time as possibly injurious, although there is no conclusive evidence of harmful results following such treatments.

Karnaky [8] has advocated using acidulated sugar in the vagina combined with occasional douches of dilute acetic acid. Little [9] states that he has treated thirty-nine cases of gonorrheal vaginitis in this way, with the number of days required to effect a cure averaging 98.5. At present the number of our own cases in which this method of treatment was used is too limited to report. Sugar tablets must be inserted into the vagina two or three times a day. In our experience the vaginal secretions are not acid if measured some hours after the sugar tablets are dissolved. We have had but little experience with sulfanilamide and wait with interest to learn what value it may have in the treatment of gonorrheal vaginitis.[9a]

Until recently the treatment of senile or postmenopausal vaginitis has been most unsatisfactory. After cessation of the secretion of estrogen following the menopause or castration, the vaginal mucosa reverts to the thin, ill developed structure of childhood. The secretions are no longer acid and the mucosa becomes once again easily infected. When infected, such patients complain of burning, itching or pain in the vagina, and coitus may be painful or impossible. The appearance of the vaginal walls as described by Davis [10] and others is characteristic. In 1935 Davis reported remarkable success in treating these cases with amniotin subcutaneously. In the majority of his cases he administered 100 rat units of amniotin hypodermically three times a week. The average duration of the treatments was six weeks. Vaginal suppositories alone did not give satisfactory results. Usually complete symptomatic relief was afforded in about ten days. Biopsies taken at intervals during treatment showed the development of the vaginal mucosa in appearance exactly similar to that of a woman during the years of menstrual life. The vaginal secretions also became acid. Davis states that ordinarily the treatment of such patients should be continued for from six to eight weeks, for if any infection or inflammation remains the symptoms will return soon after it is stopped. In any event, when treatment is stopped the vaginal mucosa reverts to that of the childhood type, and if the factors that were responsible for the original infection are again encountered reinfection will follow.

Others have confirmed Davis's observations. Jacoby and Rabbiner,[11] for instance, report like results in twenty-five cases.

In our own experience, results have been good when the condition treated was a typical senile vaginitis. Vulvar leukoplakia has not been benefited. We have had two cases, one after removal of the ovaries and one following intra-uterine irradiation, in which the shrunken vagina became so dry and sensitive that intercourse was impossible. In both instances treatment with amniotin was effective in relieving the situation. It is probable that, as well as building up the vaginal mucosa, secretion from the cervix and Bartholin's glands was restored.

8. Karnaky, K. J.: M. Rec. & Ann., Houston, Texas, May, 1936, and other articles.

9. Little, A. A., Jr.: J. Pediat. **10**: 202 (Feb.) 1937.

9a. Since the writing of this paper, treatment with sulfanilamide has been completed in a series of seventeen cases of gonorrheal vaginitis in children. In nine of these cases the results were dramtic, with clearing of discharge and negative smears developing in twenty-four and forty-eight hours. Inadequate dosage probably accounts for the falure of three cases to respond; therefore treatment with sulfanilamide has been successful in nine of fourteen adequately treated cases.

10. Davis, M. E.: Surg., Gynec. & Obst. **61**: 680 (Nov.) 1935.

11. Jacoby, Adolph, and Rabbiner, Benjamin: Am. J. Obst. & Gynec. **31**: 654 (April) 1936.

Five years ago the treatment of vaginitis in children and in women after the menopause was anything but satisfactory. These newer methods of today are yielding gratifying results.

CONCLUSION

We have had better results with the use of estrogen suppositories than with hypodermic treatments with estrogen preparations.

52 Trumbull Street.

THE ENDOCRINE TREATMENT OF MENOPAUSAL PHENOMENA

J. P. PRATT, M.D.
AND
W. L. THOMAS, M.D.
DETROIT

The menopause is an event which has attracted wide attention among the public as well as among members of the medical profession. A variety of symptoms have been attributed to the critical change in a woman's life. A sharp distinction between the physiologic and the pathologic manifestations during this epoch of life has rarely been made. A causal relation between the symptoms exhibited and the physical changes in the body have been frequently assumed but seldom established. Numerous procedures and materials have been advocated for relief or cure, but proof of their specific efficiency is usually lacking. In recent years, special attention has been directed to endocrine preparations as therapeutic agents for relief of menopausal symptoms. In the present study of endocrine therapy, control observations have been used.

MATERIALS

The materials selected for study of the menopause may be divided into capsules and compressed tablets for oral administration, and sterile ampules of oil for hypodermic injection. The capsules, which were identical in appearance, contained theelol, phenobarbital or lactose. The compressed tablets, which were identical in appearance, contained either emmenin or lactose. The ampules contained either oil alone or theelin in oil. For identification, the preparations were given a code number, which was changed frequently to keep the one prescribing them ignorant of the nature of his prescription. One of us changed the code number from time to time without informing the one who administered the preparations. Before the preparation of the unknowns was completed, eleven patients were treated with phenobarbital and six with bromides. With these seventeen exceptions, the agent prescribed was unknown until final observation was recorded.

METHOD

Two hundred consecutive menopausal cases were studied over a period of several months. Only 100 of the subjects returned often enough to justify tabulation. A complete clinical record was written, including history, physical examination and routine laboratory tests of blood and urine. By means of a special form, the presence or absence of most of the symptoms

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The capsules and oil preparations were furnished by Parke, Davis & Co. The compressed tablets were furnished by Ayerst, McKenna and Harrison, Ltd.

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commonly attributed to the menopause was tabulated. Environmental and emotional states varied so greatly that they did not lend themselves readily to tabulation; therefore, individual records were made. The symptoms investigated were taken from the current medical literature, which suggests that these symptoms belong to the menopause. Our observations failed to confirm this relationship in many instances; e. g., arthritis and hypertension. The list included changes in the menstrual cycle, hot flushes, headache, languor, vertigo, palpitation, insomnia, digestive disturbances, paresthesia, neuralgia, arthritis, weight change, trend toward masculinity, impairment of memory, emotional instability, depression, melancholia, extreme irritability, agitation, apprehension, delirium and suicidal tendency. After voluntary statements were accepted, leading questions were asked, to complete the record. Physical examination included observation on weight change, fat distribution, genital involution, blood pressure change, pulse rate, evidence of arthritis and signs of masculinity. Laboratory tests included bio-assay of the urine in only a few instances and are therefore not reported. Geist [1] has recently called attention to the lack of correlation between excretion of hormones and menopausal symptoms.

Results

Drugs	No. of Cases	Complete Relief	Improved	Doubtful	No Relief	Per Cent Completely or Partially Relieved
Unknown						
Theelol	14	8	1	..	5	64.2
Phenobarbital	21	12	4	1	4	76.1
Lactose	23	12	4	3	4	69.6
Emmenin	8	3	3	..	2	75
Theelin in oil	10	5	2	..	3	70
Plain oil	7	4	2	..	1	85.7
Known						
Phenobarbital	11	10	1	..	..	100
Bromide mixture	6	3	1	..	2	66.6
Totals	100	57	18	4	21	75

Concurrent diseases and conditions which were not menopausal were treated as indicated.

All patients were sufficiently intelligent and informed to be aware of the popularly accepted relationship between failing ovarian function and menopausal symptoms. When treatment was prescribed, the patient inferred that she was receiving some ovarian preparation. Since the nature of the preparation was unknown at the time it was prescribed, the observer was unable to correct the patient's assumption.

The dosage was varied according to the severity of symptoms and the response obtained. One or two capsules or tablets were given from one to three times a day. Injections were given daily for a period of from five to ten days. After varying intervals, the injections were repeated as indicated by the results obtained. The total amount of theelol given to a single patient in the course of treatment varied from 2 to 5 mg. The total amount of theelin varied from 12,000 to 96,000 international units (1.2 to 9.6 mg.). No untoward effect was noted in any instance.

Patients who did not return regularly for observation were not included in the final tabulation of results. This excluded many who were entirely relieved by the first course of treatment and therefore failed to return. Those who had few or no symptoms besides cessation of menstruation were also excluded.

Many different personality types were encountered, but the patients were not classified according to this criterion. The psychotic patients were observed by a psychiatrist. These patients were retained in the hospital not less than three months. Not one of this group was improved.

The use of a placebo is by no means new. Practically every physician of experience has used it at one time or another. It has rarely been used, however, as a check to determine the value of hormone therapy in the human being. A similar experience was recently reported by Aschner and Buch Casamor [2] in treating gonadal dysfunction in the male. Satisfactory results were obtained in males when no hormones were used if the patient believed that he was receiving gonadotropic stimulating therapy

COMMENT

The term menopause has been used with the generally accepted broad interpretation. Etymologically it means merely a physiologic cessation of menstruation. The climacteric, or critical age, signifies a period of life characterized by a complexity of phenomena, the most conspicuous of which is the cessation of menstruation. No term accurately distinguishes between physiologic and pathologic processes. The menopause, though loosely used, is popular among the public as well as the medical profession to express the concept of the period of transition in a woman's life from the reproductive period to senility.

The average age of women in this series at the time of observation was 45.6 years. The average age at the onset of the symptoms was 43.5 years. Eleven of the patients had an artificial menopause. The average time that elapsed between the operation and the onset of the first symptoms of the artificial menopause was ten weeks. In general, the symptoms of the artificial menopause were more severe than were those of the natural menopause.

Hot flushes are such a constant symptom of the menopause that no patients are included in this series who did not have this symptom. The frequency and duration of the flushes were recorded but showed rather wide variation. In general, they are a good indicator of the severity of the condition. Some of the patients are more impressed by the sweats than by the flushes. The degree of relief from the flushes and the sweats is the best single indicator of the amount of improvement obtained. For the sake of accuracy in estimating results it is unfortunate that the best criterion is subjective.

Languor was the second most frequent symptom noted in this series. There is no satisfactory measure of the degree of languor besides the impression of the individual experiencing it. Other contributing factors than the menopause were frequently responsible for languor. Among these may be mentioned anemia, hypothyroidism and emotional disturbance.

Different observers agree that approximately 85 per cent of women pass through the menopause without interrupting their daily routine. The 100 cases presented here belong to the remaining 15 per cent, since only those women were included who came for treatment of symptoms of the menopause.

The menopause is a conspicuous event in the life of most women. Environmental changes are frequent and often profoundly influence the life of the individual.

1. Geist, S. H., and Mintz, Maurice: Pituitary Radiation for the Relief of Menopause Symptoms, Am. J. Obst. & Gynec. **33**: 643 (April) 1937.

2. Aschner, Berta, and Buch Casamor, A.: Zur Klinik des Späteunuchoidismus und Spätkastratentums: Zugleich ein Beitrag zur Organotherapie, Klin. Wchnschr. **14**: 86 (Jan. 19) 1935.

These changes are too diverse to permit detailed discussion here. The tabulation of results gives no indication of the importance of this factor. In every instance, however, the environment was given careful consideration.

It is realized that 100 cases is a small number from which to draw conclusions. They are sufficient, however, to establish a trend. The method was chosen because it was one means of controlling observations. Medical literature contains an abundance of impressions without controls.

It is interesting to note in the tabulation of results that, regardless of the form of therapy, the majority of patients were relieved or improved. Furthermore, there is only a slight difference indicated for the different agents used.

The question arises whether those who failed to obtain relief would have been benefited by larger doses of theelin or longer periods of treatment. One of the patients in whom treatment failed received more theelin than any other patient. She was subjected to one environmental shock after another. During a three months vacation, however, she was living under ideal circumstances and remained symptom free, although she received no therapy at all. When she returned to the city, the unfavorable environment was again encountered and all her symptoms returned. She resented strongly the necessity of an artificial menopause. She was a highly sensitive woman who responded excessively to ordinary environmental stimuli.

The other failures are still under observation. They are being studied intensively to see whether they represent a group in which the symptoms of ovarian failure predominate. Other factors are being eliminated in an attempt to isolate ovarian deficiency as a primary cause.

One of the patients presenting the menopausal syndrome was seen by a psychiatrist ten years before. She presented identical symptoms on the two occasions. At the time of the first visit she was menstruating regularly and showed no signs of genital involution. The diagnosis at that time was anxiety neurosis. When seen ten years later for the same symptoms, she had ceased to menstruate and showed genital involution. The diagnosis was menopausal syndrome. In both instances she obtained striking relief from sedation. The frequent resemblance of menopausal symptoms to the symptoms of anxiety neurosis cannot be overlooked.

Life is a continuous process. During the reproductive period there is a gradual waning of ovarian function. The transition from the reproductive period to senility is physiologic and gradual. It is not a crisis. The transformation involves the body as a whole, though the change in the ovaries and the organs under their direct control is most conspicuous. In the majority of instances, it is illogical to assume that substitution for failing ovarian secretion will alter the whole body and arrest the natural aging process.

The symptoms occurring at the time of the menopause are complex. Many diseases and pathologic states may be concurrent with the menopause. Is the menopause an entity? Inclusive consideration of all menopausal symptoms really involves a large part of the field of medicine.

CONCLUSIONS

1. The symptoms attributed to the menopause are so diverse that it seems unreasonable to consider that all of them are due to ovarian failure alone.

2. The menopause is a term used loosely to indicate the physiologic transition in the life of a woman from the reproductive period to senility.

3. Pathologic conditions occurring at the time of the menopause should be distinguished from physiologic states.

4. Estimation of the merits of any form of therapy for the menopause should be based on the relief of pathologic symptoms and not on changes in physiologic states.

5. Equally good results may be obtained by many agents used empirically.

6. Substitution therapy should be reserved for those cases in which the pathologic symptoms can be demonstrated to be due to ovarian failure.

7. The method used in this study offers one means of selecting cases probably due to ovarian failure.

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ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. FRANK, GOLDBERGER, SALMON AND FELSHIN, DRS. BURCH, MC CLELLAN, SIMPSON, JOHNSON AND ELLISON, DR. LITZENBERG, DRS. LEWIS AND ADLER AND DRS. PRATT AND THOMAS

DR. EMIL NOVAK, Baltimore: The paper by Dr. Frank and his co-workers emphasized again that physicians are still floundering in the treatment of amenorrhea. The groups which they described on the basis of hormonic studies are not unlike those which can be demonstrated by serial endometrial biopsy. For example, in amenorrhea one may find a persistently scanty and atrophic endometrium or one which exhibits an essential normal cycle (except for the bleeding phase), or one may find a typical hyperplasia, this last corresponding to the polyhormonic hyperplasia described by Zondek. In the same way, endometrial studies show that excessive menstruation can occur from almost any type of endometrium. Most characteristically one finds some degree of hyperplasia, but often the endometrium is of a normal interval type or even quite atrophic. Even a secretory endometrium may be seen in certain types of functional bleeding. The papers we have heard today illustrate the usual inadequacy of blood and urine hormone studies in pointing the way toward successful treatment. Valuable as such studies are from a scientific standpoint, they are not readily practicable in the vast majority of cases, and I believe that in the present state of our knowledge endometrial studies will often furnish just as valuable information of ovarian function, and far more simply. I do not like the use of the term ovarian deficiency by Dr. Burch and his co-workers in the explanation of functional bleeding. Ovarian substance, or hypophysio-ovarian imbalance, would seem to be the underlying factor in these quantitative menstrual disorders, whether in the direction of excess or deficiency. It should not be forgotten that typical hyperplasia per se has nothing to do with uterine bleeding. It represents simply a maximum effect on the particular endometrium of a growth hormone, estrogen, which exerts a special growth effect on genital mucous membrane. But bleeding does not necessarily parallel this growth effect, for the bleeding "spill" may occur at almost any level. All physicians have seen cases of marked hyperplasia associated with long continued amenorrhea. Dr. Burch states that the degree of endometrial change corresponds to the severity of the bleeding, an observation which does not agree with mine. The thyroid type of either menstrual deficiency or excess offers the best results in treatment, but unfortunately it constitutes only a small proportion of all cases. I agree with Drs. Pratt and Thomas, and this could be stated almost a priori, that many symptoms are unjustifiably attributed to the menopause. They include in the symptoms studied in this group of cases such indefinite manifestations as languor, digestive symptoms, impairment of memory and many others of this very subjective group. Dr. Frank, formerly almost an organotherapeutic nihilist, has shown how adequate estrogenic therapy in menopausal cases brings

about disappearance of gonadotropic substances in the urine, with corresponding improvement in the patient's symptoms.

DR. ELMER L. SEVRINGHAUS, Madison, Wis.: The discussion of Drs. Lewis and Adler shows how a physiologic mechanism can be used for a pharmacologic purpose. They applied estrogen not as substitution therapy, which is the usual goal of hormone therapy, but to facilitate healing in an infection. There is excellent agreement among the different clinics trying this therapy, which is a real contribution to the cure of vaginitis. This concept of the pharmacologic use of a physiologic process explains many results with thyroid therapy. Nearly all these disturbances in the field of gynecology are hypofunctional. The one exception might be the menopause, in which with underfunction of the ovary, or absence of function after castration, there is excessive activity of the anterior pituitary in producing the gonadotropic material. The thyroid hormone tends to stimulate the rate of activity of all tissues. Consequently, stimulating results on the pituitary and the ovary may be expected from thyroid therapy. I think that is why results are seen from use of thyroid in amenorrhea and menorrhagia. Dr. Litzenberg's statement that his patients are uniformly hypothyroid needs comment. The normal basal metabolism of women is at least 5 per cent below zero, which means merely that our standards were set prematurely. Until a woman has a basal metabolism of —15, she must be considered within normal limits. The big problem before gynecology and endocrinology now is to determine how much deficiency exists in a given patient, and then to know how much material to give in a therapeutic program. Dr. Frank is studying these cases quantitatively. These studies are still to be reserved for the highly experimental clinics, because assay technics are far from being uniformly reliable, and the significance of the urinary estrogenic output, as compared with the amount circulating in the blood and active within the body, is not known as yet. Obviously, the amount in the urine represents only a small fraction of that which is active, and until a considerable number of normal individuals are studied we cannot make even an empirical decision as to the significance of that urinary excretion. I am at a loss to know what Drs. Pratt and Thomas mean by contrasting the physiologic and pathologic disturbances of the menopause. All these vasomotor and psychic symptoms may occur in patients before the menopause; but the significant thing is that, after castration of a woman who has no other disturbances, these are the symptoms reported. They occur frequently in the spontaneous menopause. There is, conversely, the experience that all these symptoms can be abated and usually completely relieved by the use of an adequate dose of estrogenic materials. Drs. Pratt and Thomas did not tell how much of the estrogenic substance per day is employed in a case. The necessary dose varies tremendously. For the present at least it would be well to stay with the standardized preparations from manufacturers who have been making these materials long enough so that one knows the materials are what the labels say they are. Estrogen will accomplish results either orally or by injection. I would prefer to stay away from the parenteral use of a foreign oil which leads to foreign body reactions, using only the oral preparations.

DR. E. C. HAMBLEN, Durham, N. C.: Drs. Lewis and Adler have proved conclusively the specific vaginal effects of estrogenic principles. Drs. Pratt and Thomas have described the generally appreciated psychotherapeutic associations of the treatment of so-called menopausal symptoms. Larger doses and more prolonged administration of estrogenic principles in oily solution than Drs. Pratt and Thomas used are necessary to secure pituitary depression as judged by urinary hormone assays. Some of the failures reported by Drs. Pratt and Thomas might have responded to more prolonged therapy. The therapeutic employment of estrogen and progestin in my experience has permitted the conservative management of many of the anovulatory types of functional menometrorrhagia. In addition to a local endometrial effect, there results beneficial depression of the pituitary permitting rest and restitution of the cystic ovaries. Such treatment may be exhibited at the time episodes of bleeding occur or may be employed cyclically following an initial curettage. Doses similar to those employed for full endometrial proliferation in castrates are frequently necessary. Such therapy is too expensive at present to warrant its general use. The employment of the so-called gonadotropic principles in functional anovulatory phases, responsible in many instances for menometrorrhagia, amenorrhea and sterility in the hope of initiating physiologic exocrine and endocrine responses in such ovaries, has been widespread and uncritical. Such principles, even when exhibited in doses much larger than those in general use, possess no claims for specificity. Among fifty-one patients with ovaries presumed to be in anovulatory phases, I have observed no evidence of any specific effect from such therapy as judged by the finding of corpora lutea at laparotomy, or by finding a progestational reaction in the endometrium. Daily doses as large as 8,000 rat units, and total doses as large as 24,250 rat units, given over a period of eight days, have been employed. In a recent series of thirty-seven patients with functional anovulatory menometrorrhagia who were treated during episodes of active and excessive uterine hemorrhage, only six showed any diminution in the amount of bleeding during such therapy. I agree with Dr. Litzenberg that thyroid extract is our main standby in endocrine therapy.

DR. FRED H. FALLS, Chicago: My experience agrees with that of Drs. Frank and his co-workers that little is to be expected from the injection of estrogenic or gonodatropic substance in the primary amenorrheas. The lack of response to the large doses they used show how utterly useless the dose usually recommended must be. I should like to ask Dr. Frank whether in his opinion the use of progestin in addition to estrogen and the gonadotropic hormone might be indicated in those cases especially in which a normal or increased amount of estrogenic hormone in the blood is demonstrable. There is some evidence to show that the various phenomena developing during the menstrual cycle are dependent on a balance between these two hormones. Drs. Burch and his co-workers emphasized that an accurate diagnosis should be made in these patients showing menorrhagia and metrorrhagia before attempting any form of endocrine therapy. How easy it is in a woman somewhat obese to overlook a small fibroid uterus. I have found definite organic changes including carcinoma, fibromyomas, adenomyomas and polyps in uteri removed from patients previously treated over a considerable period of time with endocrine therapy. Thyroid extract is valuable in these patients with menorrhagia on a basis of hypothyroidism. I have not found it necessary in these cases to use the estrogenic hormone in addition to the thyroid. Gonadotropic substances from the urine of pregnant women or from the placenta have given some favorable results in some menorrhagia cases, but I have noted usually that these results were temporary and that progestin preparations seemed to stop the bleeding when the other hormone failed. I have also noted in a few cases temporary improvement followed by failure after injections of progestin. In such cases a combination of progestin and thyroid has given good results. Thyroid deficiency as a predisposing cause of sterility is almost universally admitted. The mechanism by which this is brought about is not clear. Does the thyroid extract act directly on the ovary? Does it act on the hypophysis primarily and on the ovary secondarily, or does it act directly on the uterus? The more or less empirical use of a remedy usually precedes the scientific explanation of its action by a number of years. As regards the treatment of habitual abortion or threatened abortion by progestin, more recent experience has confirmed my earlier clinical impression and laboratory experiments demonstrating its inhibiting action on the contractions of the human uterus reported here two years ago. There is no doubt that this is a valuable therapeutic agent. I am impressed by the careful method of control which Dr. Pratt and Dr. Thomas have adopted to avoid any semblance of prejudice on their part which might develop in favor of one or another treatment. The results are thought provoking. My experience in dealing with these menopausal cases recently has been largely confined to the use of emmenin in the liquid form. Whether the effect is produced psychologically or physiologically, I am not prepared to say; but that a higher percentage of patients get a greater degree of relief than with the sedatives and estrogenic hormone injections previously used I am firmly convinced.

DR. AUGUST A. WERNER, St. Louis: Drs. Pratt and Thomas stated that "a group of symptoms occurs that is char-

acteristic for the menopause, castration and partial castration." This is an accepted fact. These symptoms are not due to failure of ovarian function per se; they are initiated by ovarian failure. Failure of ovarian function disturbs the pituitary gland, which exercises an influence over most of the other glands of internal secretion. This secondary disturbance causes imbalance of the two divisions of the autonomic nervous system and these combined factors produce the characteristic symptoms complained of by castrates and menopausal women. The duration of the menopause in some women is from three to six months; in others the duration may be five or six years. If a woman whose glandular-autonomic stabilization will require five years is treated for three months with relief of her symptoms, it can be expected that she will have a recurrence of her symptoms at a later time, and treatment must be reinstituted from time to time until they cease to recur. Some women have mild to severe psychotic symptoms at the climacteric, and if they are sufficiently severe the condition has been termed involutional melancholia. Drs. Pratt and Thomas stated that they had kept some of these psychotic women in the hospital under treatment for as long as three months without relief. We treated forty women having involutional melancholia (menopausal psychosis) at the St. Louis Sanitarium and at Missouri State Hospital No. 4. Twenty were given injections of theelin and twenty were administered physiologic solution of sodium chloride intramuscularly as controls. Six months' treatment was decided on arbitrarily. Within six months, 66 per cent of the theelin treated women had recovered, and those who were given physiologic solution of sodium chloride were not improved. We then treated the controls with theelin and had approximately 66 per cent recovery in that group. I cannot agree with Dr. Pratt that estrogenic hormones do not help these women or that such treatment is only psychic.

DR. CHARLES W. DUNN, Philadelphia: An unmentioned group of endocrine disorders, the adrenal cortical hyperplasias or tumors, are concerned in all the presentations except that of Drs. Lewis and Adler. In the adrenogenital syndrome—virilism—and in basophilism the ovarian disorder accounts for the hypo-ovarian syndrome as defined by Dr. Sevringhaus. Dr. Broster of London performs partial adrenalectomy in cases of adrenocortical hyperplasia, with good results in restoring menstrual function. In his cases, preoperatively, the menstrual picture varied; some had amenorrhea, others hypomenorrhea and others increased menses. Adult cases of this type show early onset of menses and menorrhagia, at 16 to 18 years of age, diminishing or abrupt cessation of menses, onset of hypertrichosis and frequently hypertension. Sterility and the hypo-ovarian syndrome are also part of adrenal cortical hyperfunction. Drs. Novak and Werner pointed out that we are dealing with multiendocrine disturbances. Crookes states that the pituitary pathology of basophilism (pituitary basophilic adenoma, carcinoma of adrenal cortex or thymus and arrhenoblastoma of the ovary) is a hyaline cytoplasmic change and loss of basophilic granules in the basophil cells, the presumed source of the gonadotropic fraction. Although reputed to be a hyperfunctional basophilic reaction, pathologically and clinically a subovarian state results. In such adrenal cortical disorders, Grollman believes that the pituitary changes initiate the ovarian hypofunction and in some manner stimulate the androgenic zone, which is a destructive cell area lying beneath the adrenal cortex. He believes that adrenal cortical carcinoma does not produce basophilism. This view is supported by authentic cases and one recently reported by Ullam. Patients presenting hypertrichosis, moderate hypertension and a history of sterility were treated with progesterone and pregnancy occurred. Patients simulating the Cushing type became pregnant while amenorrhic, confirming Dr. Frank's observation. As early as one month after pregnancy, patients have developed an acute clinical condition of pituitary-adrenal origin; this brings forth Grollman's belief that puberty and pregnancy induce hyperplasia of the androgenic layer. In treating these cases I have to administer higher dosage of estradiol benzoate than given by Dr. Frank and his co-workers. If dosage is low the symptoms are relieved but the menses are not influenced. Higher dosage not alone relieves the symptoms but also induces uterine bleeding in the amenorrheic cases.

DR. JACOB HOFFMAN, Philadelphia: At the Endocrine Clinic of the Jefferson Hospital we have had the opportunity of studying more than 800 cases of functional menstrual disorders, sterility and symptomatic menopause. Endometrial biopsy as well as the sex hormone determinations of the blood and urine were used in the evaluation of these cases. An analysis of our observations reveals that these patients fall into two main groups. In one the disorder is purely functional, is capable of spontaneous correction and is amenable to treatment; in the other the condition is an expression of constitutional inferiority or a deep-seated endocrinopathy and is very resistant to any form of therapy. We have employed both general medical measures and organotherapy. Controls were used in whom the sex hormone preparations were employed. Our experience has shown that the commercial preparations have only a limited sphere of usefulness. This is not surprising, for the gonadotropic substances have not been shown to exert a stimulating effect on the human ovary, while the ovarian sex hormones, though capable of stimulating the accessory genitalia, cannot activate the ovary itself. An indirect effect of these substances by way of the anterior hypophysis has been demonstrated in the laboratory animals but not in man. The use of estrogenic preparations for the relief of menopausal symptoms has been hailed as an outstanding example of the value of sex hormone therapy. We have employed estrogen as well as nonspecific therapy consisting of hypodermic injections of saline solution together with sedatives and found the former less effective, although large doses have been administered over a long period of time. I am therefore wholly in accord with the observations of Dr. Pratt and his co-workers. When it is recalled that the climacteric involves not merely a withdrawal of estrogen but also a general endocrine upheaval as well as structural alterations throughout the organism incident to the approaching senium, the beneficial effects of estrogen may well be questioned. Medical treatment yields the best and most enduring results. General hygienic measures, correction of nutritional faults and the correction or elimination of all constitutional depressive states, supplemented by thyroid extract where indicated, will favorably affect the organism as a whole and with it the gonads. Reduction of weight in the obese and an increase in weight in the thin asthenic type is often sufficient to regulate the menstrual rhythm and raise the level of fertility.

DR. MISCH CASPER, Louisville, Ky.: This symposium brings out some real advancement in endocrinology. Why do little girls have to have gonorrheal vaginitis? is the first question. Why does any one have to have gonorrheal vaginitis? Why can't this humiliating and distressing disease be banished, now that so much is known about the gonococcus and gonorrhea and there really exists something to offer in the way of the cure of this disease? The medical profession has been derelict in the handling of gonorrhea in the past; but I believe now there is an awakening, because we have something in the way of treatment to get rid of this disease. I am sure that Drs. Lewis and Adler, while not discussing gonorrhea generally, have no objection to using other means of treatment along with the endocrine treatment. The Elliott hot water treatment, hyperpyrexia, and later the sulfanilamide treatment have all proved effective in getting rid of gonorrhea.

DR. CECIL STRIKER, Cincinnati: I should like to ask Dr. Frank whether he has any fear or any evidence of malignant changes following massive doses of these hormones, and I should like to have an expression both from him and from some of the other authors.

DR. PETER B. SALATICH, New Orleans: I would like to ask Dr. Litzenberg whether the question of sterility in the male side of the picture was thoroughly studied.

DR. JEAN PAUL PRATT, Detroit: I am grateful to the discussers for helping to emphasize some of the varied manifestations of the so-called menopause. Dr. Novak emphasized the vasomotor symptoms as being outstanding, and perhaps objective symptoms. I agree in part that the hot flushes may be objective. For the most part, however, they are subjective. They seem to be such an important symptom of the menopause that we did not include cases as menopausal unless the women had hot flushes, because that seems to be the one symptom on which every one agrees when they discuss the menopause. We charted

the number of flushes. We asked the patient to do the same, but we were confronted with an unscientific observer furnishing the information. Most observations of the menopause are unscientific. It is extremely difficult to set up any experiment that will correspond with the carefully controlled laboratory experiments. Dr. Sevringhaus questions the term "physiologic or pathologic states." Life is a continuous process. There is a period of rapid growth in childhood, a period of continued rapid growth in adolescence. Then there is a flattening of the curve during the reproductive period, following which the curve trends downward to senility. Somewhere along that curve occurs the first conspicuous event of the reproductive life; namely, the first menstruation. In the mind of the public the first menstruation is puberty, but physicians know that puberty extends over a long period. The same is true of the menopause. The public is firmly convinced that cessation of menstruation is the menopause, but physicians know differently. It is a very gradual change. The function of the ovaries trends downward for a period of several years. That is what I mean by a physiologic state. It is not a sudden change in the state of the ovaries. It is a gradual process which has been going on for years. The question of the use of large doses of estrogens has been very kindly answered by Dr. Hoffman. Dr. Werner insists on keeping the psychoses in the group of menopausal symptoms. I am sorry that I cannot give the statistics furnished by the superintendent of a large institution for the insane, who told me that the expectancies of the psychoses of that type were no greater in relation to the menopause than they were at any other time in the individual's life, so that the justification for calling the psychosis menopausal is not borne out by statistics. We do not mean to imply that the menopause cannot be cured by the estrogenic hormones. Fortunately, they can cure, as well as almost anything else. It does not make so much difference in the large proportion of cases what agent is used. We were trying to determine what particular patients had evidence of ovarian failure and reserved estrogenic therapy for that particular group. The 85 per cent who go through the menopause without any particular disturbance keep most of the menopausal women from seeking medical aid, so we probably are dealing with only 15 per cent. Of that 15 per cent we found that 75 per cent were relieved by almost any form of therapy. Probably in the small group remaining it will be found that there is a definite need for some specific therapy.

DR. JENNINGS C. LITZENBERG, Minneapolis: The question was asked whether anything had been done about the male studies. I was discussing one subject only, and that is the endocrine influence on the female. It goes without saying that every one of these patients was studied thoroughly from every other standpoint, which always should be done with every sterile couple before taking up the endocrine studies. The thorough study of the husband as well as of the wife was made in every case of sterility. One should not study individual sterility alone but should approach the question as pair sterility. Any one who attempts to treat sterility without studying the male as well as the female, of course, is not doing his duty.

DR. MORRIS A. GOLDBERGER, New York: In our bio-assay and treatment of amenorrhea, only functional cases of amenorrhea were studied. Cases in which there were severe endocrine disturbances were omitted. The animal response to extracts from human beings is not positive proof that the substances obtained are definite causative factors in the production of symptoms in the human being. Our hormone bio-assays have shown that cases of amenorrhea fall into four groups: the acyclic type, the subthreshold type, the normal type and the polyhormonal type of Zondek. The presence of gonadotropic factors, or an absence of them, may be found in any of these groups. The response of the menopause patient to 30,000 rat units, as viewed objectively, consists in the disappearance of the gonadotropic factors from the urine, and the change in the vaginal smear. The patient is instructed how to prepare the smears, and when obtained they are brought to our laboratory, where they are stained with 1 per cent aqueous fuchsin. A change in the smear occurs corresponding to that in the rodent and consisting in the replacement of the leukocytes by small epithelial cells even to complete squamous cell metaplasia. These effects are definitely noticed in the menopause, and those cases of amenorrhea which respond in this way are taken out of the functional amenorrhea group and placed in the menopause group. Dr. Novak stressed the use of serial endometrial biopsies. We have done this in several of our cases but as yet have not fully correlated the results obtained with our bio-assays. Another point Dr. Novak mentioned that we also stress is that the uterus in our amenorrhea cases appears to be refractory to treatment with hormones. We agree with Dr. Sevringhaus that we do not as yet know whether or not the hormone assays are quantitatively and qualitatively the same. To Dr. Fall's question of the use of progestin in addition to estrogen in the treatment of amenorrhea we can only say that, were it to be used, a definite change in the endometrial picture to one resembling more nearly the normal premenstrual endometrium would be obtained. Bleeding may take place, but the cost of treatment would be doubled, since approximately 35,000 rabbit units of progestin is necessary. Besides, in the long run the patient would not be appreciably benefited because, in order to insure a continuation of the menstrual function, treatment would have to be prolonged. In answer to Dr. Striker, whose question concerns the fear of the use of large doses of estrogenic preparations, I may say that in adults we have never experienced any untoward effects or any changes suggesting malignancy. Bleeding, however, has been obtained. On the other hand, in prescribing gonadotropic substances, especially the newer products made from horse serum and available in high concentrations, care must be exercised in their use because of the proteins present, to which many individuals may be sensitized. When these substances are used, we invariably test for sensitivity intradermally.

A NEW DIAGNOSTIC INTRADERMAL REACTION WITH BOWEL ANTIGEN

INDICATING THE PRESENCE OF THE VIRUS OF VENEREAL LYMPHOGRANULOMA IN THE INTESTINE AND DIFFERENTIATING COLITIS ASSOCIATED WITH THAT VIRUS

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WITH THE TECHNICAL ASSISTANCE OF BETTY KRAVETZ
BALTIMORE

Idiopathic or nonspecific ulcerative colitis is an involvement of the large intestine, regional or general, of unknown etiology, resulting in an exudate of, or feces containing, blood, mucoblood or pus, or all of them. There was reason to believe that in some cases colitis with or without a stricture might be due to a virus. If this were proved, a virus as a factor in intestinal disease would come into being, and the classification idiopathic ulcerative colitis would be narrowed.

The first step in attempting to demonstrate colitis associated with virus rests, if not in the actual isolation, at least in the indication of the presence of such an agent directly from the region of suspected colonic involvement.

Patients with ulcerative colitis of indeterminate etiology were selected in whom the possible presence of a virus in the colon might be related to the colitis as suggested by their having a positive intradermal response to inactivated bubo pus due to the virus of

From the Gastro-Intestinal Section and Laboratories of the Medical Clinic of the Johns Hopkins Hospital and the Johns Hopkins School of Medicine.

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The following cooperated: Drs. Harry M. Robinson, Baltimore, and Harry B. Burr, Houston, Texas, sent generous supplies of bubo pus. Frei and chancroidal antigens were forwarded by Drs. George W. Binkley and H. N. Cole, Cleveland; Robert B. Greenblatt and Everett S. Sanderson, Augusta, Ga.; George A. Hunt, St. Louis; Collier F. Martin, Philadelphia, and Marion B. Sulzberger, New York. Margaret Johnson and Edith H. Bohanan of the Social Service Department of the Johns Hopkins Hospital assembled cases.