in combination with oestrogenic hormones and progesterone, has been carried out; (3) the normal ratio of oestrogenic hormones to progesterone and to male hormones in normal women has been ascertained; (4) the pathological disturbances of this ratio during endocrine and gynaecological disturbances in women have been discovered.

Danger of Masculinization

Even if all the above criteria should be fulfilled yet another problem remains to be solved before the therapeutic application of sexual hormones possessing definite male properties can safely be started—namely, the danger of masculinization. The cause of the natural occurrence of masculinity as a pathological condition in women may be understood better if the results of the experiments described above are taken into consideration. Our experiments have also shown that by the injection of some of the “chiefly male” hormones the rudimentary periurethral glands of female rats can be developed into a comparatively large and typical prostate, and in the same way the clitoris-like structure can be greatly enlarged. The supernormal development of these organs, and the possible growth of a beard or moustache with the appearance of other signs of masculinity, must be avoided in treating women. There is also the danger of a possible disturbance of the normal sexuality leading to the production of pathological perversions of sexual feeling.

These difficulties, however, can probably be overcome by working out the correct ratio of the male and female hormones. Experimental tests that might be suitable for this purpose are concerned with the development of the female preputial glands, the clitoris-like structure, and, though technically more difficult, the “female prostate” in rats. But only after the completion of the whole scheme of investigation outlined above can the male hormones—and of them only those which are found to be normally present in women—be applied therapeutically with the object of restoring to normal the pathological hormonal ratios which will be found in certain diseases of women.

Summary

1. Bisexual properties have been found in nearly all the sexual hormones, and the co-operative activity of most of them with oestrone or oestradiol has been demonstrated by experiments on female rats.

2. Suggestions are advanced as to the significance of these facts in regard to sexual physiology and pathology, and in relation to the therapy of general sexual disturbances in females.

3. In the present state of knowledge, however, the results obtained in our experiments and by other workers do not in any circumstances justify the use of the bisexual hormones with pronounced male activity in the treatment of diseases of women.

Grants from the Medical Research Council and from the Lister Institute have enabled us to carry out this work. I offer my thanks also to Messrs. Schering-Kahlbaum Ltd., in particular to Professor W. Schoeller, for kindly supplying us with progesterone, to Professor A. Girard for oestrone and oestradiol, and to Messrs. Ciba Ltd., in particular to Dr. K. Miesher, for all other hormones.

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TREATMENT OF THE FEMALE CLIMACTERIC BY FOLLICULAR HORMONE

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Although some years have now elapsed since preparations of oestrin and its derivatives became commercially available, considerable differences of opinion still exist on their clinical value. Since in my own case ignorance of certain principles underlying the administration of oestrin led at first to disappointment, and since further experience has convinced me of its unique value, I feel that the following observations on its employment during the last three years in the treatment of disorders of the menopause may prove of general interest.

The climacteric is associated with the decline in the secretory activity of the ovary and a secondary rise in the gonadotropic secretion of the pituitary. Clinically these changes find expression in the diminution and ultimate cessation of the menstrual flow. Amenorrhoea by itself, however, must not be accepted as a reliable index of the menopause. On the one hand the endocrine changes which characterize the climacteric, together with their secondary clinical symptoms, may originate several years before the occurrence of menstrual irregularity. On the other hand amenorrhoea may not infrequently be due to causes other than ovarian, and in such cases the signs characteristic of the menopause, such as hot flushes, gain in weight, and nervous disturbances, may appear many years after the actual cessation of the menstrual cycle.

It will be well to emphasize once again the frequent occurrence of menopausal symptoms. In a group of 1,000 normal women investigated by the Medical Women's Federation (*Lancet*, 1933, **1**, 106) only 15 per cent. passed through the climacteric without symptoms. Of the remainder 62 per cent. suffered from hot flushes, 44 per

cent. from headaches, 39 per cent. from giddiness, and 30 per cent. from nervous instability. Obesity occurred in 34 per cent., while 23 per cent. suffered from rheumatic affections; 10.3 per cent. were incapacitated for a varying period of time.

Factors bearing on Menopausal Symptoms

The severity of menopausal symptoms would appear to depend upon several factors. As in the case of other endocrine disturbances, such as those which occur at adolescence or during pregnancy, it would seem that those individuals who tend by nature to be "highly strung" are more prone to develop functional manifestations. From the prognostic point of view it is wise to distinguish between symptoms which originate at the menopause and those accentuated by the menopause. Thus of the first fifty patients treated by me eighteen had suffered from functional symptoms—that is, headaches, nervousness, dyspepsia, insomnia, muscular rheumatism, etc.—in varying degree since adolescence. Of these eighteen a hereditary tendency could be traced in fourteen. To this constitutional factor is related the undoubted influence of race. Fifteen of these fifty patients treated were Jews, and the oestrin dosage necessary to control their objective signs (tachycardia, hypertension, oedema, arthritis, etc.), together with the duration of the treatment, was on the average nearly twice as great as in a similar group of English subjects.

The duration of menopausal symptoms is subject to as much individual variation as their severity. In the majority of cases compensation usually occurs in two years. In many instances functional disturbances, such as flushes, may persist for as long as ten years, and in certain individuals these disturbances would appear to be permanent. This latter conclusion is supported by the persistence in many individuals of a high gonadotropic urinary excretion into old age, and also by the successful response to oestrin therapy of symptoms which originated thirty years previously at the climacteric. In several cases I have noticed the slow, insidious onset of typical menopausal symptoms in women between the ages of 55 and 60 who had apparently passed through a quiet menopause five to ten years previously. Anxiety states and moderate hypertension are not uncommon in such subjects, and since these respond well to large doses of oestrin I am inclined to the belief that they may be late manifestations of the climacteric. For the purpose of this review, however, no patients are included who were under 40 or over 55 at the commencement of treatment.

The Complex Origin of Symptoms

The origin of menopausal symptoms would appear to be complex, and any detailed analysis would be irrelevant to the purpose of this paper. A brief summary of my personal views is, however, necessary in order to justify the wide range of conditions which have received treatment. In general I believe that any endocrine secretion possesses at least three distinct actions:

1. A direct specific visceral effect. (In the case of oestrin, genital development.)
2. Direct non-specific effect upon the autonomic centres of the brain.—Experimental and clinical observations suggest that the anterior pituitary, the thyroid, and adrenal medulla stimulate the sympathetic centres, while the posterior pituitary, the parathyroids, the islands of Langerhans, and the secretions of the gonads stimulate the parasympathetic.
3. The regulation of endocrine "balance."

For these reasons the effects produced by abnormal secretion of any individual gland must vary with the endocrine

and psychic pattern of the individual. Any reduction in oestrin secretion will be followed not only by local changes in the reproductive organs and a disturbance of endocrine equilibrium, but also by imbalance between the sympathetic and parasympathetic systems, leading to a predominant tonus of the former. This latter manifests itself not only by psychic unrest and sleeplessness but also by disordered function of every organ and system.

It is to be emphasized that no individual symptom so produced is specific for lack of oestrin. Rather must they be regarded as the expression of a general neuro-endocrine disharmony, which may equally well result from a variety of endocrine, reflex, infective, metabolic, environmental, or other conditions. The relative importance of oestrin lack in the production of symptoms—and hence the degree of improvement likely to follow oestrin administration—can only be judged when all such other factors have been evaluated or excluded. In this connexion the subject of allergy deserves particular mention, since it is frequently acquired for the first time at the menopause, as in other states of neuro-endocrine disturbance. Food allergy, particularly to egg albumen and milk, would appear to be especially common. While suitable treatment, by exclusion or desensitization, must be given to any allergic state when present, it is my impression that tolerance for any particular allergen increases with the stabilization of the nervous state.

During the last three years I have employed oestrin in ninety-four cases of menopausal disturbances, of whom fifty have now completed treatment. Of these fifty the following were the principal complaints: headache, 46 per cent.; nervousness and depression, 46 per cent.; insomnia, 38 per cent.; abdominal pains, including mucous colitis, 26 per cent.; flushes, 24 per cent.; muscular rheumatism, 26 per cent.; articular rheumatism, 18 per cent.; vertigo and "falling," 20 per cent.; palpitations, 18 per cent.; oedema of ankles or arms, 10 per cent.; petit mal, 6 per cent.; grand mal, 4 per cent.; pruritus vulvae, 6 per cent.; leucorrhoea, 6 per cent.; hypertension was found in 16 per cent. While these figures cannot be regarded as representative, it is interesting to note the comparatively small number who complained of flushes.

It will thus be seen that headaches, nervousness, insomnia, and abdominal pain are the commonest complaints. Such symptoms, however, are only the grosser manifestations of the menopausal state. Associated with them, or at times occurring independently, numerous other phenomena may occur which are remarkable for their great variety. Some of these would appear to be due to autonomic discharge of central origin, others to peripheral or biochemical effects. The close interdependence of the autonomic nervous system, endocrine glands, and circulating metabolites, however, clearly prohibits any clear-cut classification on such lines, and, moreover, is apt to stultify the effects of such symptomatic treatment as nerve section.

The following is a brief description of some of the menopausal phenomena which have occurred in my series, together with specific case histories where relevant.

1.—The Menopausal Psychoses

These mostly take the form of irritability, depression, loss of confidence, and mental exhaustion. In the severe states some pre-existing and often hereditary tendency can often be demonstrated. It is well, therefore, to emphasize once again that oestrin treatment will only restore an individual to that state of health which was enjoyed before the onset of the menopause. Tall, thin, hypo-

sthenic individuals in particular appear to derive but little benefit from oestrin in the presence of long-standing psychic disturbances.

When symptoms are mild the beneficial effect of even small doses of oestrin (3,000 international units, or 0.3 mg., of oestrone by mouth each day) is often immediately apparent. Such patients not only profess to feel more composed and "consolidated," but not infrequently discontinue spontaneously a long-standing barbiturate habit. In all cases the dose of the latter which is necessary for sleep may be progressively reduced.

2.—Vascular Spasm

In its tonic form vascular spasm may give rise to hypertension and possibly also to the characteristic angio-neurotic oedema of the extremities, face, or trunk. The latter condition responds quickly and favourably to oestrin administration, as observed in the following case.

Case 1.—An unmarried woman aged 46 had had menstrual irregularity for six months and pain and a sensation of "fullness" in both forearms for two years, always occurring at night. To obtain relief she has to lie with her hands above her head, and she feels that she would like to cut the finger-tips and let the blood run out. Both wrists are oedematous and stiff, and there is a history of six months' severe cramp across the chest on waking in the morning, and six months' muscular rheumatism. There has been a great enlargement of the breasts during the last four years.

All symptoms were rapidly and completely relieved by oestrone, 1 mg. intramuscularly in oil twice weekly, with 0.3 mg. by mouth daily. Injections were discontinued after three months with no return of symptoms. Now, nine months after the starting of treatment, any reduction of 0.3 mg. of oestrone daily by mouth is followed by recurrence of retro-sternal pain.

The results obtained in cases of hypertension might be expected to be in proportion to its duration. The following table gives the records of eight cases of high blood pressure.

Case No.	Menopause	Blood Pressure at Start of Treatment	Duration of Treatment	Blood Pressure at Finish
44	Castration 5 yrs.	265/160	6 months	230/140
29	" 3 yrs.	290/150	6 "	200/130
35	3 years ..	180/100	3 "	130/70
11	1 year ..	190/110	12 "	140/100
3	6 months ..	190/95	12 "	130/70
36	6 " ..	200/120	6 "	140/95
21	6 " ..	190/100	12 "	135/70
30	Now ..	180/100	3 "	130/70

It is important to remember that the symptoms associated with high blood pressure are due more to local vascular irritability than to the hypertension itself. Even in those cases where, owing to arterial degeneration, little reduction in actual pressure can be effected, complete relief of symptoms may be given.

Case 2 (Case 44 in table).—A married woman aged 49 had undergone panhysterectomy in 1931, and had had severe headaches since the age of 33. Her condition before treatment was one of repeated vomiting, nervousness, severe and frequent migraine attacks. On examination her blood pressure was 265/160, and there was hypertensive retinitis and albuminuria. The renal function was good.

All headaches and vomiting disappeared after three weeks of oestrone administration, and have not recurred. Now, six

months after commencement of treatment, the blood pressure remains comparatively unaltered at 230/140, but the patient is symptom-free on a weekly oestrone intake of 2 mg. intramuscularly and 2 mg. by mouth. No fresh retinal haemorrhages have been observed, and the urine is clear of albumin.

The origin of hypertensive retinitis is not without interest. High blood pressure itself does not afford a comprehensive explanation, and in many cases I would prefer to regard it as the local expression of an underlying vascular irritability. I have recently observed a well-marked "hypertensive" retinitis affecting the right eye only in a menopausal subject whose blood pressure was normal at 135/90 and in whom the renal function was good.

Transient vascular spasm is of common occurrence. When it affects the brain it may occasion migrainous headaches, transient and often recurrent hemiplegia (which in the presence of arterial degeneration may be followed by thrombosis, but which otherwise responds quickly to two or three capsules of amyl nitrite), grand mal and petit mal, retrobulbar neuritis, and spasm of the retinal vessels. The typical attacks of giddiness may perhaps also be due to local ischaemia of the labyrinth, and the tinnitus aurium to a similar condition of the cochlea.

Three cases of menopausal epilepsy received oestrin treatment; all of these patients had previously received luminal or prominal for a minimum period of six months. The first patient suffered from major fits every three to four weeks. On 0.3 mg. oestrone daily by mouth she has remained free for twelve months. The second patient had two to four major fits every day. For nine months she has received oestrone by injection and by mouth, and during this time she has experienced transient attacks of dizziness without falling, but on no occasion has she lost consciousness. In the third case the attacks of major epilepsy were reduced by oestrin treatment from an average of four a week to one every fortnight.

Case 3.—This patient, a married woman aged 49, whose health had previously been excellent, had a history of amenorrhoea for twelve months, with headaches, insomnia, nocturnal "vasovagal" attacks in which the heart would flutter like a wild bird, vertigo and falling, and oedema of ankles. She was also gaining weight. For six months prior to treatment this patient had experienced five attacks of transient hemiparaesthesia. During one of these her right arm and leg became useless and her speech unintelligible for twenty minutes. After three months on 1 mg. oestradiol benzoate intramuscularly on alternate days, with 0.3 mg. oestrone by mouth daily, she was symptom-free apart from occasional mild palpitations. Now, nine months later, she remains well on a weekly dose of 2 mg. oestrone intramuscularly and 2 mg. by mouth. There have been no recurrences of her cerebral symptoms.

Similar transient spasm may also affect the viscera and extremities. Spasm of the coronary arteries may give rise to spastic angina pectoris. This latter process will further embarrass an already diseased heart muscle, and the most gratifying results have followed the administration of oestrin to those patients whose old rheumatic carditis has undergone decompensation at the menopause.

Case 4.—A married woman aged 52 had had rheumatic carditis since adolescence, with amenorrhoea for three years, twelve months' insomnia, headaches, and depression, and three months' marked dyspnoea and oedema of legs and thighs. On examination the apex beat was found to be 4½ inches out, and there was auricular fibrillation, with a pulse rate of about 130, ascites, and a congested liver.

She received out-patient treatment. For the first three months digitaline Nativelle 1/600 grain with luminal 1/2 grain night and morning, together with 2 mg. oestrone intra-

muscularly and 2 mg. by mouth each week. Digitalis and sedatives were then discontinued. Her condition has since remained stable for nine months on 0.3 mg. oestrone by mouth daily. There is now slow auricular fibrillation at 76, but no oedema and no dyspnoea. She is doing full housework for the first time for four years.

The superficial resemblance between menopausal and cardiac symptoms is worth noting. Dyspnoea, palpitations, vertigo, and oedema of the ankles are common to both conditions, and in the presence of a chronic carditis the correct interpretation of symptoms is occasionally difficult. In similar fashion the combination of the menopausal symptoms of headache, hypertension, retinitis, oedema of face and extremities, with frequent micturition, is apt to be mistaken for chronic Bright's disease. I have observed two cases of intermittent claudication of the legs commencing at the menopause, both of which responded to treatment. It is my impression, however, that this symptom is more characteristic of the male climacteric.

It would seem that the wide range of rheumatic manifestations which characterize the climacteric may also have a vascular origin. Under this group may be mentioned diffuse muscular rheumatism, periarticular arthritis—which may or may not be combined with synovial proliferation—and neuritis. In the absence of any secondary allergic cause these conditions, in particular the periarticular form of rheumatism, respond most satisfactorily to adequate oestrin replacement. My experience has shown that comparatively large amounts are required and that these must be continued over a minimum period of six months before satisfactory improvement is obtained.

Case 5.—This patient, aged 55, had had amenorrhoea at 48, with insomnia, depression, and leucorrhoea. For five years she has been confined to the house with rheumatism and was unable to climb stairs. She was treated unsuccessfully with massage, vaccines, and gold. On examination gross periarticular thickening of knees was present, with much synovial proliferation and coarse crepitation; there was also osteoporosis and narrowing of the joint space.

After twelve months' weekly administration of 2 mg. oestradiol benzoate intramuscularly and 2 mg. oestrone by mouth, the joints have returned to normal size and fine crepitations only can be elicited. The patient can now go upstairs and walk a mile in comfort, but her knees are still somewhat stiff on resting. She sleeps well, has no leucorrhoea, and is enjoying life.

3.—Visceral Spasm

In addition to the irritability of the vascular system there would also appear to be an increasing irritability of all smooth muscle throughout the body. Clinically this visceral irritability occurs more often perhaps in the splanchnic area, particularly when there is local irritation. For this reason gall-stones, uterine fibroids, or renal calculi, which undoubtedly in many cases have been present for many years, may first give rise to symptoms at the climacteric. In my series two cases of repeated and severe gall-stone colic occurring for the first time at the menopause in bronchitic subjects have responded well to adequate oestrin therapy.

4.—Functional Disturbance of the Gastro-Intestinal Tract

These functional changes are characteristic of overaction of the sympathetic system with the suppression of parasympathetic functions. At the menopause symptoms due to spasm of the various sphincters—superior oesophageal, cardiac, pyloric, ileo-caecal—are extremely common: together with this there is usually a contraction of the iliac colon and a muscular atony of the body

of the stomach and caecum. Similar secretory disturbances accompany these motor changes; thus there is an inhibition of gastric acid secretion with the occurrence in many cases of true achylia, and an active secretion of mucus not only by the stomach but also by the colon. It seems possible that these functional disturbances, and in particular the alteration in gastric acidity, may be responsible for the microcytic and even macrocytic anaemia which often occurs at this age.

Of the patients in this series fifteen complained of symptoms due to splanchnic discharge. In these cases it was unusual for the pain to be limited strictly to any one particular portion of the intestinal tract: thus epigastric pain was frequently associated with left iliac fossa pain and a condition of mucous colitis. Relief was given to all these patients by a combination of dietetic and oestrin treatment.

5.—Glandular

No cases of menopausal glycosuria have received treatment. True hyperthyroidism is occasionally an accompaniment of the menopausal nervous state, and in three cases not included in this series considerable improvement followed the administration of oestrin before operation.

My connexion with the Manchester Royal Eye Hospital has enabled me to observe the frequent occurrence of certain ophthalmic conditions at the menopause. Two cases of choroiditis have been treated with disappointing results, four cases of persistent or recurrent iridocyclitis have shown dramatic improvement, and two out of three cases of occlusion of the central retinal artery have ultimately regained 6/18 vision.

Two cases of pin-point vision have responded to oestrin therapy, the perimeter records and history of one of these being here recorded:

Case 6.—This patient, a married woman of 48, had a history of amenorrhoea for twelve months, headaches and dizziness for twelve months, and failing eyesight for three months. The administration of 0.3 mg. of oestrone daily by mouth was begun on April 7, 1936. Vision on April 19: corrected, right, 6/9 J8; left, 6/9 J8. Retested October 6: corrected, right, 6.5 J1; left, 6/12 J1. The patient took her discharge on January 11, 1937, but returned on August 8 with slight recurrence of nervous symptoms.

Certain other conditions have also appeared to respond well to treatment, but no opinion can as yet be formed owing to the natural tendency of these to undergo spontaneous remission. Among this group may be mentioned certain types of disseminated sclerosis and encephalitis which first showed at the menopause.

Some conditions would seem to be very resistant to oestrin therapy. No improvement has, for instance, been made in cases of menopausal asthma and bronchitis which have been treated solely by oestrin. Here the allergic factor would appear to be of greater importance, though it would seem that the development of the allergic state was facilitated by the neuro-endocrine disturbance. Low backache is also a common symptom which at times is difficult to relieve. In some cases its persistence may indicate that the oestrin dosage is inadequate. In two cases relief has only been obtained by the additional administration of corpus luteum hormone, one international unit of which has been given on alternate days.

Symptomatic treatment has been reduced to the minimum. In the early stages some sedative, such as luminal, prominal, or ergotamine tartrate, has been necessary to induce sleep, but in all cases it has been possible materially to reduce the drug and in many to discontinue

it altogether. The greatest care has been taken to exclude any psychological effect. Such a factor is extremely difficult to keep out altogether, for the very attendance of the patients at hospital is in many instances sufficient to give them a suggestion of some benefit. This has been avoided as far as possible by the use of control injections of olive oil and of tablets of similar size and colour. In the majority of cases such a substitution was detected by patients in the first week, for they almost invariably experienced a return of their nervous tendencies and headaches.

Points in Administration of Oestrin

Certain points concerning the administration of oestrin may well be mentioned:

1. *Mode of Administration.*—Two routes are available for oestrin replacement, the oral and the intramuscular. The latter route is about five times as efficient as the former, and hence considerably cheaper for hospital use. The oral route, however, is effective even when large

1 mg. oestrone (10,000 I.U.) given intramuscularly in oil solution twice weekly, combined with 0.1 mg. (1,000 I.U.) three times daily by mouth. Ten individuals have required a dose of 1 mg. oestradiol benzoate (10,000 international benzoate units)* intramuscularly two or even three times weekly, combined with the oral administration of 3,000 units of oestrone daily, while only three cases have required 50,000 benzoate units twice weekly for an initial period of four weeks at the beginning of treatment. When any doubt exists as to dosage I have found the vaginal smear test of Papanicolaou to be of considerable assistance. There would appear to be no direct connexion between body weight and dose, but high doses are usually indicated in the hypersthenic, hypertensive individual with rheumatic symptoms.

Duration and Cost of Treatment

Just as the daily requirements of oestrin vary with the individual, so also does the duration of treatment. In five cases symptoms were relieved and the administration

FIG. 1.—Case 6: Left perimeter chart on March 19, 1936.

FIG. 2.—Case 6: Left perimeter chart on January 12, 1937.

The field of vision on both sides gradually increased to the extent shown by the above charts, which were taken just before beginning and at the end of treatment with oestrone.

doses are required, and is the treatment of choice for the private patient. The majority of the cases under review received a basic daily dose of 0.3 mg. oestrone by mouth, any additional requirements being given parenterally.

2. *Latent Period.*—While very often there is immediate improvement in nervous tendencies and headaches, the administration of oestrin must be continued for a minimum period of three months before its maximum effect can be observed. This would appear to hold particularly true in the cases of articular rheumatism, hypertension, and severe anxiety states. In the early stages of treatment transient relapses may often be precipitated by infection or disturbances of environment.

3. *Dose.*—There is a wide individual variation in the optimum dose. For mild symptoms such as nervousness, insomnia, and flushes a dose of 0.1 mg. oestrone (1,000 international units) three times daily by mouth may be adequate. Seventeen of the first fifty cases became stabilized on this amount. No smaller dose was employed, for it was found that equal benefit could be given to such cases by ordinary medical measures. In twenty cases the initial minimal requirements have been

of oestrin discontinued in as short a time as three months. In the light of later experience discontinuation at that stage is often premature. In sixteen cases it has been found necessary to continue the initial optimum dose for a period of three to six months, and in seventeen cases for six to twelve months, before any reduction was possible. In twelve cases reduction in dosage, even after twelve months, was followed by a return of symptoms. In three of these reduction of dose after two years has been followed by a recurrence of headaches, cardiac symptoms, or rheumatism. In such cases it seems possible that the permanent administration of small doses of oestrin may be of benefit. Recurrence of symptoms has occurred in one case twelve months after the termination of treatment. Any reduction in dose must be effected gradually and over a long period of time. It is my practice never to attempt such reduction until the patient has been symptom-free for two months, when the dose is tentatively reduced by one-third. No cases of tolerance to oestrin have occurred.

* The international benzoate unit (I.B.U.) is equivalent to five international units (I.U.).

In two cases the intramuscular injection of an oily solution was followed within twenty-four hours by the appearance of an urticarial eruption, one following 1,000 international units of menformon and the other following an injection of 10,000 international benzoate units of progynon. In neither of these cases did any reaction follow the oral administration of oestrone, and it is possible that the cutaneous eruption was an expression of sensitiveness to oil rather than to the hormone.

Of great practical importance in the treatment of menopausal disturbances is the question of cost. The price and activity of commercial preparations of oestrin show considerable variation. In the above series the Organon preparation of oestrone (menformon) has been employed in pills of 0.1 mg. (1,000 I.U.) and in oil solution containing 1 mg. (10,000 I.U.) to the cubic centimetre, while larger doses have been obtained with progynon (Schering), 1 mg. of oestradiol benzoate (10,000 I.B.U.) being contained in 1 c.cm. of sesame oil.

The cost of initial treatment works out at about seven shillings a week for private patients. A reduction of some 30 per cent. is obtainable by hospitals. The treatment of a hospital case of average severity will therefore amount to approximately £1 per month in oestrin alone.

Since the menopause is directly or indirectly responsible for a great amount of suffering in any community the question of the responsibility of the hospitals for the provision of this treatment is immediately raised. On the one hand it is true that the wholesale use of this remedy at present prices will soon involve even a small hospital in considerable financial expenditure. On the other hand it is equally true that the menopause, though a relatively innocuous phase in the life of the average woman, is undoubtedly responsible in about 5 per cent. of women for the onset of chronic ill-health, permanent disablement, or even sudden death. If untreated many of these unfortunates ultimately swell the medical and surgical waiting lists of hospitals, in which the cost of their board and lodging alone will amount to between £5 and £6 a fortnight. Quite apart from this consideration, however, it would seem illogical for any hospital to deny its patients the established benefits of oestrin therapy while permitting the expenditure of equal sums of money on the treatment of many less sinister conditions. It is to be hoped that the ingenuity of the organic chemist will in the near future provide a solution to this problem.

Summary

In this article I have endeavoured to emphasize the importance of the climacteric in the production of a wide range of morbid conditions, and the unique value of substitution therapy in their correction. I sincerely hope that its publication will stimulate a more general practical interest in this gratifying subject. To those who are not yet familiar with the employment of oestrogenic substances I would stress again the following points:

1. Selection of Cases.—The use of oestrin does not obviate the necessity for the search and removal of non-endocrine factors. At its best oestrin can only restore an individual to that state of health which was enjoyed before the onset of the climacteric.

2. As with other endocrine treatment, the dose must be adequate for the requirements of the patient and treatment must be prolonged.

I wish to express my appreciation and thanks to the Board of Management of the Manchester Northern Hospital for sanctioning the heavy expenditure incurred in the running of my endocrine clinic.

TREATMENT OF MENSTRUAL IRREGULARITIES BY A NEW SEX HORMONE PREPARATION

PRELIMINARY NOTE

BY

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Of recent years the advance of knowledge about the sex hormones has been immense; however, as Novak wrote, "the results of gynaecological organotherapy have been disappointing, while the accomplishments of gynaecological endocrinology have been numerous and brilliant." Kaufmann showed how, by large doses of oestrone and progesterone scientifically administered, a normal type of menstruation could be produced by substitution therapy. The end-results of such treatment, because they depend on substitution, are in many cases disappointing, as menstruation fails to persist for long following cessation of injections. It is therefore to the gonadotropic hormones that attention has now been focused with the aim of correcting menstrual irregularities from the regulator itself. So far, whereas reliable luteinizing gonadotropic hormones have been made available for clinical use, there has been no corresponding follicle-stimulating hormone for therapeutic use. Recently the opportunity has occurred to use a preparation called "antostab," which is claimed to have follicle-stimulating properties.

It is not within the scope of these notes derived from clinical material to discuss the experimental evidence in regard to the preparation, which is made from the serum of pregnant mares. In animal experiments it has been shown to differ materially from the gonadotropic hormones derived from the urine during pregnancy, in that it produces follicle stimulation in immature rats to a very marked extent, thus corresponding more to the hormones of the hypophysis itself. It is also capable of follicle stimulation in hypophysectomized rats, whereas the gonadotropic hormones of urine produce only luteinization. The preparation has similar properties when injected in monkeys, producing marked increase in weight of ovaries. Dosage is based on mouse units, one M.U. being the minimum quantity required to be injected to double the weight of the ovary of sexually immature three to four-weeks-old mice in three to four days. In the following short series of cases two to three ampoules of antostab (100 M.U. per ampoule) were given weekly.

From its properties it would appear that the preparation would be of most use in the treatment of amenorrhoea, and six consecutive cases of amenorrhoea, hypomenorrhoea, and oligomenorrhoea were given injections of antostab. One of these cases has been excluded from the notes as a small mole was found to be the cause of the amenorrhoea. It was expelled spontaneously after injections of antostab, probably owing to oestrone stimulation.

Notes of Cases

Case 1.—An unmarried woman aged 28 who had not had a period for ten years. The periods had started at 15 and continued irregularly for two years and then stopped. On examination the uterus was small (1½ inches in length by probe). Injections were started, and after four had been given there was a period, loss being slight; injections were continued, and a month later there was a period lasting three days. During the next cycle a curettage was done on the twenty-second day, which showed endometrial changes corresponding to about the sixteenth day. Secretion was present in the cells, but there