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Menopause, with special reference to endocrine therapy

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SENIOR THESIS

THE MENOPAUSE

With special reference to endocrine therapy.

April 20, 1933.

Harry A. Jakeman

A discussion of all phases of the menopause would be practically impossible in a paper of this nature. Everyone connected with the medical profession, however, is well acquainted with this syndrome and realizes the importance of its place in the medical curriculum regardless of the particular line of medicine in which one may be interested.

By way of introduction, I will discuss briefly the menopause as to etiology, symptomatology, and course, the chief object of this paper being that of therapeutics.

Tilt, in 1882, was perhaps the first man to write intelligently and scientifically upon this subject. His work was published in book form. In this publication, he attempted to define the condition as follows: "The terms 'climacteria' in Latin; 'climacteric disease', 'change of life', 'critical time', 'turn of life', in English; 'temps critique', 'age de retour', and 'menopause', in French; and 'aufhoren der weiblichen reinigung' in German; are understood to mean a certain period of time, beginning with those irregularities which precede the last appearance of the menstrual flow, and ending with the resettlement of health".

Tilt recognized the fact that this phenomenon was, in all probability, due to ovarian changes and he called attention to the atrophied condition of the reproduction system of women going through this change. Tilt says, "While involution is taking place, the ovaries disturb the viscera, with which they have worked harmoniously for thirty years". At that time, the nature of the disturbance was not known but was thought to be similar to

that made manifest by the coming into power of the ovaries at puberty, because the symptoms at both periods of life are very similar.

Treatment at this time consisted chiefly of sedation and general constitutional measures - baths, etc. Bromides were used by Tilt with a fair degree of success. Bleeding was also done by many practitioners at this time.

Some fifteen years later, Currier published his work on the menopause. In this work Currier states, "For many centuries, the importance of the menstrual function in women has been a recognized fact among critical observers. Its significance has of course, been differently interpreted by observers in different ages and in different conditions of intellectual development. Among the crude, the barbarous, and the superstitious, the solution of such a problem would not be one which would be universally satisfactory. Even among highly developed nations, like that of the Greeks, the interpretation could not be expected to conform to the facts because of imperfect knowledge in physiology and anatomy".

The Egyptians, who investigated so many matters concerning the human body, realized that menstruation was an important function. This is shown in the books of Moses, much information of which was derived from Egyptian sources, and in which a menstruating woman was declared ceremonially unclean, coitus with her being forbidden. But while the importance of menstruation was quite generally recognized among the more acute of the ancient observers, it was not so with the menopause. By some it was passed over as a matter occult and inexplicable, and, in general, it failed to receive that broad and philosophic treatment with which so many questions were discussed by the ancients.

Currier defined the menopause as the condition which exists and the collective phenomena which appear in connection with the cessation of menstruation. This cessation takes place gradually in most cases, the intervals between the menses lengthening, and the latter finally failing altogether, after a period from one to three or four years. During this time, the phenomena are varied in character. With some women there is scarcely any consciousness that anything unusual is occurring aside from the fact that the inter-menstrual intervals are longer than usual. With other women, the hemorrhages, if less frequent, are much more profuse. The nervous system may be unaffected or there may be disturbance of both cerebro spinal and sympathetic systems. Vasomotor disturbances are extremely common, and mental disturbances are by no means rare. In cases in which there is predisposition to the development of new growths, such growths may develop at this time.

Atrophic changes take place in all the genital organs as the menopause progresses.

Finally, the menopause may be as uneventful as any of the other necessary experiences to which the female economy is subjected, but it is also susceptible to variation as far as possible in the opposite direction.

While Tilt considered the menopause as a serious, critical time in a woman's life, Currier was prone to consider it a normal, physiological process through which every normal female must pass. In fact, nearly all writers at this time were beginning to become more conservative as to their ideas regarding the menopause.

Treatment of the menopause as outlined by Currier, shows very little improvement or advance as compared with that of Tilt. Currier's outline consisted chiefly of sedatives, bleeding to relieve congested organs, and

curettage. In conclusion, Currier says, "There is little additional which can be said in regard to the general treatment of those who are passing through the menopause. Those who are not sick, but think they are, must be disillusioned with gentleness but firmness. They must be assured that the process is a physiological one through which the great majority of women pass unharmed; and yet the unusual sensitiveness of both body and mind at this juncture must be fully recognized and proper caution enforced against all means which could destroy the sensitive equilibrium. Those who are sick must be treated upon rational principles, not by superstition or tradition. Surgical conditions should be recognized promptly and promptly treated and those who are susceptible to relief by drugs should receive remedies which are tried and reliable, not the nostrums and cure-alls of the quacks".

In 1921, Emil Novak published his work on the disorders of menstruation in which he included a detailed discussion of the menopause. The advance between the time of Currier and Novak is remarkable. Novak regards the menopause as marking the termination of the reproductive stage of a woman's life, the most prominent clinical manifestation of this transition period being the cessation of the menstrual flow.

In Novak's experience, he found that more women ceased to menstruate between the ages of 45 and 50 than between the ages of 40 and 45, the average being about 47 years.

Speaking generally, it seems to be true that the earlier the menstrual function is established, the longer it will continue. In other words, if puberty occurs at an early age, the menopause is likely to be late in its appearance, the reverse being equally true.

According to Sanes, the climacterium is usually late in the case of women who have led an active **sexual** life, especially if they have given birth to a number of children. On the other hand, it is likely to occur early in unmarried women.

As a rule, the menopause occurs earlier in the women of cold climates than in those of the tropics.

An unusually early or unusually late menopause is said to be noted in certain families as a hereditary trait. Examples of such families are cited by Currier and others.

The menopause, as a general rule, occurs earlier in poor, hardworking women than in those living in idleness.

The menopause is frequently seen at an early age in stout women. Cases of this type are now looked upon as due to a deficiency of the pituitary secretion. The two most prominent symptoms encountered in these cases are obesity and sexual hypoplasia, manifesting itself in the woman as scanty menstruation or an actual cessation of the process.

General diseases associated with wasting and general debility tend to bring about an earlier menopause than usual, the cessation of the function in such cases being apparently an effort on the part of nature to conserve the strength of the woman.

In the great majority of cases, the effect of local disease in the pelvis is to delay the occurrence of the menopause.

Tilt has published a very interesting table as to the approximate age at which there is a cessation of menstruation. I shall include it on the following page:

Age of cessation	Paris B. De Boismont's cases	London Guy's cases	London Tilt's cases	Total cases
21st year	2	-	-	2
22nd "	1	-	-	1
25th "	-	-	-	-
26th "	1	-	-	1
27th "	1	1	1	3
28th "	1	1	-	2
29th "	1	-	-	1
30th "	-	1	10	11
31st "	3	1	-	4
32nd "	2	-	4	6
33rd "	-	2	1	3
34th "	4	1	2	7
35th "	6	3	6	15
36th "	7	1	2	10
37th "	4	5	7	16
38th "	7	5	6	18
39th "	1	7	10	18
40th "	18	33	42	93
41st "	10	24	17	51
42nd "	7	24	26	57
43rd "	4	23	24	51
44th "	13	24	23	60
45th "	13	45	49	107
46th "	49	34	31	74
47th "	13	25	42	80
48th "	8	38	37	83
49th "	7	25	32	64
50th "	12	37	49	98
51st "	4	14	27	45
52nd "	8	13	16	37
53rd "	2	8	9	19
54th "	5	2	7	14
55th "	2	1	6	9
56th "	2	2	4	8
57th "	2	1	2	5
58th "	-	-	4	4
59th "	-	-	1	1
60th "	1	-	1	2
61st "	-	-	2	2
Total	181	400	501	1082

Average age of cessation (1082 cases) - 45 years 9 months. The average duration of the menstrual function was found to be 28.95 years by B. de Boismont, and 31.33 years by Tilt.

There are marked individual variations in the duration of the menopausal period. It must be borne in mind that the cessation of the menstrual function is only one, though perhaps the most striking, of a whole group of changes which mark the retrogression of the reproductive function. Properly speaking, the menopause embraces all these various phenomena and from this viewpoint, its duration is from a few months to several years. The average duration may be placed at from two to two and one-half years according to Novak.

As the woman approaches the climacteric age, even while the menstrual function is still regular, she is likely to experience more or less of the vasomotor disturbance which, next to the disappearance of the menses, is the most important manifestation of the menopause. From time to time, there will be an intense though transitory flushing of the head and neck, accompanied by a sensation of flashing heat. This is frequently followed by sweating, sometimes copious. The temperament of the woman is quite likely to undergo some change though only exceptionally, is this very profound. Usually this change is evidenced only by unusual nervousness, irritability, and peevishness. By this time, there has probably been more or less disturbance of the menstrual rhythm. Whereas the menses have been recurring at regular four week intervals, and have been lasting perhaps four or five days, they now become usually more scanty, lasting only a day or two. There may be even a complete skipping of one period. This may be followed by scanty menstruation for a month or two, and then will come another period of amenorrhea. In this gradual manner, the menstrual function tapers off into complete disappearance. The vasomotor symptoms usually continue for a longer or shorter time after

the cessation of menstruation, their disappearance also being gradual as a general rule. In the majority of cases, there is a tendency to laying on of adipose tissue, sometimes amounting to an actual obesity.

This is the typical course of the menopause. However, the symptoms may be so slight as to be scarcely noticeable and in other cases, they may be very severe. As before, it is stated that the duration of the symptoms varies greatly. The psychic changes may go on to insanity though rarely is this true.

All the anatomic changes demonstrable in various organs at the menopause are indicative of the universal retrogression which characterizes this period. Marked atrophic changes are seen in the tissues of the vulva. The fat of which the labia are so largely composed disappears almost entirely, so that they become little more than two long skin folds. The clitoris becomes very small. As a result of the so-called senile atrophy, with its attendant thinning of the epithelial layer, the mucous membrane of the vulva loses its velvety, vascular appearance, and becomes thin, pale, and transparent looking, giving the surface a rather pasty appearance. The vagina becomes narrow and contracted, the result of the same process of senile atrophy in which there is a replacement of parenchymatous by interstitial tissue. The vaginal mucosa like that of the vulva, becomes thin and atrophic. The cervix becomes very small and short. The uterus also becomes very small and hard, the endometrium becomes thin and avascular. The fallopian tubes also participate in the retrogressive processes of the menopause, becoming shorter and thinner. The fimbriae disappear or become very inconspicuous as do also the longitudinal rugae in the mucosa. The size of the ovary is much changed in the majority of cases. The surface is not glistening as in the case of the young woman, being now of an opaquely white appearance. The

peculiar wrinkling at this time resembles the surface of a peach stone. The mammary glands also become small and atrophic in the majority of cases.

With the foregoing discussion serving to introduce the menopause in general, a more detailed discussion of therapeutic measures will be attempted in the following pages.

The higher the standard of general health and resistance with which the woman enters upon the menopause, the better her chance of passing through it with a minimum of discomfort. It is scarcely necessary to discuss at any length the importance of such factors as care in diet, proper sleep, bathing, avoidance of constipation, and especially, the avoidance of worry and anxiety of any sort. Strict insistence by the physician on the carrying out of these measures and an intelligent cooperation on the part of the patient, will do much to relieve the suffering of the woman who is passing through this trying period.

The woman who approaches the menopause in good physical health is much less likely to suffer severe disturbances than the one who arrives at this period worn out by physical disease, many child births, domestic cares, anxieties, and other such causes. Of special importance is the avoidance of worry and anxiety. The brunt of the menopausal storm seems to fall upon the woman's nervous system and this should be spared in every possible way. Members of her family should be urged to show her every consideration in this trying period whenever pronounced temperamental changes may make themselves apparent.

Drugs are almost always necessary in addition. Of sedative drugs, those in most common use are opium by mouth, and the bromides, phenobarbital and similar drugs. To secure sleep, it is almost always necessary

to give some hypnotic such as barbital, medinal, sulphonal, chloral, or paraldehyde. Sometimes alcohol at bedtime will secure sleep. In the majority of cases, Elixir triple bromide will give very good results - the dosage depending upon the severity of symptoms.

The most recent advances in therapeutics have been made along the lines of endocrinology, the results in some cases having been gratifying and in others, very disappointing.

The ovaries have a twofold function. First, they have an excretory function of producing and discharging ova, and second, an incretory function of regulating the growth and maintaining the function of the genital organs. In 1827, Von Baer demonstrated the mechanism of ovulation, and for long after, it was believed that the stimulation of this process accounted for those phenomena that are now known to be the result of internal secretions.

The present knowledge of the physiology of the female reproductive organs was initiated by Knauer who, in 1896, showed in experimental animals, that transplantation of ovaries prevents the usual atrophy of the uterus that follows ovarian extirpation. This experiment proved that the ovaries must produce an internal secretion which, acting through the medium of the blood, preserves the integrity of the genital organs. Knauer's conclusions were immediately verified by other investigators (Grigorieff, Ribbert, and Rubinstein). In the year 1900, Halban added a new and important phase to the subject by showing that if an immature female guinea-pig is castrated and an ovary transplanted subcutaneously, normal puberty occurs. This proved that the ovaries produce an internal secretion that governs the anatomical and physiological development of genital organs, and also for the atrophy with ovarian dysfunction at the menopause.

Clinical attempts at substitution therapy were made by administering ovarian extracts for all kinds of menstrual disorders but with little success - a failure which has clouded the career of ovarian hormonology up to the present time. But the result of animal experimentation with these same extracts has been a different and remarkable story.

Adler in 1912 was the first to produce sexual activity in ovariectomized animals by the injection of watery extracts of ovary. Adler's work marks the turning point in the history of the search for the ovarian hormone.

Most people thought of the internal secretion of the ovary as a single substance but were perplexed at the multifarious and contradictory functions of which it was capable.

The final triumph of the female sex hormone came in 1928 when Allen and Doisy in this country, and a few months later Butenandt in Germany, announced the isolation of the hormone in crystalline form from the follicle.

But there were also many doubters who still believed that the corpus luteum must elaborate a specific hormone entirely distinct from that of the follicle liquid. Corner, in 1929, settled this question beyond dispute when he isolated the corpus luteum hormone which he called "progestin". The relationship of theelin and progestin will be discussed later.

Allen and Doisy identified the follicular extract by the changes it produced in the uterine and vaginal epithelium of rodents. The extract was also standardized by this means. The vaginal smear from a rat's vagina at rest or atrophied from castration consists chiefly of leukocytes. Under the influence of natural or artificial oestrous, the smear shows great numbers of non-nucleated squamous epithelium. The rat unit as defined by

them is the "highest dilution of an extract which, when given to a mature spayed rat in three injections at four hour intervals during the first day, will result in cornification and desquamation of vaginal epithelium on the morning of the third day".

Corner established a test for the corpus luteum secretion similar in nature to that used for the follicular secretion. The experiment was carried out as follows: A doe rabbit is mated and eighteen hours later is subjected to removal of both ovaries and the excision of a small portion of the uterus. Corpus luteum extract is administered for five days and on the sixth day after mating, the animal is killed, the embryo recovered if present, and the uterus submitted to histologic examination and comparison with the specimen removed at the time of castration. Under the influence of the extract, the uterus undergoes the characteristic progestational changes. To the eye and under the microscope, the condition of such a uterus can in no way be distinguished from that of normal pregnancy of the fifth or sixth day except that after large doses, the proliferation may be even greater than in normal pregnancy.

The same experiment was performed using folliculin (theelin) instead of progestin, but none of the progestational changes could be produced.

The synergistic relationship between the follicle and corpus luteum has been demonstrated by a number of striking experiments.

Corner and Hartman, working separately on the sex cycle of menstruating monkeys, both found that these primates sometimes menstruate in regular course without any preceding ovulation or corpus luteum formation in the ovaries. The endometrium in such cases does not show the pre-menstrual changes typical of true menstruation following ovulation. They therefore concluded that in primates at least, there are two types of menstruation, one where there is ovulation, and a pre-menstrual growth of endometrium

and one where these changes are absent. They then injected theelin into castrated monkeys and produced menstruation, but without the pre-menstrual proliferation of the mucosa. Corner, and also Hisaw, next tried sensitizing the mucosa by injections of theelin and then following this with a series of injections of progestin. After this double treatment, true menstruation ensued with characteristic pre-menstrual proliferation of the mucosa. From this experiment, they reasoned that the function of the follicular hormone seems to be that of putting the uterus in the proper physiological condition so it can respond to the corpus luteum hormone. Neither of these substances can produce progesterational proliferation in the castrate uterus when given alone. If, however, it is first brought into condition typical of oestrus through the injection of follicular hormone, and is followed immediately by corpus luteum treatment, progesterational proliferation results.

We come now to a relationship between the internal secretions of the ovary and those of the hypophysis. Knowledge that such a relationship exists dates back to 1901 when Frolich described his famous syndrome of hypo-pituitarism, adiposogenital dystrophy, and hypo-sexualism.

Later experiments by Zondek and Aschheim proved that by transplanting a fresh piece of anterior lobe in an infantile mouse, a condition of oestrus was invariably brought about.

On the other hand, anterior lobe transplantation has no effect on the vagina and uterus of an ovariectomized animal. In a normal animal, it causes oestrus and also ovulation and luteinization in the ovaries.

It was soon found that two substances were contained in this pituitary extract as the same result was not always obtained. The two substances were isolated - chiefly by Zondek and were called Prolan A and Prolan B, Prolan A

being a follicular ripening hormone and Prolan B a luteinizing hormone. Zondek also holds that there are two other substances contained in the anterior lobe, and summarizes the situation as follows:

PROLAN

1. Growth hormone
2. Prolan A - follicular ripening hormone.
3. Prolan B - luteinizing hormone.
4. Metabolism hormone.

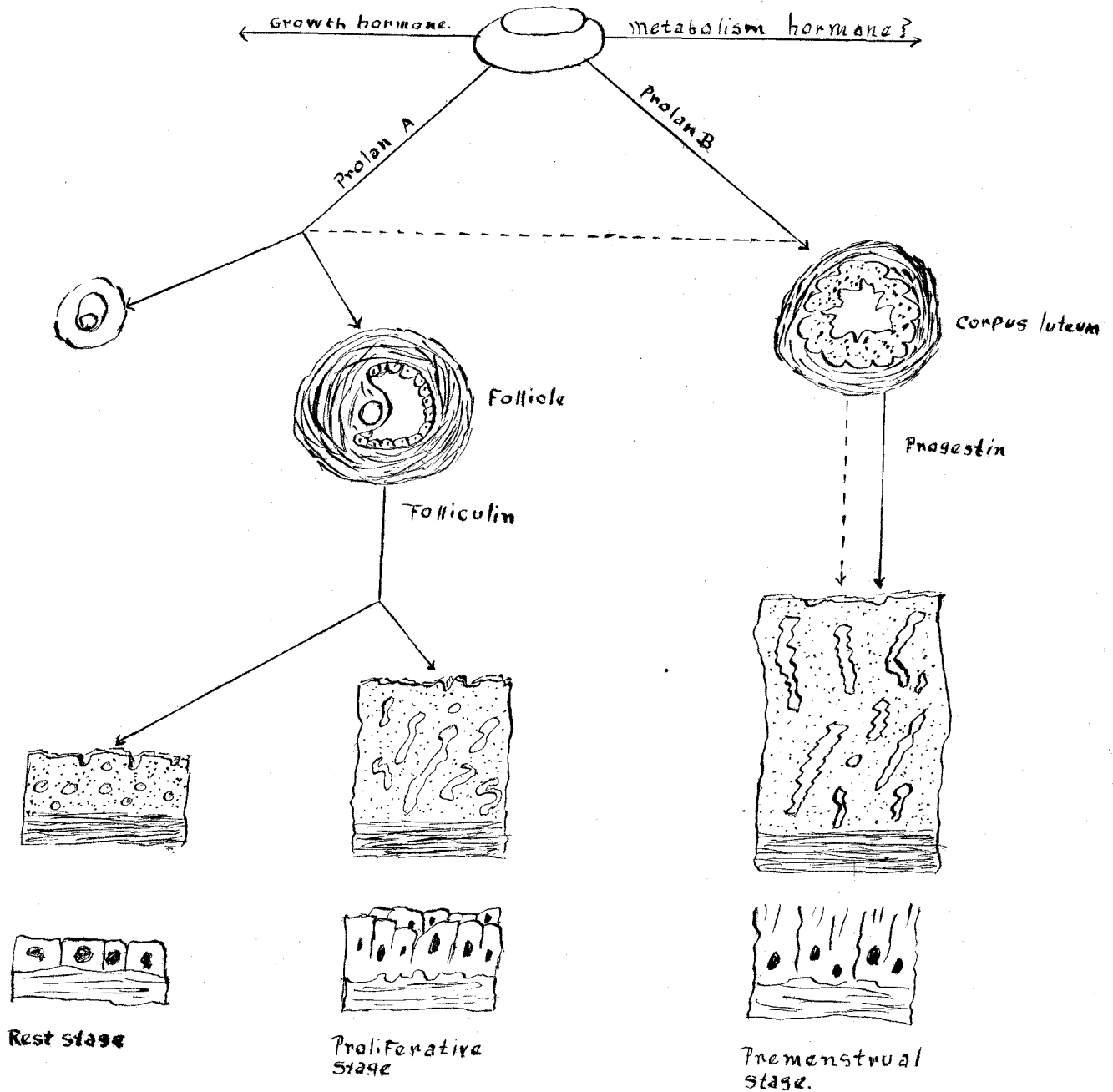
Zondek, after making this discovery, correlated the pituitary hormones with those of the ovary as follows:

1. The female sexual function manifests itself in the following way: the anterior lobe of the hypophysis is the motor of the sexual function and the hormones of the anterior lobe are the superordinated specific hormones of sex.

2. Prolan A sets off follicle ripening and incites the theca cells of the follicle to the production of folliculin which in turn induces the proliferative phase of the endometrium.

3. Prolan B effects the change of the granulosa and theca cells to lutein cells and incites in them the production of progestin which changes the proliferative phase of the endometrium to one of secretion (pre-menstrual, pregravid, pregestational stage.)

Correlation of the hormones of the hypophysis and the ovary are very well illustrated in Zondek's diagram, appearing in Grave's work on the female sex hormone and illustrated on the following page.



Prolan A, starting from the hypophysis stimulates the growing follicle to the **production** stage of folliculin which, in turn, stimulates the proliferative stage of the endometrium. A small amount of folliculin is excited in the corpus luteum as indicated by the broken line. Prolan B stimulates the lutein cells of the corpus luteum to the production of progesterin. The hypophysis also elaborates the special growth hormone and a probable metabolic hormone.

Frank found that the urine and serum of women going through the menopause, contained little or none of the female sex hormone using the vaginal smear test of Allen and Doisy.

Bearing in mind the foregoing facts, the clinical application of these extracts will be discussed.

The premise that menopause symptoms are associated with a cessation of ovarian function is both reasonable and logical. As a corollary, it may be stated that the loss of the dominant ovarian secretion - the female sex hormone would appear to be a most important factor, although the increase in pituitary hormone must be taken into account. On this basis, attempts to replace this loss of female sex hormone by a substitution therapy are surely indicated.

Since so many hormones have been identified and described it is unreasonable to believe that any one hormone alone can be responsible for the symptoms encountered in the menopause. It will be necessary as pointed out by Frank and others, to analyze chemically or by other means, and to determine in just what hormone or hormones we are lacking, and to substitute accordingly.

According to Frank, in addition to the usual clinical examinations, which in those cases which are worked up, include a careful history, anthropometric measurements, basal metabolism, differential blood count, and, when indicated, sugar tolerance, seller roentgen and visual field examinations, certain hormone tests should be performed.

The hormone tests which Frank advocates in properly selected instances include the evaluation of the female sex hormone blood level thruout a cycle, or, if no periodicity exists, over a period of from five to six weeks, with simultaneous determination of the hormone excretion through the urine. Tests for the prepituitary hormone have been studied, but thus far no satisfactory results have been obtained. The tecnic for the female sex hormone are now sufficiently standardized to permit the study of a considerable number of cases each month in small laboratories not possessing special equipment.

The treatment of menopausal symptoms has yielded varying results in the hands of different gynecologists. Kurzok offers an explanation for this in his paper on "Follicular hormone in the urine as an index of therapy in the menopause." Kurzok found that those patients who are not benefited by ovarian therapy have ovarian hormone in the urine while those that are benefited have none. Kurzok has determined that every normal woman during her active sex life excretes from ten to twenty rat units of follicular hormone per liter of urine. This level of excretion is fairly constant, though there are minor variations within these limits during the menstrual cycle.

Kurzok has grouped cases of menopause as follows:

- (1) No ovarian hormone found in urine.
 - (a) Artificial menopause (x'ray or operation)
 - (b) Some cases of spontaneous menopause.
- (2) Ovarian hormone present in the urine.
 - (a) Some cases of spontaneous menopause.

The subjects that show no ovarian hormone in the urine

are very distinctly benefited by therapeutic injection of the hormone, while those that show ovarian hormone in the urine are not at all benefited by the treatment. When both ovaries have been removed at operation or when sterilization due to radiation is complete, no follicular hormone is to be found in the urine. In the spontaneous menopause group the subjects that menstruate normally and have menopausal symptoms, ovarian hormone is always found in the urine, and the administration of more ovarian hormone is of no benefit. When the patient menstruates infrequently and the excretion of ovarian hormone is sporadic, then follicular hormone is beneficial. In subjects that are not menstruating, follicular hormone may or may not be found in the urine; it is only in the latter group that good results are obtained.

All cases of menopausal symptoms are investigated and treated in the following way: A twenty-four hour specimen of urine is collected from 7a.m. to 7a.m. The urine collected at 7a.m., at the end of the 24 hours is kept in a separate bottle. The larger quantity of urine collected on the previous day is subjected to a quantitative follicular hormone determination. The separate morning specimen is tested for the presence of gonadal stimulating hormone, prolactin A, by the method of Zondek. When ovarian function has ceased the findings are as follows: Ovarian hormone, negative; prolactin A, positive. Zondek has shown that when the ovaries cease functioning prolactin A immediately appears in the urine. On the other hand, if the ovaries are

functioning ovarian hormone is found in the urine and prolactin A is absent. Only when there is no ovarian hormone in the urine according to Kurzok is theelin indicated as a therapeutic measure. There is apparently no reason for injecting ovarian hormone when the patient is already excreting considerable quantities of the hormone in her urine.

Kurzok treats patients having hormone in the urine by means of triple bromides and calcium lactate, the purpose being to depress the irritability of the vasomotor and the other centers involved.

Theelin has been given orally to women, whose urines were followed for its excretion over a period of one or two months. Eight cases are reported by G.V. and O.W. Smith, which includes four amenorrheic patients, three sterile and one normal control. The results would indicate that in women as in rabbits theelin is excreted only when the organism has been exposed to the action of corpus luteum. It appears possible by this means to differentiate between a persistent corpus luteum, irregular appearance or total absence of corpus luteum, and cyclic activity of the corpus luteum.

In Kincaid's experience there are two types of patients who may be benefited by ovarian therapy: The sterile woman who has not conceived, apparently because of the lack of sufficient ovarian hormone, and the woman suffering from the symptoms so often seen at the beginning of the menopause.

Kincaid reports three cases of menopause occurring pre-

maturely in which he used theelin in massive doses(100 rat units a day for 6 days). Gratifying results were had in all three cases.

Two objections are generally raised regarding the hypodermic use of theelin: first, the need to use a needle and the necessity of monthly repetition. A third objection can be raised, namely, the cost of the preparation which, judged by usual drug prices, is high. The patients generally feel however that the injections are worth the cost, and readily submit to monthly injections when necessary. The local reaction from hypodermic injection has been found to be very slight in amount, and not contraindicative to its use.

Kincaid closes his paper with this statement: "It seems from my experience, that any woman is entitled to a trial of treatment with follicular hormone, who presents her self to her physician, giving a clear cut history of diminishing menses accompanied with subjective symptoms of the menopause, in the absence of any other demonstrable pathologic condition.

Definite conclusions cannot be drawn from three cases, but it is further testimony that ovarian therapy is meeting with a certain degree of success.

King of Johns Hopkins has published a paper in which he attempts to compare the therapeutic effect of ovarian therapy with that of bromides and pheno barbital. The results were recorded as follows: If symptoms disappeared entirely under treatment the result was expressed as "plus 100;" if the symptoms

were much improved as "plus 75;" improved substantially "plus 50;" slightly improved, "plus 25;" If symptoms became much worse under treatment the result was entered as "minus 100;" rather severe exacerbation of symptoms was called "minus 75;" less severe "minus 50;" slightly worse under treatment "minus 25."

Phenobarbital was used essentially to control the results of ovarian treatment, its use justified by the vasomotor and neurogenic nature of menopause symptoms. Phenobarbital gave somewhat better results (plus 33.7 per cent) than those obtained from ovarian substances as nearly as could be estimated.

In a smaller number of observations (eleven) there was no exacerbation of symptoms under bromide therapy. This group claimed the greatest degree of improvement (plus 47.7 per cent) However, the number of cases in this group is smaller than those in the other groups except the follicular extract group, which also contains eleven observations.

In the corpus luteum group 28 observations were made on 17 different patients. A standard preparation was given by mouth in the usual dose (one 5 grain tablet t.i.d.) or in double the usual dose. The results show an average improvement of 19.6 per cent, which is not so good as the results with phenobarbital or bromides.

Whole ovary (5 grain tablets t.i.d.) showed improvement of 22 per cent in twenty five observations.

Follicular extract 5 to 25 rat units daily was used in

a group of eleven patients in this series, the beneficial result was estimated as "plus 9.1 per cent."

Corpus luteum increased the basal metabolic rate 3.1 per cent, whole ovary produced no change. The follicular extract decreased the basal metabolic rate 3.6 per cent.

From these results the following conclusions were drawn:

1. Corpus luteum and whole ovary by mouth and follicular extract subcutaneously are probably useless in the relief of symptoms of the menopause.

2. Bromide or phenobarbital or a combination of the two is distinctly helpful in the treatment of such symptoms, probably not specifically but as general mild sedatives.

3. Corpus luteum may raise a low metabolic rate in a patient at the menopause, but this effect is not sufficiently striking or constant to warrant definite conclusions. Fresh whole gland and follicular extract seemed to have no significant effect on basal metabolism.

Before considering the foregoing conclusions too seriously it must be borne in mind that this work was completed in 1928, much advance has been made since that time. I do not believe that doses of follicular extract ranging from 5 to 25 rat units daily are sufficient to draw any conclusions. As will be pointed out later doses of follicular extract consisting of 100 rat units daily have been given with gratifying results. Furthermore it has been definitely shown by research workers in the past few years that the older commercial preparations of corpus

luteum and whole ovary had very little or no potency. This fact has been generally recognized by gynecologists thruout the country and has led to a closer union between the clinician and research worker. I shall refer to these results later in this paper.

The effect on the basal metabolic rate is significant, and proves only further the interrelationship of the endocrine system.

As pointed out by Schoeller, Dohrn and Hohlweg animal experiments have clearly shown that the complete developement of female characteristics in an individual is only to be expected when the follicular hormone is produced in adequate amounts. Follicular hormone therapy is therefore, justifiable in all cases due to ovarian hypofunction.

Climacteric changes form the chief indication for follicular hormone therapy, and it will also favorably influence conditions due to partial or complete artificial suppression of ovarian function.

In this connection the relief of vasomotor disturbances, which form a frequent and distressing symptom, is most important. The symptom complex is not, however, confined to the cardio vascular system. Cutaneous manifestations such as pruritus and eczema, intestinal symptoms in the form of severe constipation, arthritic conditions which are refractory to anti-rheumatic treatment, are all met with and form a most favor-

able field for substitution therapy with the follicular hormone, mental changes, especially the frequently occurring psychic depression, are also benefited. Here the generalized tonic effect of the follicular hormone undoubtedly plays an important part since, in addition to readjusting local disturbances, it produces a condition of euphoria which is in full harmony with the somatic regeneration which successful hormone treatment produces in women. This general rejuvenation has also been observed in elderly women in whom the climacteric symptoms have already subsided.

In contrast to the results reported by King, I shall present 25 cases reported by Geist and Spielman of New York. Theelin was used in all cases. Theelin represents the purest product obtainable, and assays as labelled, 50 rat units per c.c.

The preparation was administered by intramuscular injection in increasing doses beginning with 50 rat units three times weekly. The patients were always carefully interviewed regarding the effects of injections in regard to exacerbation or improvement of symptoms. Before treatment complete physical examinations, blood pressure readings, complete blood counts, basal metabolism, x-rays of sella turcica and joints when indicated, and weight were recorded. The symptoms which were stressed and which were usually present were hot flushes, sweats, headache, joint pains, insomnia, palpitation, libido, paresthesias, and psychic disturbances. The majority were observed and treated from four to eighteen weeks.

The results were as follows: Four of the twenty five cases were markedly improved, eight were slightly improved, in eight there was no improvement at all and in three there was improvement with bleeding.

Type total	Markedly improved	Slightly improved	Unimproved	Improved with bleeding
Natural 14	4	4	3	3
Artificial 11	0	4	5	0

The eight cases reported as slightly if at all improved are of little value. For the sake of accuracy they have to be designated as improved. As far as improvement in the individual symptom is concerned, it was found that the joint pains were almost never improved, headaches rarely, sweats only with improvements in flushes; palpitation, paresthesias, and insomnia were improved more often.

It is interesting to note that the natural menopause appears more amenable to treatment than the artificial of the 14 cases treated eleven were improved, seven markedly so. Here also it was observed that in three of these cases the menstrual periods were reestablished with complete alleviation of symptoms. In later case reports we shall see however, that much success has been had in the treatment of artificial menopausal symptoms, it is apparently a question of dosage.

In order to illustrate just how these cases were managed, I shall present the cases reported by Geist and Spielman.

Case 1. A. S. aged fifty, married, natural menopause, Aug 1928. Symptoms were as follows: Flushes 20-30 per day, accompanied by sweats, headaches present for fifteen years, worse since menopause. Joint pains also present for fifteen to twenty years. Physical examination negative. Blood pressure 135/105. Weight 150. Urinalysis essentially negative. B.M.R. negative. Blood count showed hemoglobin 65 per cent. and lymphocytes, 52 per cent, otherwise normal. She was treated with sedatives, at first, then thyroid with improvement. She received 14 injections of theelin, from February 19 until Mar 12, 1931, in increasing doses up to 150 rat units per injection. There was slight improvement.

Case 2. E. B. Aged forty three, married natural menopause Jan, 1930. Complained of flushes 1-2 per day, sweats not marked, headaches, joint pains, occasional insomnia. Physical examination except for a blotchy skin with acne was essentially neg. B.P. 136/80. Blood count normal. B.M.R. minus 3 per cent. Urinalysis neg. She received 100 rat units per injection. She stated that she felt better, but original symptoms were very mild.

Case 3. E. G. Aged thirty-eight, married, natural menopause Dec 15 1931. This patient complained of three flushes per day, occasional headaches, joint pain in left shoulder, present before cessation of menses. Slight palpitation, psychic disturbances, insomnia. Libido present. Physical examination negative. B.M.R. minus 4 per cent. Blood count normal. B.P. normal. She received 14 injections from Mar 3 until May 25, 1931. There was slight improvement in symptoms, which were originally mild.

Case 4. A. S. Aged 47, married, weight 147, natural menopause, Jan 30, 1931. Symptoms appeared Sept, 1930. Flushes every half hour, sweats, headaches, joint pain in right shoulder, palpitation, marked insomnia, libido absent. Physical examination essentially negative. B.P. 142/78. B.M.R. minus 21 per cent. Urinalysis neg. Theelin was begun April 18, 1931 and was continued until April 27, 1931, she received 6 injections with slight improvement. In view of the B.M.R. minus 21 per cent, she was placed on thyroid gr 1/4 t.i.d.

Case 5. R. L. Aged 47, married natural menopause April 1930. Symptoms began about that time. They included flushes, profuse sweats, headaches pain in left knee, psychic disturbances and insomnia. Blood count and basal metabolism were not done. Physical examination negative. Patient still has occasional periods of bleeding. She received theelin from April 27, 1931 to June 8, 1931, receiving 9 injections up to 250 rat units per injection. She improved so that all symptoms disappeared except the joint pain. She then bled from May 23 to May 26.

When seen subsequently, she was having only 2 mild flushes per day. In this case the improvement associated with the bleeding was so marked that further treatment was stopped.

Case 6. R. R. Aged 43, married, natural menopause Feb 15, 1931. Symptoms immediately after this including frequent flushes, severe headaches, joint pains inelbow and palpitation, and insomnia. Physical examination essentially negative. B.P. 165/100. Weight 191. B.M.R. minus 25 per cent. Complete blood count normal except for eosinophiles of 5%. She received theelin from June 8 until Aug 20, three times a week, 9 injections all together up to 300 rat units per injection. Symptoms were mild. Under treatment they completely disappeared according to her statement at the last examination. This patient was very cooperative and very grateful for the treatment received. This probably influenced improvement considerably.

Case 7. A. K. aged 42, married, natural menopause five years ago. Complained of flushes every half hour, sweats, backache, palpitation, insomnia, libido absent. B.M.R. plus 16%. Complete blood count normal. B.P. 165/115. Physical examination essentially negative. Reveived 8 injections between Aug 31 and September 26, 1931, dose gradually being increased to 300 rat units per injection. This patient improved considerably. At the last examination, no other symptoms except palpitation were present.

Case 8. A.M., aged 40, married, natural menopause, period in December, 1930, then Mar 4, 1931. She complained of flushes, sweats, pains in the elbow and feet and palpitation. Some insomnia. Physical examination was negative. B.M.R. minus 3%. Urinanalysis negative. Blood count normal. This patient received 7 injections of Theelin up to 200 rat units per injection from April 13 to May 11, 1931. During which time she had two episodes of bleeding with complete alleviation of symptoms. As she was menstruating treatment was stopped. Theelin was probably a factor in causing the bleeding. Her symptoms aside from the time she was bleeding, were only slightly improved.

Case 9. B. B., aged 44, married, natural menopause June, 1930. Symptoms appeared August, 1930, complained of flushes five times daily, headaches, joint pains in arms, leg and back, palpitation, psychic disturbances. Libido always absent. Physical examination negative. B.P. 156/90. B.M.R. minus 4%. Blood count except for 43% lymphocytes was normal. Urine negative. She received 15 injections of theelin up to 150 rat units per injection. She showed some improvement. Flushes were reduced to 1 or 2 per day and other symptoms were also improved. She also reported increased libido. She then had a period

in April and another period in May. Treatment was discontinued as symptoms disappeared with the bleeding.

Case 10. D. L. aged 44, married, natural menopause May, 1929. Symptoms immediately afterward including moderate flushes, some sweats, headache, stiffness in the joints, moderate palpitation, and insomnia. Libido present. Physical examination negative. B.P. 160/90 weight 149. B.M.R. minus 2 and 1%. This patient from the very beginning showed a marked globus hystericus with associated nervous symptoms which were entirely uninfluenced by treatment and were based on difficulties at home with her grown children. She received 15 injections between Jan 12 and Feb 16, 1931, in increasing doses up to 125 rat units per injection. Improvement was marked, the only symptoms which persisted were joint pains and insomnia. Hysterical condition was not affected, but patient responded very well to the interest shown in her case which probably influenced the improvement.

Five cases of artificial menopause are also reported, but since little or no relief was obtained it is not necessary to include them in detail.

In two cases of kraurosis marked improvement was noted using theelin in increasing doses.

The following conclusions were noted:

1. The evaluation of improvement or non-improvement in menopause symptoms as a basis for judgment of the efficacy of the preparation was found to be exceedingly difficult.
2. Seven menopause cases of the 25 patients were definitely improved, 3 with the reestablishment of menstruation. The others were either unimproved or so slightly improved as to be negligible.
3. Two patients with kraurosis on whom vulvectomy had previously been performed showed marked improvement of the itching.
4. In several cases of natural menopause, bleeding, possibly menstruation, followed the injection of theelin.

5. The natural menopause seems to be more amenable to treatment than the artificial climax.

6. Substitution of the female sex hormone alone does not in all cases relieve the menopause syndrome.

7. Other factors such as reduction of the quantity of the quantity of anterior pituitary hormone may improve the result.

Werner and Collier in studying the effect of theelin injections, (200 rat units daily, for 28 days, 300 rat units daily the second 28 day period, and 400 rat units daily the third 28 day period) on castrated women, report the following results:

1. Theelin restores the breasts and genital tract of women to apparently the normal sexual state after previous castration atrophy.

2. Theelin produces changes in the atrophied endometrium of castrated women that approximate or equal the interval changes found in the normal women at the time of ovulation.

3. Theelin does not produce the pregravid changes in the endometrium of castrated women.

4. The bleeding from the uterus of castrated women induced by theelin occurs from an endometrium approximating or equaling in development the interval changes found in the uterus of normal women.

5. Theelin induces bleeding from the uterus of castrated women qualitatively indistinguishable from menstruation in normal women.

6. This bleeding from the uterus of castrated women is accompanied by the subjective symptomatology usually experienced by normal women during menstruation.

7. Theelin relieves the subjective symptoms that occur in women following castration.

8. Four ovariectomized women to whom large doses of theelin were given state that "libido was markedly increased."

9. Excessive doses of theelin were given to women intramuscularly over a period of from eighty nine to ninety three days without seeming discomfort, until a dosage of 300 to 400 rat units daily was reached.

It is evident that the marked difference in results obtained by Geist and Spielman as compared with those obtained by Werner and Collier can be explained upon a basis of dosage. It is evident that castrates should require more hormone than those in which the ovaries are intact.

In a recent study of menopausal cases Sevringhaus calls to our attention these facts. In a series of 32 menopausal cases hot flashes occurred in all, paresthesias in 16, insomnia in 19, and psychotic pictures in 17. Obesity was found in only 13, and hypertension in 10. Of this series 6 had artificial climacteric produced by radiation or surgery, and there were 3 patients with a spontaneous premature menopausal picture, possibly to be considered as ovarian insufficiency.

The use of simple psychotherapeutic procedures and small doses of folliculin daily or oftener has been found very help-

ful in the psychotic cases as well as in the simpler vasomotor types and the pseudothyrotoxic types. The value of frequent small doses rather than large doses at longer intervals in certain selected cases will be pointed out subsequently in this paper.

Hamblen has reported 40 cases of menstrual disorder in which he used follicular and hypophyseal hormones. With the exception of several patients, to whom the vaginal pessaries incorporating the active hormone were supplied, the hormones were administered intramuscularly. When it was possible, a single hormone was used. In the majority of patients the hormones were administered daily in doses of 100 rat units for two weeks with rest intervals of two weeks. Administration in this manner was repeated until results justified discontinuation. If it was possible, the hormones were administered during the inter-menstrual phase of the cycle. Sedatives were not dispensed for the relief of subjective symptoms or combined in any way with these treatments. The only measures adjuvant to the endocrinal therapy were the correction of dietetic and hygienic errors.

There was no untoward reactions at the sites of injections. In a few instances patients received the anterior pituitary luteinizing hormone complained of slight local pain, 24 to 48 hours after a certain injection, investigation usually revealed that the injection had been made too superficially.

Again for the sake of illustration I shall include, in detail, the cases reported by Hamblen.

Case 1. Mrs J. T., aged 47, para 6-5-1, came to the dispensary complaining of nervousness and headaches. During the past eighteen months her menstrual periods had gradually grown more scanty and more irregular. For the past 6 months she had experienced marked vasomotor instability, characterized by fainting spells, flashes, and emotional instability. General physical examination revealed nothing of particular importance. Pelvic examination showed no pelvic abnormalities. She was given theelin, 100 rat units daily for two weeks, she noticed at the end of this treatment a disappearance of the emotional and nervous symptoms after two weeks rest, she reported a menstrual period, which persisted and lasted for a week. She was given another two weeks treatment with theelin and the relief of the presenting symptoms continued. She had continued, however, to have a scant sanguinous discharge and, accordingly, was admitted to the hospital for a curetage of the uterus. The curettings were reported to show hyperplastic endometritis. Bleeding has not recurred since the operation and after two weeks or rest another series of theelin injections will be given.

Case 2. Mrs W. S. Mc., aged 53 was seen in the dispensary to which she came with the symptoms of flashes, nervousness, and vertigo since the climacteric two years previously. She also complained of a low grade lumbar backache of an inconstant character. Physical examination and pelvic examination were essentially negative. The patient was slightly underweight. Laboratory findings were within the range of normal. She was given theelin, 100 rat units daily for two weeks and then three times weekly for four weeks. After a week of treatment the patient was free of subjective symptoms. There was no return of menstruation.

Case 3. Mrs G.G., aged 46, para 6-0-6 had had scanty and irregular menstruation for the past year. The symptoms which brought her to the gynecological clinic were extreme nervousness, loss of appetite, gaseous eructations, and an inconstant lumbar backache. Physical examination disclosed no important abnormalities. The patient was slightly underweight. Pelvic examination revealed no pelvic disease. Laboratory findings were normal. She has been under treatment for the past 6 months, during which time she has received theelin, 100 rat units three times a week for two weeks with rest intervals of two weeks. She has received relief from her symptoms, except the backache. The menstruation has become more regular but still remains scanty.

Case 4. Miss L.G., aged 47, was referred to our clinic for diagnosis and treatment. She had had no menstruation for 17 years. Her complaints were very varied, and included marked emotional instability, extreme nervousness, manifested by gross tremors, and many indefinite and inconstant pains. A diagnosis of involuntional psychosis was made by the neurological consultant. Her physical examination revealed nothing of consequence except marked vasomotor instability, gross tremors of extremities and exaggerated reflexes. The wassermann test was negative. A trial of theelin was made. She was given 100 rat units three times a week for eight weeks without any improvement or without any relief of symptoms. There was no return of menstruation.

Case 5. Mrs A. M., aged 46 was referred to the clinic with symptoms of morning parietal headaches, flashes, emotional and vasomotor instability and marked melancholia. These symptoms had appeared during the last year and had been much intensified following the cessation of menstruation seven months previously. Physical examination revealed nothing of importance except a coarse tremor, refractive error of the eyes, well corrected with glasses, and a moderate obesity. Laboratory examinations were unimportant; She received theelin, 100 rat units, daily for three weeks with rest intervals of one week for three months. The subjective symptoms, except occasional slight headaches, were, relieved after the first two weeks of treatment. There has been no return of menstruation.

Case 6. Mrs B. S., aged 40, para 8-225, was admitted to the hospital, complaining of an almost constant frontal headache of approximately 6 months duration. During this time there had been a marked decrease in menstrual flow, associated with extreme nervousness, flashes, emotional instability and increased severity of the headaches. Blood pressure at time of admission was 210/160. Urinalysis gave normal findings. Blood urea was 66 mgm. per 100 cc. Physical examination revealed a moderate enlargement of the heart with good regularity and no murmurs; eyes and sinuses were normal. Radiography of the sella turcica revealed a slight hypoplasia. She was given a 1/4 grain hypodermic injection of morphine at the time of admission for the immediate relief of an almost unbearable headache. Subsequent treatment consisted of a diet of moderately restricted protein and the administration of anterior pituitary luteinizing hormone 200 rat units daily for ten days. During this time the patient was confined to bed in the hospital. After two days of this treatment, the headache disappeared and during the last two days of the treatment there occurred the first free and normal menstrual cycle the patient had had in six months, without the usual symptoms and with no headache. At the time of discharge from the hospital her blood pressure was 150/96 and blood urea was 38 mgm. per 100 cc. She is to receive further treatment.

Case 7. I. R., aged 24, para 0-0-0, was referred to the dispensary for treatment of symptoms following a hysterectomy and bilateral salpingo-oophorectomy in another hospital in July, 1930. The patient complained of loss of appetite and weight, insomnia, failure to regain strength, and nervousness. Physical examination and laboratory tests revealed no abnormalities. She was given theelin, 100 rat units daily for two weeks. She reported at the end of the treatment a complete relief of subjective symptoms. She recently returned to the clinic after a month's rest from treatment and during this interval, had had no return of symptoms.

Case 8. Mrs. J. G., aged 30, para 4-4-0, complained of nervousness, insomnia, flashes, and frequent attacks of vertigo. Her operative history included an operation elsewhere in 1927, at which time a left oophorectomy and right partial oophorectomy were done. She had received radium therapy elsewhere in 1928 with resulting cessation of menstruation. Her symptoms dated from that time. General examination and laboratory findings were unimportant, except for marked emotional and vasomotor instability. She received theelin, 100 rat units daily for two weeks. There was a reduction in the severity of the symptoms and at the end of the treatment, there was a noticeable improvement of vasomotor balance. She was unable to continue further treatment.

Case 9. E. B., aged 29, was referred to the gynecological clinic for treatment. She had had a bilateral salpingo-oophorectomy in 1919. During the past two years, she had experienced flashes, vasomotor instability, characterized by nervousness, frequent sweats, and weakness, and inconstant and ill-defined headaches. Physical examination and laboratory tests disclosed no important findings. She was given theelin, 100 rat units daily, for two weeks with relief of symptoms and disappearance of vasomotor instability. At the end of two weeks, with rest from the treatment, she reports no return of symptoms.

Case 10. Mrs. I.K.H., aged 44, was referred to the clinic for treatment. She complained of melancholia, emotional instability, flashes, and nervous instability. These symptoms dated from radium therapy elsewhere three years previous which resulted in the cessation of menstruation. General examination disclosed only moderate obesity. Laboratory findings were of no importance. She was given theelin, 100 rat units daily, for three weeks. During the latter part of this treatment, she began to complain of pelvic cramps, associated with a sensation of fullness in this region and discontinued treatments in fear that menstruation was returning. She received an almost complete relief of subjective symptoms; menstruation did not result from her treatments.

Case 11. Mrs. R. L., aged 45, para 6-0-6, complained of general malaise, dizzy spells and numbness in the left flank, following an operation in August, 1930, which involved bilateral salpingo-oophorectomy and supravaginal hysterectomy. General examination, pelvic examination, and laboratory studies gave normal findings. She was given vaginal pessaries, each containing 50 rat units of follicular

hormone, one to be used each day. She continued this treatment for six weeks with almost complete relief of her symptoms, except for the numbness in her left flank.

Case 12. E. H., aged 20, was referred to the gynecological clinic complaining of weakness, loss of appetite, pains in the muscles of the extremities and loss of weight, following an operation in December, 1930, which involved bilateral salpingo-oophorectomy. General physical examination revealed chronic infection of tonsils, malnutrition, and subnormal weight. The patient was of diminutive stature. Laboratory findings were within the range of normal. She was given theelin, 100 rat units daily, for three weeks. There was an almost complete disappearance of symptoms and she has gained five pounds.

The remaining patients treated were those complaining of dysmenorrhea, etc., and do not have a place in this paper.

Hamblen draws these conclusions from the results obtained in cases of the menopause (natural and artificial). "Thirteen patients with symptoms associated with the menopause were treated. The relief of subjective symptoms was excellent in eight patients and good in four. One patient received no benefit. There was no effect on menstruation in ten cases; menorrhagia developed in one patient; and menstruation became more regular in two patients."

Mazer and Ziserman in their recent work on the female sex hormone, have come to the conclusion that variations of clinical manifestations occurring in the climacterium are undoubtedly an expression of the combined effects produced by different stages of activity on the part of the glands of internal secretion. The endocrine pathogenesis, if it may thus be termed, is of a pluriglandular nature. The hypersensitivity of the sympathetic nervous system, as evidenced by the vasomotor symptoms, may reasonably be attributed to the lack of female sex hormone. Although the symptoms strongly resemble the syndrome of hyperthyroidism, there is usually no evidence of an increased basal exchange. The administration of female sex hormone in these cases

is the most rational and clinically the most effective method of controlling the distressing vasomotor symptoms.

The use of the female sex hormone by mouth has been a question of much debate. However, normally, the glands of internal secretion supply their products to the body as they are needed in small quantities and without demonstrable disturbances physiologically. In order to imitate nature, it is essential to administer glandular products in small, frequently repeated quantities. It is apparent that this is impossible when the products are given by the hypodermic needles. The oral administration of glandular products is ideal if the hormone is not affected by the gastric and intestinal secretions and if it is properly absorbed. The efficacy of the oral administration of female sex hormone is still debatable. Large doses given hypodermically are eliminated rapidly through the urine and other channels before concentration in the uterine mucosa is possible. Small doses at short intervals is ideal, but is hard to carry out unless given orally, the patient usually objecting strenuously to more than one hypodermic injection daily. The administration of the hormone by means of vaginal pessaries is also unsatisfactory because they can usually be employed only before retiring. Furthermore, the gelatin mass almost invariably escapes from the vagina.

Recent experimentation by Schoeller, Dohrn and Hohlweg tends to show that the peroral effect of follicular hormone preparations depends not only on the dose administered, but also on the presence of certain concomitant substances which further the adsorption of the hormone. Using favorable concomitant substances (alcohol in various strengths) in suitable amounts, it was found that the relationship between the effective subcutaneous and peroral doses was 1:4.

approximately.

Bowman and Bender have recently studied the effect of female sex hormone in cases of involuntional psychosis.

Severe cases of involuntional melancholia were treated with ovarian hormone in the form of Squibb's amniotin. The method and amount of treatment varied. A careful study before and after treatment was made of the blood pressure, basal metabolism, blood chemistry, and the galactose tolerance.

Two cases showed a good social recovery. Three cases were unimproved and now show a chronic picture. Two cases died - one of anemia and broncho-pneumonia, and the other of carcinoma of the uterus.

In giving amniotin, the possible restoration of the menstrual cycle was considered. The results were quite different. Except in case 1, where a very slight flow occurred on two occasions, the effect of treatment was to cause complete cessation of the menses. In three cases, there was menstruation up to the time of treatment, but none after treatment started. In case 2, menstruation continued for two months after treatment and then ceased. Case 6 had had a pan-hysterectomy so that no changes were possible. Case 7 had had the menopause eleven years previously and treatment produced no effect.

Very little change occurred in the blood chemistry during treatment. Where such changes did occur, they were usually in the direction of a more normal condition. However, some cases did show disturbances in weight, arterial tension, an increase in non-protein nitrogen not due to any apparent cardio-renal-vascular disease, a low blood cholesterol, disturbances in sugar curves, and low basal meta-

bolism. These may all be favorably influenced by glandular therapy, especially the specific female sex hormone. Such therapeutic measures may improve the patient's general physical condition, alleviate distressing symptoms, remove abnormal sensations which may be feeding delusional trends, shorten remissions, and in some instances are apparently associated with complete clinical recoveries.

An intelligent application of such therapeutic measures specifically directed against known symptoms and laboratory findings, may offer a valuable means of treating properly selected cases. Patients who show depression, indecision, delusional trends directed against the environment, and without visceral disturbances and their associated hypochondriacal trends, will probably not be benefited by such treatment. Re-establishment of menses should not be the aim. On the other hand, it may be possible to hasten a complete cessation of menses where the disturbance includes an annoying continuance of scanty, irregular menses or metrorrhagia of the menopause not due to uterine pathology. The combination of the sex hormone, especially with thyroid in cases of low metabolism, and with pituitary, obviously suggests itself.

Novak in a recent article is very enthusiastic over the recent advances made in endocrine therapy. He states, "Not so many years ago, the subject of endocrinology would have had to be approached almost apologetically, for the profession had, to use a slang expression, become 'fed up' on the immense amount of misinformation and speculation emanating from the early enthusiasts on the subject. Such a cynical attitude is no longer justified, and indeed, is no

longer evident. The reason for this is obvious. No longer is endocrinology a happy hunting ground for clinicians armed only with high-powered imaginations, or for commercial pseudo-scientists with something to sell. The field is now being painstakingly worked by an army of scientific investigators."

Novak points out that the older commercial preparations of the ovary or corpus luteum, formerly so widely used, produce no objective results whatever, and that their subjective effects are very questionable. Some observers have reported favorable results but the psychic factor associated with the menopause must be born in mind.

Novak calls attention to the fact that theelin has no direct effect upon the ovary, its use being purely substitutional. Theelin can not produce the complete menstrual cycle; its use should be followed by progestin, but as yet no commercial preparation of progestin is available. Novak has used, however, the anterior pituitary luteinizing substance prepared especially by Park, Davis, and Company, following injections of theelin, with a fair degree of success. This substance is not available, however, at the present time. Theelin followed by the above preparation will produce menstruation, but not at regular intervals, and requires monthly injections which are objected to rather strenuously by the patient.

Marked improvement in cases of menopausal symptoms has been reported by Novak using theelin in doses of 50 to 100 rat units daily for at least six days.

Geist and Spielman have also carried out experiments using amniotin as a therapeutic measure in the menopause.

Amniotin (Squibb) is prepared from the fetal fluid of cattle by precipitation with alcohol, acetone, and ethyl ether. The resultant oil is further extracted with alcohol and benzene and the resultant filtrate contains the amniotin which can be dissolved in water. The assay is carried out according to the technic of Doisy. The rats after the injection of the material must show fully cornified vaginal smears.

This series consisted of 43 cases. In 10 there was no improvement, in 22 cases there was varying improvement, and in 11 cases the improvement was related to the appearance of vaginal bleeding after treatment.

Amniotin was given in suppository form and by subcutaneous or deep injections. The result was summarized as follows:

In one group of cases amniotin seems to have influenced a return of the menstrual period with a temporary relief of symptoms; in other cases it caused a distinct alleviation of symptoms while the substance was exhibited, but the relief was not of a permanent nature. What influence the psychic effect of the treatment played is hard to evaluate. However, it is evident that the substitution of a single hormone that is not being produced by the individual, is not sufficient to prevent entirely the symptoms of the menopause, and it is certain that other factors are included in the problem of the menopause and its associated symptoms.

Clinical studies of supposed hypofunction of the ovaries are seriously handicapped by the lack of an objective and mathematical index of ovarian activity. The situation is analogous to the observations made on hypothyroid syndromes before basal metabolic rates were measured. But both clinical and fundamental scientific profit accrued from the more or less empirical association of certain symptoms with deficiency of thyroid secretion. It must not be forgotten that even technically perfect basal metabolic measurements showing low rates do not in every case demonstrate a hypothyroidism. Clinical observation is just as necessary as before. The status of observations on the menopause and other menstrual irregularities is one of rather imperical grouping based on the history and physical findings. Lacking specific tests for ovarian activity in the human female, the clinician must make diagnoses that are probable rather than certain. The closest approach to a specific test for the female sex hormone has been previously discussed.

Severinghaus and Evans have also used amniotin in the treatment of menopausal symptoms and report the following results:

Group	No of Cases	Benefited	Doubtful	No relief
1. Menopause, with flushes and insomnia.	15	10	1	4
2. Headaches with suspected menopause.	3	2	-	1
3. Involutional psychosis.	3	-	-	3
Totals	21	12	1	8

It appears that in this series of cases amniotin possesses the activity for the human female which the animal experiments of Allen and Doisy would lead us to predict. In the hot flushes, insomnia, nervous instability, and headaches attributable to the menopause, artificial or spontaneous, amniotin has given very satisfactory relief.

The manufacturers of this preparation (E.R. Squibb and Son) as well as others, have recommended the use of much larger doses than were employed. For the menopausal symptoms, doses of about 10 units daily are adequate, and may occasionally be excessive. Pessaries give results equally as good as hypodermic injections. The occasion for the use of pessaries is the avoidance of the need of a hypodermic. There are two difficulties to be encountered however. One is that unmarried women are apt to object to this method. The other is that except with very firm closure of the vaginal sphincter there is sufficient drainage after the melting of the gelatin to occasion discomfort and loss of material. This is preventable by the use of wool or cotton vaginal tampons.

In 1864 Frankenhauser described a nerve supply of the uterus and located a sympathetic nerve plexus lateral to and on each side of the cervix uteri in the transverse parametrium. At puberty, certain hypertrophic changes occur in these two large ganglia and regression changes likewise occur at the menopause independent of other sympathetic nerve ganglia. If we remove the uterus by a sub-total hysterectomy and leave the ovaries

the patient may, for a year or so, have no untoward symptoms, but later organized exudate and granulation tissue cause atrophy changes in the cervical ganglia, and ovarian deficiency is then evident. Experiments conducted by Kennedy show that regenerative changes occur in these ganglia after castration or menopause on the administration of sistomensin, which is a solution of oestrin in oil. According to Kearns climacteric neurosis improves greatly on the injection of sistomensin.

The explanation of the biological behavior is expressed by regenerative changes in the mucosa of the uterus and also by checking immature development in the corpus luteum. Sistomensin will also supply the corpus luteum hormone when it is decreased in the menopause.

Present day treatment with the female sex hormone has been dealt with very thoroughly by Emmert of St Louis. According to him, if we sift the enormous and often conflicting literature on the female sex hormone we find only a few outstanding facts which seem to be definitely established. We know that the ovary remains in the dormant state from birth until the approach of puberty, and that during this first epoch in the life of the female it does not as yet produce any hormone in appreciable amounts.

In contradistinction to the sex gland the other endocrine glands are active from the very beginning among these, the pituitary gland, which is composed of two lobes, secretes different hormones in each lobe. It is the hormone produced in the anterior

lobe of the pituitary gland which has a fundamental influence upon the sex organs because it stimulates the ovary both as to growth and function. Under the influence of the anterior part of the hypophysis the follicles of the ovary ripen and secrete a hormone, which in turn causes a growth and proliferation of the endometrium in the uterus. After the rupture of the follicle there is established in the latter the corpus luteum which also produces a hormone that in its action is similiar to the hormone contained in the follicle.

We must, therefore bear in mind that the anterior lobe of pituitary is a sort of super-sex gland. Without the pituitary gland there is no activity of the ovary, and without the ovary there is no activity of the uterus.

Subnormal activity or hypofunction of the ovary is characterized by the absence or scantiness of menstruation, frequently accompanied by obesity and sterility. The exact classification and grouping of these cases is extremely difficult. Still more unsatisfactory is the present state of treatment. For many years therapy for all functional disorders consisted of the oral administration of the whole ovary or certain parts of it. Then it was realized that in any dried product there could be only a minute quantity of actual hormone, and this tiny amount was sure to be effectively destroyed by the gastric juice long before it could possibly be absorbed into the organism. Then extracts for intramuscular use appeared on the market, little more success was had with them. Claims made by

endocrine enthusiasts always stirred up hope, but the same results could not be produced in the hands of other men, and when men like Allen and Doisy, Frank, Graves and others clearly demonstrated that the commercial preparations contained only small amounts of hormones, it was realized that with our endocrine enthusiasts the wish had largely been father to the thought.

Since that time the hormone has been definitely standardized and has also been obtained in pure form. Hand in hand with this goes the isolation of the anterior pituitary hormone.

These two discoveries mark a new milestone in the development of organotherapy. From now on we shall be in a position to work with accurate amounts of a definitely determined substance. The anterior pituitary hormone shall be used to stimulate the ovaries and while we are waiting for the ovaries to respond to the stimulus of the pituitary we shall inject the ovarian hormone so that the uterus may not be deprived of the essential need of the ovarian secretion. In other words in ovarian hypofunction we shall carry out a stimulation and a substitution therapy simultaneously. Where, however, there is no ovarian tissue left, as after castration, or where it is definitely atrophied, as after menopause, there is obviously no need for pituitary hormone and only ovarian hormone is required to substitute for lack of secretion from the sex gland.

Collip in his work on the human placenta found that it contained at least three distinct active principles, or hormones. These three substances were alike in that all have been observed to be oestrogenic in the immature female rat.

The first fraction was identified to be theelin. The active principle present in the second fraction (85 per cent alcohol soluble) is very similar to theelin in its ultimate physiological effects. It is ineffective, however, in the castrate, and hence it may be concluded that it functions directly or indirectly by stimulation of the intact ovary. It also differs from theelin in the degree to which it is effective by oral administration. The third fraction prepared from the alcohol insoluble material of the original extract is similar to the other two in that it is oestrogenic. It differs from the second or emmenin fraction on three main points: (1) it is ineffective by the oral route; (2) it produces corpora lutea in the immature rat coincident with induced oestrus; (3) it causes an increase in the rate of growth of the accessory sex glands in the immature male.

The two oestrogenic placental hormones other than theelin which have been described appear to be the counterparts respectively in placenta of prolan A (oestrogenic) and prolan B (oestrogenic and luteinizing).

Collip treated 18 cases of the menopausal syndrome with emmenin, in 14 there was definite improvement. There was no improvement in castrates. Collip states; "Observations of this type of case lead one to conclude that the duration of this symptom complex is of prime importance, since no relief was obtained in cases of long standing, whereas the symptoms were relieved for a time at least in certain cases where the con-

dition was of recent origin - that is, less than one year since the last menstrual flow."

A dose corresponding to 75 grams of placenta daily, given in divided doses in water or orange juice before meals, has been used in the majority of cases. There are individuals who do not tolerate the extract well. The cause of this could not be discovered; but in any case in which untoward symptoms, such as nausea or vertigo, have been observed, the dose was temporarily reduced until tolerance was acquired.

It was also found that during the course of treatment with the ovary stimulating hormone of the placenta certain patients have manifested symptoms of nausea, whilst others experienced some discomfort in the pelvic region. Others stated that they had experienced dreams of a vivid and unusual character. Severe headache and mental depression have also occurred. As a rule the patients voluntarily expressed a feeling of well-being in from four to five days after withdrawal of the extract. It is interesting to note that in view of the well established fact that the extract is without effect on the oophorectomized rodent, clinically one cannot expect relief from menopausal symptoms after pan-hysterectomy. One such case was studied, with the anticipated failure to obtain any beneficial results.

Collip has definitely established thru extensive experimentation that the active principle obtained from the placenta "emmenin" is an ovary stimulating hormone, probably pituitary in nature, and may be found effective in the activation of

ovaries which are hypofunctional. Collip also discovered that the hormone is non-protein in character and is unaffected by digestive enzymes. It may therefore be administered orally.

Now let us consider the secretion of the corpus luteum, and its possible relation to the menopause.

In Corners original experiments on the corpus luteum he discovered that the alcoholic extracts of the corpus luteum, freed from phospholipids, contain a substance which when injected into castrated adult female rabbits induces a characteristic alteration of the endometrium identical with the progestational proliferation previously shown to be due to the presence of corpora lutea in the ovaries. A similar effect is sometimes but not always produced in immature rabbits 8 to 12 weeks old. Extracts of follicular fluid containing large amounts of theelin do not produce progestational proliferation, nor have extracts of human placenta given positive results. It appears, therefore, that the extracts of corpus luteum contain a special hormone which has for one of its functions the preparation of the uterus for reception of embryos by inducing progestational proliferation of the endometrium.

In the human menstrual cycle the progestin secreted by the active corpus luteum following ovulation normally prevents further ovulation and brings about the characteristic premenstrual, secretory changes in the endometrium, the ovarian follicle hormone, theelin being a necessary factor in this

process. The decrease in progesterin toward the end of the cycle is followed by menstruation. To account for the rise and cadence of the corpus luteum and the concomitant variations in progesterin it is necessary, for the present to postulate that when the graafian follicle reaches a certain stage in its growth under the influence of the gonad - stimulating hormone of the anterior hypophysis there takes place increased hypophyseal activity, with consequent ovulation and luteinization.

From the foregoing explanation it is evident that progesterin prevents menstruation, or in other words is antagonistic to the action of theelin, consequently, progesterin would be indicated in cases of excessive flow, rather than cases of amenorrhea, that are encountered in the menopause. Since however there is no commercial preparation of progesterin available at the present time it is impossible to prove this point clinically. It has been proven experimentally however that the hormone progesterin inhibits the production of theelin and promotes its excretion.

Glismann in studying cases of excessive hemorrhage, recommends the use of lipo-lutin, a potent lipoidal extract of corpus luteum, which is prepared by Parke, Davis and Company. This product has been found to be very useful in preventing abortion and excessive menstrual flow due to endocrine imbalance, however it has been used in cases of post menopausal bleeding with an equal degree of success. The reason for this

is readily seen, bearing the foregoing discussion in mind.

Geist and Matus in a recent study of post-menopausal bleeding have found the cause to be chiefly benign and malignant tumors, however they call attention to the importance of a study of the circulating blood and the tumor for the presence of hormones that may lead to a clearer understanding of the mechanism of the bleeding.

We shall now consider the pituitary hormones as to their possible therapeutic value in relation to the menopause.

Nelson in recent experimentation observed 8 rats out of several hundred, that exhibited no oestrous change for at least five weeks. These animals were apparently in the best of health and quite normal in every respect except for their reproductive cycles. Age, inanition, and vitamin B deficiency could be ruled out as causative factors, since the history of each animal was known. The possibility suggested itself that some factor in the normal pituitary gonadal relationship was inactive in these animals.

After a period of anoestrous lasting from five to seven weeks one ovary and a portion of the uterus were removed in each instance. All material was fixed in Bouins and prepared for histological study. Two weeks was allowed for recovery. No oestrous changes occurred in any case. Seven of the animals were injected intramuscularly with one fresh anterior lobe (rat) each day. The 8th animal was given subcutaneous injections of an extract prepared from sheep pituitary.

In every instance oestrus occurred on the third or fourth day following the instigation of treatment. The smear of flaky, cornified cells was typical in every respect of a normal oestrus and was preceded by the usual pro-oestrous picture. Subsequent autopsy revealed the typical condition of oestrus.

The rapid response of these non-cyclic females to anterior pituitary therapy seems to justify the initial supposition that some factor in their pituitary-gonadal relationship was inactive. We are reasonably certain at the present time, that, of the entire endocrine series the anterior hypophysis is the only gland which is fundamentally concerned with the normal functioning of the gonads. In all probability other glands, notably the thyroid, have their roles in the maintenance of gonadal function, and disturbances in them may well be reflected in the gonads. However, all recent work has served to relegate them to a position of minor importance and has elevated the hypophysis to the major role.

Nelson summarizes his work as follows:

1. Eight adult female rats, which for at least five weeks had shown no oestrous changes in their vaginal smears, were given daily implants of anterior lobe, or daily injections of an extract prepared from anterior lobe material.
2. Oestrous occurred, in each instance, on the second or third day subsequent to the instigation of treatment.
3. The ovaries and uteri prior to treatment presented a picture approximating that of dioestrus, while the remaining

ovaries and uteri removed subsequent to the occurrence to the induced oestrus were either of oestrous or meta-oestrus character.

4. When copulation was permitted at the time of induced oestrus successful pregnancies resulted.

5. The pituitaries of these females were capable of promoting precocious maturity in a young rat when introduced intramuscularly.

6. No further oestrus changes could be demonstrated beyond the initial induced oestrus.

7. It is concluded that the etiology of the aberrant ovarian behavior observed in these animals probably was some derangement of the normal hypophyseal-gonadal relationship, possibly the non-release of the gonadal stimulating hormone.

In Hewitts work on extracts of the anterior pituitary, it was found possible to obtain extracts of anterior lobe of pituitary glands having the following effects.

- (1) Growth promoting (filtered alkaline extracts)
- (2) Growth promoting and oestrous-inhibiting (unfiltered alkaline extracts)
- (3) Premature maturity-and ripe follicle producing (acid extracts treated with kaolin, etc.).

It would seem therefore that three effects may be produced by extracts of anterior lobes. Evidence from histological, surgical, pathological and bio-chemical fields presents a strong case for the existence of hormones in the anterior pituitary lobe controlling growth and the female reproductive cycle. Two inferences may be drawn: Theoretically one is faced with

the presumption that the anterior lobe may control the ovarian cycle, and practically; one may hope for the establishment of replacement therapy indisturbances of growth and the female reproductive system.

Evans, Meyer and Simpson in studying the relation of prolan to the anterior hypophyseal hormones arrived at these conclusions:

1. Prolan does not easily repair the gonadal deficiencies of hypophysectomized animals.
2. There is always a definite limit to the weight of the ovary which can be stimulated by prolan in the immature rat within a definite time interval (100 hours).
3. Hypophyseal hormones completely repair the gonadal deficiencies of hypophysectomized animals.
4. The hypophyseal gonad-stimulating hormone does not show the limited effect on the ovary of the immature rat found to be characteristic of prolan. The development of the ovary provoked by the hypophyseal hormone corresponds to the dose level.
5. Only very small amounts of prolan, measured in terms of dry weight are required to give the minimal effect on the ovary. The amount of hypophyseal hormone needed to give a minimal effect is always much greater. This is in contrast to the fact that higher doses of hypophyseal hormone provoke much greater ovary weights than can be obtained with any amount of prolan.

6. In earlier experiments the effect of prolan was increased to the maximal effect obtainable by injecting hypophyseal sex hormone simply by combining prolan with small amounts of crude hypophyseal preparations, containing both gonad-stimulating and growth hormones. The combination of prolan was made with doses of hypophyseal preparations which, given alone, were minimal or just sub-minimal in gonad-stimulating effect. Later prolan was added to the hypophyseal extract (growth hormone) which, when administered alone, were devoid of any effect on the ovaries of immature animals and in this way also secured maximal effects.

7. This activation effect is a specific reaction. If the hypophyseal extract is destroyed by heating, the combination of heated hypophyseal hormone with prolan is no longer any more effective than prolan alone.

8. Low concentration of pure hypophyseal sex hormone combined with prolan do not result in activation effects. On the other hand sex free growth hormone is typically activated by prolan.

Fluhmann published a collective review in 1931 dealing with the interrelationship of the anterior hypophysis and the ovaries. The majority of his conclusions have been included in this paper, however it may be of interest to include his summary of the use of ovary stimulating substances for therapeutic purposes.

Of special importance to the practitioner is the possibility arising from experimentation on the anterior pituitary like sub-

stances, of obtaining an ovary stimulating substance which may be employed for the treatment of amenorrhea, delayed menses, scanty menstruation and sterility. This work must be considered as still in the experimental stage but it is of interest that investigation along this line is proceeding hand in hand with the physiologic studies. The extracts at present in use therapeutically are either made from the urine of pregnant women, as for example, prolan, or from the placenta, as emmenin.

Encouraging results in the treatment of so-called "hypo-ovarian" conditions from the use of the German preparations prolan, pre-hormone and homhormone, have been reported by Zondek, and others. Zamkoff has also had very encouraging experiences from the use of urine from pregnant women, and good results from the injection of whole blood or blood serum from human pregnant donors have been reported by de-Maortua and Esch. Zondek has employed prolan for the treatment of pelvic inflammatory disease in view of his previous observation that the administration of this extract causes a local increase of temperature, and believes that in association with bed-rest this method of therapy is highly commendable. This contention is supported by Montag, but on the other hand an adverse report has been given by Bauer and Lehfeldt, who in addition failed to obtain successful results in 10 cases of menstrual disturbances attributed to ovarian dysfunction. Fellner believes that feminin is preferable to anterior pituitary hormone from a therapeutic standpoint in view of the danger of injury to the ovaries.

Martin has successfully used prolan in high doses for patients with intractable menorrhagia, and suggests this as a possible means of producing a hormonal castration.

The treatment of 135 cases of deranged ovarian function by the oral administration of the placental extract emmenin has been reported by Campbell and Collip. These authors note unsatisfactory results in the treatment of primary amenorrhea, but find a high percentage of patients with improvement in cases of 2ndary amenorrhea, oligomenorrhea, dysmenorrhea, polymenorrhea, and menopausal symptoms. They have also obtained an arrest of the bleeding in certain forms of menorrhagia and metorrhagia by the hypodermic administration of Collips "anterior-pituitary-like" placental extract.

CONCLUSIONS

1. The menopause is a normal physiological process through which all women must pass. The symptoms may be very severe in some cases while in others it may be as uneventful as any of the other necessary experiences to which the female economy is subjected.
2. The average age of cessation of menses is approximately 45 years 9 months. The average duration of symptoms is about two to two and a half years.
3. All organs of the female reproductive system are subjected to atrophic changes during and following the menopause. These changes associated with the usual symptoms are due to the withdrawal of the female sex hormone.

4. Drugs are almost always necessary in addition to other therapeutic measures. Elixir triple bromides has been found to be very useful due to its depressing action on the vasomotor centers.

5. The older commercial preparations of whole ovary and corpus luteum formerly used have little or no potency, and are quickly destroyed by digestive enzymes.

6. Theelin is of definite therapeutic value in the menopause. Excessive doses (100-200 R.U.) may be given without producing untoward symptoms. In the artificial menopause the dose must be large, since no ovarian function is present. In milder spontaneous cases the dose need not be so great, since some ovarian function is still present. In involutinal states small doses are of definite value. The vaginal pessary has been unsatisfactory. Theelin is of value when administered orally, when accompanied by favorable concomitant substances. The ratio of subcutaneous and oral administration is 1:4.

7. In all probabilities progestin is of value in cases of excessive flow, rather than in cases of amenorrhea. However it may be of value in certain cases of post menopausal bleeding. There is no satisfactory commercial preparation of progestin at the present time.

8. The anterior pituitary hormone is of value in some cases of menopausal symptoms. It is evident that pituitary would be of no value in the artificial menopause. In cases where some active ovarian tissue remains it would be indicated. The comm-

ercial preparation antuitrin-S has not been in use long enough to draw any definite conclusions.

9. The symptom complex of the menopause is not due to a decrease or absence of only one hormone, the entire endocrine system is involved. Consequently perfect results cannot be obtained by substituting only one hormone. Properly conducted laboratory procedures as outlined, will give us much information as to the presence or absence of certain hormones, having this information, the results should be much more encouraging. However as yet the laboratory procedures are not perfected and the expense would make the procedure impractical. There is also the question of concentration of extracts. At the present time it is necessary to inject large amounts of material to get the desired effect, this amount will eventually be decreased as it has been in various serums and antitoxins in use at the present time.

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