Lutein extract in the treatment of decreased menstruation and the premature menopause / Ellice McDonald, M.D., New York.

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LUTEIN EXTRACT IN THE TREATMENT OF DECREASED MENSTRUATION AND THE PREMATURE MENOPAUSE

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Disturbances of menstruation are always difficult of treatment. The factors which cause and control menstruation are so little known and understood that treatment is largely empirical and experimental. Investigation into the function of the ovary and its influence on menstruation and pregnancy are, however, beginning to shed new light on these processes, and give hope of the relief of these conditions by scientific treatment.

INTERNAL SECRETION OF THE OVARY

The function of the ovary and the effect of its internal secretion are becoming better understood, and the influence of the corpus luteum on menstruation and pregnancy are now being studied experimentally in animals.

Brown-Séquard[1] appears to have been the first to suggest an internal secretion for the ovary and supposed that it was concerned in the secondary sexual characteristics. Since then many investigators have sought the presence and mechanism of the production of this internal secretion. Gustav Born[2] first suggested the hypothesis that the corpus luteum of the ovary was a gland with an internal secretion which affected the uterus and presided over the nidation and development of the ovum. Fraenkel,[3] by means of extensive experiments claims to have maintained Born's hypothesis that the corpus luteum is a gland with an internal secretion and that

1. Brown-Séquard: Compt. rend. Soc. de biol., 1889.
2. Born: Quoted by Fraenkel, Arch. f. Gynak., 1903, xviii, 438.
3. Franekel: Arch. f. Gynak., 1903, lxviii, 438.

the corpus luteum causes the menses. He claims that as the corpus luteum is an organ sharply defined from the rest of the ovarian substance, and surrounded by connective tissue, histologically it resembles a gland, being similar to the liver or suprarenal. He holds that there is no essential difference between the true and false corpora lutea, which are ovarian glands controlling the nutrition of the uterus from maidenhood to menopause and causing insertion and development of the fertilized egg, and menstruation when the egg remains unfertilized.

TROPHIC INFLUENCE OF CORPUS LUTEUM

These facts are upheld by a long series of his experiments on rabbits, in which he found that if the corpus luteum was destroyed during the early part of pregnancy, while embedding of the ovum was in process, pregnancy always terminated. The trophic influence of the corpus luteum, carried by the vessels, is exercised on the uterus and is necessary to the insertion of the egg. The influence of the so-called false corpus luteum was also determined on non-gravid animals by burning them out, when temporary atrophy of the uterus occurred. Also, in a number of non-gravid women at operation, the corpora lutea were burned out, with the result that menstruation remained absent for one or two periods.

Daels[4] attacks Fraenkel's conclusions as being too sweeping. He denies the hypothesis of a specific function of the corpus luteum in regard to the embedding and development of the ovum. He also denies that the development of the corpus luteum, with its internal secretion, produces menstruation or that maturation of the follicle and menstruation are in a regular causal relation to each other.

While Fraenkel's conclusions are sweeping and can be maintained only by facts very difficult of proof, Daels' denial of the value of his work in its entirety is unjustified, and it may be considered proved that while maturation of the follicle and the secretory action of the corpus luteum may not cause the menses, at least menstruation is much influenced by it. We know undoubtedly that menstruation cannot occur without the ovaries and that the formation of the corpus luteum is a peri-

4. Daels: Surg., Gynec. and Obst., February, 1908.

odic affair, and may be of the same periodicity as menstruation. It is probable, therefore, that the corpus luteum may have an action on the uterus as a hormone, or "chemical messenger." Just as the injection of dilute mineral acid into the duodenum provokes a secretion of pancreatic juice, so the secretion of the luteum may stimulate the uterus to menstruation or aid in embedding the ovum.

Kleinhaus and Schenck[5] have brought additional evidence of the influence of the corpus luteum on fertilization. Their experiments show that, after the embedding of the ovum, destruction of the corpus luteum does not cause interference with the pregnancy; but before the ovum is embedded, termination of the pregnancy usually occurs.

INFLUENCE OF THE OVARY ON UTERINE NUTRITION

Carmichael and Marshall,[6] from their experiments on rabbits, also show the great influence of the ovary on uterine nutrition. They state that removal of the ovaries in young animals prevents the development of the uterus and Fallopian tubes. These remain in an infantile condition, but otherwise, the growth and general nutrition of the animals seems unaffected. They state that removal of the uterus in the adult animal does not give rise to any degenerative change in the ovaries if the vascular connections of the latter are intact. Bond,[7] however, claims there is evidence that there is a substance, a clear watery saline fluid, of low specific gravity, which is elaborated in the uterus between menses, which stimulates the growth of the corpora lutea, and that its absence favors overgrowth of the lutein tissue in the ovary. Holzbach,[8] however, has shown that the ovaries will persist in their function in women after removal of the uterus, and that an adequate amount of ovarian tissue, capable of function, was found in four patients, reexamined several years after the first operation of hysterectomy.

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5. Kleinhaus and Schenck: Ztschr. f. Geburtsh. u. Gynäk., 1909, lxi, 2.

6. Carmichael and Marshall: Brit. Med. Jour., Nov. 3, 1907.

7. Bond: Brit. Med. Jour., July 21, 1909.

8. Holzbach: Arch. f. Gynäk., 1905, lxxx, 2.

Rebaudi[9] had also shown that the removal of the ovary is prone to cause a compensatory hypertrophy in the other glands of internal secretion. He removed the ovaries in animals and found within two weeks a gradual progressive hypertrophy of the islands of Langerhans in the pancreas. He then found that when the corpora lutea alone were destroyed with the cautery, the changes occurring in the islands of Langerhans were essentially similar to those which occurred when the whole ovary was removed. He presents this as direct proof that the corpora lutea are organisms of internal secretion, and that they represent the main, if not the only, tissues of the ovary having an internal secretion.

INFLUENCE OF THE THYROID AND SUPRARENAL GLANDS ON SEXUAL CHARACTERISTICS

The influence of the thyroid amongst glands of internal secretion on the menstruation and sexual characteristics is not unknown. Disturbances of menstruation are common with exophthalmic goiter. Patients under my care have had menstrual disturbances following thyroid medication for obesity. The menstrual flow was more profuse, and in some cases, twice monthly. Galante[10] reports three cases of goiter in which there was marked change in the menstruation following galvanization of the thyroid gland.

The suprarenal gland has been shown in a forcible manner by Bullock and Sequeiria to have an influence over sexual development. Several cases in which the suprarenal was the seat of a tumor were collected, and showed that there was marked precocious sexual development in children, with development of the uterus and secondary sexual characteristics.

These evidences of the effect of the glands (other than the ovary) with an internal secretion, show that it is possible that compensatory action may occur in the absence of the direct ovarian or lutein internal secretion.

OVULATION

The time of ovulation is not, as a rule, synchronous with menstruation, but rupture of the follicle may occur at any time in the menstrual cycle. Leopold and Hav-

9. Rebaudi: Gynéc. mod., December, 1908.
10. Galante: Ann. di elettr. med. e terapia fisica, 1909.

ano,[11] from the investigation of 95 cases at operation, found that in only 59 did ovulation occur at the same time as menstruation, so that it is possible that ovulation may occur at any time in the month. Villemin[12] states that rupture of the follicle usually occurs ten or twelve days before menstruation, and that the period after rupture corresponds to the production of the corpus luteum. These facts are interesting in determining the time at which lutein therapy should be applied each month.

It is obvious, therefore, that the consensus of opinion of experimenters and investigators is that even if the corpus luteum of the ovary is not the cause or exciting stimulus of menstruation, at least this internal secretion of lutein has a distinct influence on the production of menstruation. Therefore, it is possible that if this lutein or corpora lutea is supplied to the organism, menstruation may be influenced in some degree. With this aim, numerous investigators have obtained corpus luteum extract of the ovary from animals, with the hope of being able by opotherapy to influence menstruation and particularly, the surgical menopause.

Fraenkel reported good results with the lutein extract, and Ferroni[13] made a study of the effect of injections of corpora lutea of the ovary in animals, and reported much better results from the lutein alone than when the whole ovary was used. He believed that the effect of the injected corpora lutea was cyclic, and that there was profound metabolic change. Magalhaes[14] also reported good results with the lutein extract clinically. Many others have reported good results.

CLINICAL EXPERIMENTS

With the hope of being able to benefit some of the persistent cases of premature and surgical menopause, I have been for nearly five years experimenting clinically with a desiccated extract of corpora lutea of the ovary of cows, obtained by skinning the outside of the ovary with a sharp knife in order to obtain as much of the essential substance as possible, drying and powdering. The cow was chosen on account of the relatively large amount of lutein cells present.

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11. Leopold and Ravano: Arch. f. Gynäk., 1909, lxxxviii, 3.
12. Villemin: La Gynecologie, May, 1908.
13. Ferroni: Ann. di Obstet. Gynec., May, 1907.
14. Magalhaes: Brazil med., Aug. 22, 1907.

I did hope to continue this study until 100 cases had been treated and the results studied, when more definite conclusions might be formed and correct therapeutic indication decided; but the publication of an article by Morley,[15] with conclusions contrary to mine, led me to report this small series of 20 cases at this time. Morley, using the same product, supplied the lutein extract to ten physicians, who returned a report of 18 cases to him. Fourteen were cases of surgical menopause, and one physician treated as many as five. It is needless to say that in a condition as obscure as the surgical menopause, as easily subject to spontaneous variations of condition, and as dependent on the individual verbal report as to the condition, this form of investigation is to be deprecated. The surgical menopause is a condition which time cures and psychotherapy may benefit. It can not be expected that definite conclusions can be drawn from one case or therapeutic indications be discovered by five. I have, therefore, been induced to report this small series with the hope that physicians may not be led to expect to find in lutein extract a universal panacea for that protean disturbance, the surgical menopause.

I have treated in all twenty cases. Ten of these cases were of scanty menstruation or approaching premature menopause. Ten were cases of surgical menopause. These cases will be discussed according to these two classes.

PREMATURE MENOPAUSE

The condition of premature menopause is one which attacks comparatively young women, between twenty and thirty-five years, and is marked by lessened menstruation, with various nervous manifestations, such as headaches, flushes and other neuroses. The condition is said by some writers not to occur before 33 years, but the establishment of the complete menopause often extends over several years, and the first effects of the condition are frequently to be observed in much younger women. It is usually associated with the lack of sexual function, as the condition is more common among spinsters and quite often dates from an illness or some definite change in nutrition or environment. This lack of sexual function in these women is curiously in conson-

15. Morley: Jour. Mich. State Med. Soc., November, 1909.

ance with the experiments of Bond who found that, in unilateral oöphorectomy in animals, the hypertrophic changes in the ovary with the formation of corpora lutea were maintained if repeated copulations were allowed.

In these ten cases of scanty menstruation, seven patients were benefited by the administration of extract of corpora lutea, gr. v. (0.3 gm.), three times daily before meals. The earlier the case was treated, the more definite seemed to be the results. The three chronic cases, in which the patients were not benefited were well-established cases with marked nervous symptoms, and did not respond to the treatment. One of the patients improved after dilatation of the cervix with the administration of the corpora lutea extract; but as it was doubtful whether the corpora lutea extract, which had been ineffectual, without the operation, was in any way responsible for the improvement, the case was classed amongst the unimproved.

The menstruation, in the seven cases of improvement, increased in amount and duration of flow. Two patients reported marked change in the character of the flow. In one very remarkable case, the patient was brought back to her normal duration of flow, of four days, while taking the lutein extract, and while untreated, menstruated two days. She was treated for three alternate months and flowed four days, while at the three alternate months untreated, she flowed two days. This seemed definite evidence of the effect of the corpora lutea in this case.

SURGICAL MENOPAUSE

Amongst the ten cases of surgical menopause, one patient was made distinctly worse, and the treatment had to be discontinued. Five were not improved and four reported some improvement. The patient who was made worse had had hysterectomy for fibroid tumor, in which an ovary had been left. The treatment was begun immediately after the operation, and caused such severe disturbance at the time of the expected menstrual period that treatment was discontinued. The patient did not suffer as markedly from the surgical menopausal symptoms after the discontinuance of the lutein extract. It is possible that the lutein excited the activity of the remaining ovary.

Another case was one of removal of both tubes and one ovary, with resection of the second, in the hope that by leaving a remnant of the ovary menstruation would continue. The remnant of the ovary remaining was about 2 by 1 cm. The menstruation did not appear for three months; after treatment for one month with lutein extract, menstruation reappeared and continued regularly thereafter. The small remnant of ovary has swollen to the size of a hen's egg, and there is pain in that region before menstruation. It is thought that the enlargement is cystic in character.

The remaining cases of surgical menopause in which the patients were benefited by the lutein extract were those in which the treatment was begun after operation, and there was no way of judging how severe the menopausal symptoms would have been without treatment.

The five patients not benefited had had hysterectomy where the menopausal neurosis was well established.

Thus, in the ten cases of surgical menopause, only one patient was definitely helped. Five were absolutely uninfluenced, and three were doubtful.

If patients with surgical menopause, in whom the uterus has been removed, are expected to be benefited by the lutein extract of the ovary, why are not those patients who have had hysterectomy, with retention of the ovaries, much benefited by the presence of these lutein-forming organs with their internal secretion? Holzbach[16] has shown that the ovary after operation retains its function, and he also states that those patients who retain a functioning ovary suffer in a more marked degree from symptoms of the surgical menopause. The majority of gynecologists now, I think, believe that the retention of the ovary after hysterectomy is ineffectual in the control of the surgical menopause, unless sufficient of the uterus remains to allow menstruation.

INTERNAL SECRETION ONLY ONE FACTOR

The manifestations of the surgical menopause are too varied and extreme to allow explanation by the mere absence of the internal secretion of the ovary. The internal secretion of the ovary is but a factor in the process of the menstrual life. It may be the hormone or "chemical messenger" which stimulates the uterus to one of its functions. Let no one expect to control these

16. Holzbach: Arch. f. Gynäk., 1905, lxxx, 2.

physical changes and nervous alterations of the surgical menopause by the supply of an artificial internal secretion of the ovary unless, at the same time, a new uterus to menstruate can be supplied.

But the study of this condition of surgical menopause, with its nervous and often psychopathic symptoms, is one fraught with many pitfalls. Patients are often so influenced by any treatment that it is difficult to decide which is the help. Time cures the condition and the treatment often gets the credit. I have had patients benefited by Eddyism, osteopathy, cold baths and chromium sulphate. However, in my ten cases of surgical menopause, I cannot be sure that any patient was definitely helped except that one in whom the uterus was retained. Gellhorn[17] has reported a somewhat similar case, in which menstruation, which had been absent for six months, reappeared after the administration of ovarian extract, and a regular flow ensued.

Amongst the seven cases of scanty menses or premature menopause, definite improvement resulted. In all cases there was an attempt at the same time to improve the nutrition. Three married women voluntarily stated that there was a definite increase in sexual desire. I did not question any in this regard. One patient, a woman over 45, with commencing menopause, has been under treatment for three years, with the result that the menses are still regular, and after she had been under treatment for eight months she conceived and miscarried. Her last child was born 18 years before this. She still continues the medication in the hope that she has discovered the fountain of youth.

The greatest result in every case was obtained when treatment was begun early and when the treatment was given over at least two weeks of each month. A few patients complained of nausea after meals or in the morning during the treatment.

CONCLUSIONS

The results of this study, small though it be, extending over five years, seems to indicate that the control of the surgical menopause need not be sought in the corpora lutea. Its value is in cases in which the uterus and ovaries or uterus alone are retained. Particularly is it valuable in the treatment of scanty men-

17. Gellhorn: Zentralbl. f. Gynäk., Oct. 17, 1907.

struation and the premature menopause. I have treated a number of cases at the outdoor dispensary of the Kensington Hospital for women, with extract of the whole ovary, and never saw any definite results therefrom. But the lutein extract, being the essential part of the ovary, does seem to help in some degree, and should be accompanied in suitable cases, by dilatation of the uterus, with the use of the stem pessary following operation, as advised by Manson.

At least, the administration of lutein is indicated after operations on pregnant women in whom miscarriage is feared. This is particularly true in the early weeks of pregnancy, during the embedding of the ovum, as it has been shown experimentally that the corpus luteum has a definite effect under such circumstances.

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