup> Hirst<sup>11</sup>) have reported pregnancies in previously sterile women which they have attributed

6. Zondek, B., and Aschheim, S.: Zur Funktion des Ovariums, Klin. Wehnschr. 5: 400 (March 5) 1926.

7. Wintz, A.: Die physiologisch-chemische Wirkung des Follikelsaftes, Arch. Gynäk. 113: 457, 1920.

8. Sharlit, Herman; Corscaden, J. A., and Lyle, W. G.: Symptoms Associated with the Menstrual Cycle and the Effects Thereon of Ovarian Therapy, Am. J. Obst. & Gynec. 10: 246 (Aug.) 1925.

9. Sajous, L. T. M.: The Corpus Luteum in Therapeutics, New York M. J. 103: 227, 1916.

10. Solomons, B.: Sterility, Surg. Gynec. Obst. 30: 173 (Feb.) 1920.

11. Hirst, J. C.: The Use of Corpus Luteum Extract Hypodermically in Cases of Repeated Abortion Without Demonstrable Cause, Am. J. Obst. 77: 662 (April) 1918.

to the effect of corpus luteum administration. I have had one such suggestive case. As we have seen, there is much evidence that the corpus luteum in its normal habitat inhibits menstruation and ovulation, and that its persistence causes sterility (Beard,<sup>12</sup> Prenant,<sup>13</sup> Loeb,<sup>14</sup> Ochsner,<sup>15</sup> Hess,<sup>16</sup> Williams<sup>17</sup>). If it is assumed that the corpus luteum does in some cases cure sterility, a curious inconsistency presents itself. The biologic explanations of this contradiction are ingenious but not clear. It would seem that one of three alternatives must be chosen: first, that the corpus luteum preparations cannot really cure sterility (possible); second, that the theory of corpus luteum inhibition is wrong (improbable), and, third, that the corpus luteum contains complex varying elements, hormonal and otherwise, about which little is known (probable).

As to the different ovarian preparations there is much contradictory evidence. I shall treat the subject by giving my own experience. I began using desiccated corpus luteum for menopausal symptoms many years ago when the drug was first exploited. I was encouraged by an occasional success but found the preparation unreliable and often productive of digestive disturbances. I then employed the whole ovary with distinctly better results. On account of this obvious improvement it occurred to me to eliminate the corpus luteum altogether and try the remaining ovarian substance. The clinical results from this preparation were strikingly more uniform than from the other two. At that time the portions of the ovary that remained after removal of the corpus luteum were thrown away as useless. Preparations from it could therefore be furnished at low cost and were designated by Parke, Davis & Co., who were preparing the material for me, as the "ovarian residue." I published a report of my results in 1917.<sup>18</sup> In recent years I have employed the residue almost exclusively and in large amounts. I secure the substance put up in capsules directly from the manufacturer (now Hynson, Westcott & Dunning) to insure its being fresh. The commercial preparation in tablet form I have found to be of little value. My explanation of the comparative failure of corpus luteum preparations was that at certain stages the corpus luteum is effete, functionless, and in the process of disintegration. In the indiscriminate collection of these bodies, there must be many that are inert, perhaps even toxic; hence their effectiveness must be inconstant. There was at that time sufficient theoretical evidence that the follicles produce an active hormone, the elaboration of which I thought must be more uniform than in the changing corpus luteum. I at first used the residual ovarian tissue of pregnant pigs, on the theory that follicle atresia is more active during pregnancy. It afterward became impossible to secure the ovaries of only pregnant animals. There was, however, no particular change in the results with nonpregnant and pregnant ovaries combined.

The foregoing explanation based purely on empiric clinical evidence was criticized as unsound. Recent experimental work on the localization of the sex hormone lends confirmation to my results. Allen and Doisy,<sup>5</sup> in their earlier experiments, were unable to

demonstrate any hormone in the pig's corpus luteum. Frank<sup>5</sup> showed that it would produce the vaginal reaction in mice only in intense concentration. He furthermore pointed out that only in one stage, namely, at the beginning of retrogression, does the corpus luteum store the sex hormone. My early observations that corpus luteum extracts were sometimes toxic have been verified by experimentalists (Frank,<sup>19</sup> Livon<sup>20</sup>) who described toxic effects following the intravenous and intraperitoneal injection of corpus luteum extract, such as dyspnea, convulsions, and death (Kennedy<sup>21</sup>).

Moreover, my contention that the ovarian substance should theoretically be more stable than the corpus luteum has received further confirmation from the recent work of Frank, who was the first to demonstrate the sex hormone in the follicle liquid. In contrast to the corpus luteum, he finds the follicle hormone highly potent even in the pure unconcentrated state. His observations have been amply confirmed by others.

I conclude, therefore, that for gynecologic purposes, with the exception of abnormal uterine bleeding, ovarian preparations devoid of the corpus luteum or at least those which include the whole organ with its follicle apparatus, are the rational choice.

Whatever the type of preparation used, there is no doubt that it must be used in a comparatively fresh state in order to be potent. It is interesting to note in the literature dating from the earliest articles that the majority of those who report success in the treatment have secured their drugs directly from the manufacturer.

#### CONCLUSIONS

1. Ovarian substance is a near-specific in the treatment of hot flashes and the vasomotor disturbances of the menopause.

2. It is ineffective in permanent amenorrhea with hypoplasia, but is useful in certain conditions of menstrual deficiency.

3. It is ineffective in the treatment of menorrhagias and metrorrhagias.

4. It is occasionally useful in cases of essential dysmenorrhea not associated with marked hypoplasia, and is frequently successful in treating the moliminal symptoms of dysmenorrhea.

5. In the treatment of sterility, instances of pregnancy following ovarian therapy are sufficiently common to suggest that in certain cases of deficient ovulation ovarian therapy may effect a cure.

6. Preparations of the whole ovary or the ovarian residue are more efficacious than those of the corpus luteum alone, since they contain the more highly potent hormone from the follicle apparatus and are free from the toxic and inhibitory elements that contaminate the corpus luteum.

7. Fresh gland preparations are imperative.

8. There is sufficient clinical and experimental evidence to encourage the hope that ovarian extracts, now admittedly feeble and inconstant in their action, will under the direction of research be produced of such potency as to be of constant specific value in the treatment of a limited number of functional pelvic disorders.

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15. Ochsner, E. H.: *Surg. Gynec. Obst.* **31**: 496 (Nov.) 1922.  
16. Hess, E.: Die Sterilität des Rindes, Hanover, 1921.  
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18. Graves, W. P.: Ovarian Organotherapy, *J. A. M. A.* **69**: 701 (Sept. 1) 1917; *Gynecology*, ed. 3, p. 67.

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