given massive doses of ascorbic acid by injection. One of them received 500 mg. intramuscularly, another 800 mg. intravenously, and the remaining three 500 mg. by the same route.

Results

In reviewing the twenty-five cases after several weeks' treatment by oral medication with 100 mg. of ascorbic acid daily no evidence could be found of any marked improvement in the amount of wheezing, the incidence of attacks, or the general condition. None of the five patients who received injections of ascorbic acid in doses of 500 mg. or over experienced any relief in their symptoms after a period of twenty to thirty minutes, and the amount of adrenaline subsequently required to relieve the spasm was in no way diminished. Thus it was impossible to confirm the statement of Hochwald (1936) that asthmatic symptoms could be relieved by large intravenous injections of ascorbic acid. It may be mentioned that in these five cases symptoms were severe in two instances and slighter in three.

Conclusions

The investigations described above have not shown ascorbic acid to be of any value in the treatment of bronchial asthma when given in comparatively large doses either by injection or by mouth.

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R. Benda (*Prag. med. Z.*, January 25, 1938, p. 67) does not agree that a retroverted uterus discovered during a routine examination and producing no symptoms should be left untreated. He recommends replacement and insertion of a pessary in all cases. Operative treatment is indicated if after one year's conservative treatment the uterus still becomes displaced after removal of the pessary. Replacement of a gravid retroflexed uterus should only be undertaken in hospital. Although spontaneous replacement may take place, and although it may be aided by lying in the prone position, it must not be left to chance. When retroversion is due to pelvic peritonitis conservative treatment of the pelvic inflammation is indicated. The insertion of a ring pessary in the treatment of uterine prolapse is only of value when the levatores ani are still intact. It is valueless when the neck of the cervix is elongated and when cystocele or rectocele is present. Of the various operative procedures Benda advises Wertheim-Schauta's method of interposition of the uterus between the vagina and bladder, or Halban's fixation of the uterus to the bladder. He attacks anterior and posterior colporrhaphy as an operation attended by an appalling proportion of relapses. Measures for the prevention of uterine prolapse include careful forceps deliveries, more frequent use of episiotomies, and exercises in the puerperium. Benda advocates that women should be encouraged to get up five days after a normal confinement, but they should not be allowed to do their ordinary work for some time afterwards.

THE FEMALE CLIMACTERIC AND THE MENOPAUSE

BY

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The recent advances made in the physiology of the sex hormones have tended to stimulate rather than to satisfy our curiosity. The shafts of light that have been shed on a few isolated points have by contrast served merely to accentuate the darkness of surrounding ignorance. This is particularly true of the existing knowledge of the female climacteric. The common employment of the terms "menopause" and "climacteric" as though they were synonymous advertises the looseness of present conceptions, for although both these conditions possess certain similar features there is no possible justification for regarding them as identical. Some of this confusion may be due to the tendency to make deductions from the similarity of the symptoms of the artificial and of the physiological menopause. Such argument by analogy is always risky (as in the case of the experimental diabetes of pancreatectomy and its supposed clinical counterpart), and in view of the unknown causation of the physiological menopause any inferences should be drawn with extreme caution. Since a clear differentiation between the menopause and the climacteric is becoming increasingly important, the two subjects are here reviewed from both the theoretical and the clinical standpoint.

The Menopause

The use of the term "menopause" should be restricted to its literal meaning of the cessation of the menses, which should also imply the termination of the menstrual life. The cause of this permanent amenorrhoea is not known, but it is commonly accompanied by two principal endocrine changes. First, there is a relative diminution in circulating oestrogens, which are almost or completely absent from the blood stream three years after the cessation of the menses in probably at least 50 per cent. of women. It is doubtful, however, if the menopause is due directly or solely to a decline in the ovarian secretion, since full endometrial hyperplasia, which may be regarded as a specific oestrogenic function, may persist for many years after the establishment of amenorrhoea. Its occurrence has been variously reported in forty out of 804 and fifteen out of 130 post-menopausal subjects (Novak and Yui, 1936). The site of formation of these oestrogens is not known, but some at least may originate in the ovary. In the second place, there is an increased content of prolactin in both the pituitary gland and the urine, but the significance of even this finding is not appreciated. The increased content of prolactin in the pituitary is probably more characteristic of a resting than an actively secreting state, and it may be of interest to quote the work of Engelhart and Häusler (1936-7), who reactivated the senile ovaries of rats by the implantation of pituitary tissue.

The Climacteric

The term "climacteric" is derived from the Greek, meaning "a rung of a ladder," and originally was used to describe certain critical epochs, in the life of both men and women, at which the body was believed to undergo radical changes. These epochs were supposed to recur at intervals of nine years, the two important ones being at adolescence and at the sixty-third year, the

latter being referred to as the "grand climacteric." The term may therefore be used to signify certain changes in function, and to a less extent in structure, which take place at or after middle age. These changes lack any uniformity and show great variation in severity. The most distinctive mental changes are a progressive introversion of the mind, with depression, inertia, and insomnia, while the normal physiology of the body is subject to innumerable disturbances, the majority of which are characterized by transient or persistent sympathetic discharge (Donald, 1937): common among these latter symptoms are headache, dizziness, various rheumatic affections, and swelling of the extremities or face.

In the past no investigator has drawn any practical distinction between the menopause and the climacteric, and hence no attempt has been made to establish any endocrine relation or difference between these two conditions. From the clinical view-point there can be but little doubt that involutionary changes affect glands other than the ovaries. A mild degree of myxoedema is considerably more common than states of true hyperthyroidism, the occasional occurrence of which may perhaps be due to the trophic influence on the thyroid gland of a hypertonic sympathetic nervous system. Similarly, the majority of cases of diabetes mellitus which originate at the climacteric would appear to be due to a depression of insular activity, and only a small percentage of cases may be attributed mainly to excessive glycolysis from sympathetic discharge. I have seen several cases the symptoms of which bore a striking resemblance to Addison's disease, even to the characteristic pigmentation and fall in blood chlorides. It would therefore seem likely that these multiple glandular disturbances may possess some common origin, which for reasons previously mentioned may well be a reduced secretion of the anterior pituitary.

It will thus be seen that the climacteric differs from the menopause in being a general rather than a local disturbance, and in being a chronic immeasurable clinical state rather than a clear-cut observable symptom.

Relation between Menopause and Climacteric

In the past it has been assumed that the menopause initiated the climacteric and that the two conditions were clinically inseparable. This conception is open to considerable criticism and doubt. Since the principal symptoms of the climacteric are to a large extent non-specific in nature and essentially nervous in origin, their time of onset, severity, and chronicity may be regarded as the resultant of at least two intrinsic forces: (1) the fundamental constitution of the individual, in which I include the basic endocrine pattern and its consequent influence upon the tone and equilibrium of the autonomic nervous system; and (2) the individual degree of endocrine change which occurs at the climacteric. In general the more unstable a nervous system is, the smaller are the degrees of endocrine change which are capable of disturbing it. Now since this constitutional factor varies so widely in different individuals, considerable variation in the onset and severity of climacteric symptoms might be expected, even supposing that the rate and degree of endocrine involution were constant. In point of fact, however, much evidence has recently accumulated to suggest that these endocrine changes also are subject to great individual variation.

Although in many women oestrogenic substances are absent from the blood and urine three years after the menopause, in many others this reduction is extremely

gradual, for these substances have been found to persist in considerable quantity in both the circulation and the urine for twenty years or more after the menopause (Robson *et al.*, 1934; Frank, 1934; Frank, Goldberger, and Spielman, 1934; Frank, Goldberger, and Salmon, 1936). A further indication of this persistent oestrogenic secretion may possibly be given by some observations which I have made on the amounts of oestrone and oestradiol that are effective in producing proliferative bleeding in the post-menopausal subject. The work of Kaufmann and others has demonstrated that approximately 25 mgm. of dihydroxyoestrin injected intramuscularly are required to produce proliferation of the endometrium in the castrated subject. In the treatment of the climacteric by oestrogenic compounds, however, ten out of 120 patients have reported the occurrence of uterine haemorrhage after very much smaller amounts. Details of these cases are summarized in the accompanying table:

Case No.	Age	Years past Menopause	Duration of Treatment in Weeks Prior to Haemorrhage	Weekly Replacement of Oestrin in Mg.	Total Replacement in Mg.
1	69	18	13	1 B; 2 O	13 B; 26 O
2	63	17	5	6.3 O	31.5 O
3	63	11	4	1 B; 2 O	4 B; 8 O
4	58	18	4	2 B; 2 O	8 B; 8 O
5	57	10	6	2 B; 2 O	12 B; 12 O
6	56	5	9	2 B; 2 O	18 B; 18 O
7	54	4	24	1 B; 2 O	24 B; 48 O
8	50	2	20	2 B; 2 O	40 B; 40 O
9	50	1	6	2 B; 2 O	12 B; 12 O
10	48	1	5	2 B; 2 O	10 B; 10 O

B = Dihydroxyoestrin benzoate, given intramuscularly. O = Oestrone, given by mouth.

Cases 3, 6, and 7 were curetted and typical endometrial proliferation was found. Case 2 had a recurrence of haemorrhage after six weeks of further treatment by 0.6 mg. oestrone daily by mouth.

The figures show that there is a marked difference in response between the castrate and the post-menopausal subject.* From these considerations two conclusions may justifiably be drawn:

1. The severity of climacteric symptoms need not be in proportion to the degree of endocrine change. This has already been pointed out by Salmon and Frank (1936), who found that such symptoms could not be correlated either with the amount of circulating oestrogens or with urinary prolan, and yet these symptoms could be relieved by the adequate administration of oestrin.

2. Great individual variation may be expected not only in the severity and chronicity of the climacteric but also, and more particularly, in its time of onset.

From the theoretical side alone, therefore, there is reason to suspect that the menopause and the climacteric may not always possess a close temporal relation.

Practical Considerations

How are these theoretical considerations borne out in practice? In probably 80 to 90 per cent. of women the menopause is closely related to the onset of climacteric symptoms. These symptoms usually coincide with the cessation of the menses, but may precede or follow the establishment of amenorrhoea by a few years. While this close association of the menopause to the climacteric

* One apparently indisputable case of uterine bleeding in a castrate following the administration of only 2 mg. of dihydroxyoestrin has, however, been reported. (Werner, A. A., *et al.*, *J. Amer. med. Ass.*, 1937, 109, 1027.)

is usual it is by no means invariable. The following case-histories are typical of many others in my possession:

ILLUSTRATIVE CASES

Case 1.—Mrs. C., aged 65. This patient cannot remember exactly what her age was at the menopause—probably about 48. "Had far too much to do to be bothered about that sort of thing." She put on a little weight at that time, but had no flushes or any other symptoms. She experienced good health until two years ago, when she became more easily fatigued, and subsequently developed giddiness with falling, so that she was afraid to go out of doors by herself. She also had insomnia, depression, and slight puffiness of the ankles. Blood pressure 175/115. The patient was referred for special advice on account of her rapidly failing vision, associated with pallor of both optic disks. The subjective symptoms cleared rapidly with 0.1 mg. oestrone thrice daily by mouth, with six injections of 1 mg. oestradiol, given twice weekly at the commencement of treatment. Six months later, with correction, she was reading 6/6 J1 in both eyes.

Case 2.—Mrs. W., aged 68, thinks the menopause must have occurred near the age of 46, "since her little girl was about 2 years old at that time." She may have experienced occasional flushes about then, but was not inconvenienced in any way. She always enjoyed good health until five years ago, when she had an attack of sciatica. Shortly afterwards, symptoms of rheumatism began in the fingers, and for the last three years she had suffered from recurrent neuritis of the arm, pain and stiffness in the knees, insomnia, listlessness, and mental depression. The rheumatism, on account of which she first presented herself, had previously been treated unsuccessfully with gold and physiotherapy. She failed to show any decisive improvement from small desensitizing doses of vaccine, and was accordingly placed upon 0.1 mg. oestrone, three times daily by mouth. In three months she was able to kneel and rise without pain, and her fingers, though much deformed, were also painless. The patient protests against any suggestion that treatment should be discontinued, since with it she feels so much stronger, more energetic, and more cheerful.

Case 3.—Mrs. L., aged 70. She does not remember the date of the menopause, but thinks it must have been about the age of 50. She cannot recollect any symptoms at that time. Her health was excellent until three years ago, when "her age began to tell on her heart." She suffered from palpitations, shortness of breath on exertion, oedema of the ankles and to a lesser extent of the wrists, insomnia, and mental depression. There was also some pain and stiffness in both knees. The heart was found to be much enlarged, and the first heart sound was of poor quality. The blood pressure was 165/120. She was given 0.1 mg. oestrone thrice daily by mouth, with 1 mg. oestradiol intramuscularly twice weekly, and within six weeks she had lost all subjective symptoms. The oedema had disappeared, and her usual optimism and ability to sleep had returned. She has continued to improve during the last six months.

Case 4.—Mrs. R., aged 70. The menopause occurred at about the age of 50. She suffered from occasional flushes at that time, and has had peri-articular rheumatism of the knees with muscular rheumatism for the last six years, with dizziness, headaches, insomnia, and depression for two years. The subjective symptoms were rapidly controlled with 0.1 mg. oestrone thrice daily by mouth and 1 mg. oestradiol intramuscularly once a week.

It will thus be seen that while the menopause was undoubtedly accompanied in these cases by occasional mild phenomena such as hot flushes or some gain in weight, the onset of that wide assortment of nervous symptoms which characterizes the climacteric was delayed for fifteen years or more.

Conclusions

Both on theoretical and on clinical grounds, therefore, it is important to differentiate between the climacteric

and the menopause. The former, unlike the latter, is not an epoch but an era: it represents not a simple change but rather the summation of innumerable independent factors; it is a chronic state of potential nervous disharmony which need of necessity bear no relation to the menopause, but which may mature or be activated many years later. Ten years ago these considerations might have been thought of academic interest. To-day, however, they possess a practical significance which it is difficult to overstress.

Good health depends upon normal function. The importance of abnormal function in the production of morbid symptoms and morbid structural change is great, and is by no means fully appreciated. The function of the body is the expression of its physical constitution, of which the neuro-endocrine pattern forms the backbone. Just as the constitution is modified in the first third of life by the endocrine changes of adolescence, so the functions of the body are modified in the last third of life by the changes of the climacteric. These functional changes are responsible in later years for the facilitation of many diseases and the causation of much ill-health. It is true that the exact nature of these changes defies analysis and will continue to do so for many years to come, but the means for the relief of much suffering is already to hand. X rays, gonadotropic preparations, insulin, thyroid, testosterone, luteal hormone, and oestrin all have their place in the treatment of these conditions. The employment of these remedies will vary according to the requirements of the individual cases, and in the absence of any measurable indicators is largely a matter of detailed clinical analysis and not a little experience. While financial considerations may limit the use of certain of these preparations, such restrictions seldom apply to oestrin. In those cases where the symptoms of the natural climacteric may be attributed mainly to lack of this hormone, its replacement can, when necessary, be effected entirely by injection and be administered by the patient, relatives, or district nurse. There are very few cases whose requirements exceed 1 mg. of oestradiol two or three times a week, while the majority may be kept comfortable on less. Such treatment cannot be considered as a luxury any more than can the treatment of the diabetic by insulin. It is wrong to regard the functional disturbances of the climacteric as innocuous or unavoidable, and therefore to be tolerated. Rather must they be looked upon as a warning of potential organic change which, if disregarded, may ultimately lead to permanent degeneration of all tissues, particularly the heart and kidneys.

I have endeavoured to emphasize this distinction between the climacteric and the menopause in order to counteract the common impression that indications for endocrine, and particularly oestrin, therapy are limited to a short period which follows the cessation of the menses. The delayed or late climacteric is by no means uncommon, and much suffering can be spared by a wider appreciation of the virtues of oestrin in its treatment.

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