CLIMACTERIC STRESS: ITS EMPIRICAL MANAGEMENT

BY

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This is the last medical paper that Dr. Malleison wrote before her tragic death near Suva in May, when she was returning home from a visit to New Zealand. She had sent us an earlier draft, but only a week before she died she wrote to say she was revising it. The final manuscript, here printed, reached Britain with her effects a few weeks ago.

No one would deny that there is a prejudice against treating climacteric symptoms. The average woman even expects her doctor to be unhelpful about the matter. The practitioner has several good reasons for his attitude: a condition whose boundaries are ill-defined and whose aetiology is obscure is not likely to exert much appeal. Moreover, he has usually met cases where oestrogenic therapy has caused uterine bleeding—a complication which reacts back on the physician, and which wholly outweighs any gains which the therapy may bring.

The most confusing aspect of the climacteric is the subjective disturbance, and that is all I shall consider here. Until such time as the biochemists clarify the climacteric events there is everything to be said for getting the clinical picture as clearly defined as possible, and then for treating symptoms in a frankly empirical manner. The therapy of the condition has already outstripped its theory, so that possibly the therapeutic responses themselves offer some clue to the underlying hormonal events.

Significant Features and their Recognition

If our concept of the menopausal syndrome were reconsidered along purely clinical lines, an entity might emerge which would be more simple to diagnose and much more interesting to treat. In fact, the really important symptoms can surely be reduced to two. The woman complains of an unaccountable fatigue, often coupled with an inability to relax or sleep, and/or she experiences an alteration of emotional poise—a slight change in character which takes the form usually of a negative mood, either of irritability when the mood is directed outwards or of depression when it is directed towards herself.

Such changes may not be easy for a woman to recognize in her own personality or to complain about. Furthermore, an attuned ear is needed to receive such complaints. It is too easy perhaps for the practitioner to dismiss fatigue as being due to anaemia, advancing years, or domestic worry, and irritability can present itself as part of the apparently neurotic disposition which these patients exhibit. Women seldom mention depression unless the confidence is met half-way. It is feminine lore to fear insanity at this age, so that many feel it wiser to say nothing about this baffling state. The practitioner who understands these two main disturbances and can recognize them in their varied forms or disguises will find much that is rewarding to study.

If the discomforts of the climacteric occurred in some recognizable order, the problems of diagnosis would hardly exist. Unfortunately there is no pattern whatever in their timing: any symptom may start months before menstrual rhythm has altered or months after menstruation has ceased. In some cases subjective stress is conveniently accompanied by hot flushes, which makes the diagnosis more simple. But

40% of women experience no flushes (Medical Women's Federation, 1933), and in those who do a phase of stress may not synchronize in any way at all. The practitioner who requires corroborative evidence for such a diagnosis may fail entirely to understand the disturbance.

The assessment of climacteric stress is difficult for other reasons, too. It seems the lot of woman to be always tired, and, since her mood is proverbially fickle, she invites the risk of having her climacteric complaints misjudged. Moreover, no one is more difficult to help than the woman in a typical menopausal mood. Her self-doubting makes her condemn herself for seeking help, so that she confuses and belittles her own suffering: she may be touchy, negative, and obstructive. The practitioner, at the point of exasperation, can at least recall that this attitude is itself pathognomonic.

Menopausal Fatigue

Exhaustion tends to be most marked in the pre-menstruum, if the cycles are still recognizable. Women may find it difficult to distinguish what may be called "bodily" exhaustion from "nervous" exhaustion; either or both may occur, and they appear insidiously. The person best able to assess the fatigue is the patient herself—generally she is definite that it is disproportionate to the circumstance. Nervous fatigue is described as the "head being made of cotton-wool" or "as though the head would burst." Concentration fails and loss of memory causes alarm. The woman feels quickly at the end of her tether, so that any extra demands appear as an imposition. Coupled with this may be an increase in muscular tension which makes rest and relaxation difficult: stiffness in the neck, shoulders, and jaw may cause tiresome discomfort. Light sleep or even serious insomnia may supervene. Throughout these restless phases, autonomic disturbances—flushes, palpitation, headache—may play their part, and general anxiety completes the picture. In addition to these symptoms there may be sudden phases of prostrating exhaustion, coming before meals, which the patient usually forgets to mention. That such attacks have a hypoglycaemic element can be shown by their response to prophylactic glucose.

Often there is the problem of subclinical hypothyroidism, which runs as an inconspicuous substratum to many climacteric complaints. Fatigue from this source is persistent and may be accompanied by depression and by a slowing of movement and mental processes. Lethargy is most marked in the mornings, the woman feeling better as the day goes on. There will be present at least some classical signs, and to the observant eye the facies presents the best clue. There may show a slight coarseness of feature, a "suet-pudding" facies, dry skin, thinning outer eyebrow, malar flush, spade-like hands, combined with a slow pulse and subnormal temperature. The patient will claim some of the following symptoms: lack of concentration, cold extremities, chilblains now or in childhood, indigestion, constipation, increasing frigidity; menorrhagia is more common than not. Some of these subjects have put on weight, but a minority remain thin. Some women have a short phase, perhaps two or three years, of thyroid insufficiency at the climacteric and recover: in others a chronic state of myxoedema becomes established.

Differential Diagnosis

The diagnosis of fatigue obviously cannot be easy, but if the type of exhaustion and the circumstance suggest a climacteric element, and if physical illness does not appear to be present, it may be simplest to establish the diagnosis by therapeutic response. The rationale of treatment with oestrogen or other sex-steroids is discussed below, but it is relevant here to mention that if fatigue is going to yield to such therapy a trial of two weeks' duration will be ample to establish the point. Alternative investigations such as blood counts, chest x-ray, etc., will take longer to do, and will cost more than these simple measures.

For cases suggestive of hypothyroidism there is everything to be said for trusting clinical judgment rather than laboratory assay. Usually the degree of insufficiency is but slight, and a favourable response to thyroid extract is far more use than a laboratory report. Furthermore, one should never forget that even a gross myxoedema does not always show a negative B.M.R. or a high blood cholesterol. In his classic paper, "Myxoedematous Madness," Asher (1949) describes cases of gross or fatal myxoedema where the laboratory findings had been normal. If trial by thyroid medication is given to a patient with fatigue an interval of three to six weeks may be needed before a judgment can be made. Although most women will tolerate $\frac{1}{4}$ gr. (32 mg.) rising to 1 gr. or 2 gr. (65–130 mg.) daily, cases of long-standing insufficiency are best started on very small doses— $\frac{1}{4}$ gr. (16 mg.) or even $\frac{1}{8}$ gr. (8 mg.) daily may be the utmost they can tolerate at first. With trial therapy of this sort it is necessary to see the patient, or to have a telephone report, within two or three weeks. If the dosage has been too high, or if the woman is intolerant of thyroid, palpitation or restlessness may occur, but these will resolve directly treatment is discontinued and no harm will result. Used in this way, thyroid medication can be of the greatest value. In fact, there can be few conditions so amenable to treatment which are so often overlooked in medical practice.

Menopausal Misery

Women at the climacteric may find themselves unduly sensitive; feelings are too readily hurt and attacks of weeping come unexpectedly. Such women feel doubtful of their own capacities and unsure of their value to other people. At these times neurotic traits in the disposition—phobias, obsessions, masochism—are very liable to reach the surface. Not unnaturally, women are shocked on realizing that their customary control is lacking and they are most unlikely to want such feelings discussed. The family doctor, therefore, though he may be consulted for insomnia, may not always realize the degree of anxiety that has been reached.

Perhaps the most distinctive feature of a menopausal mood is its duration: it may be so long-drawn-out that even the woman herself forgets what her normal pitch of feeling used to be. To her family she may become a different person—a role by no means easy to reverse. In most cases, of course, nature readjusts the balance, and the period of strain gets forgotten. But in some women depression or negativism, if untreated, seems to become a permanent state. Depression may be accompanied by feelings of worthlessness and self-distrust, and ultimately a state of involutional melancholia may occur. The problem of menopausal negativism is a colossal one. Unlike depression, irritability can hardly be hidden. Home can be disrupted by the nagging of a wife, children made unhappy, whilst the woman herself is wretched with temper and remorse. In industry, these factors are well recognized, and many firms refuse to employ women over 35 years. The middle-aged woman, even if she is not rude, may prove obstructive and obstinate: for example, teachers, nurses, and forewomen in responsible positions may inflict great suffering on others. Paranoid tendencies may emerge sometimes in an alarming way and will need wisdom and judgment in their management, as well as hormonal treatment. Prolonged attacks of irritability, unrelieved by hormonal alteration, can readily change into a steady paranoid feeling. The woman becomes obsessed by trivial complaints against her near relations: sometimes, just for a few minutes, she will get her difficulty into perspective, only to lose it again. I see every reason to give hormonal therapy to these subjects at once. Although these serious conditions are in the small minority, they exist in all classes of society, and, if medical opinion were better informed, it seems likely that much suffering and sometimes perhaps the development of psychosis could be avoided. Obviously sedatives, coupled with explanation, change of environment, psychotherapy, and so on can play their part, but, in fact, more specific and far quicker results may be reached by hormone therapy.

Assessment of Subjective Symptoms

The significance of these subjective symptoms was long overlooked. Down the ages the menstruating woman has been regarded as unclean, and in many creeds she still requires ritual purification. Hence, tribulation at the menopause has been tacitly accepted as belonging to this disgraceful heritage—a condition not to be admitted to at all. Unfortunately, at about the time that the oestrogens were discovered the psychogenesis of bodily symptoms was coming into vogue, and the female sex got saddled with morning sickness and the discomforts of the premenstruum and climacteric as hysterical symptoms; that is, a woman was either rebelling inwardly because pregnancy had been established or mourning because it was failing to be so. Thus medical interest in the hormonal basis of these symptoms got deflected for a while.

In fact, there is everything to indicate that subjective disturbances of this nature are directly caused by a hormonal imbalance, a discomforting biochemical state which seems as apt to occur in the healthy, well-balanced woman as in the sickly or hysterical. If this assessment is true, it would explain why hormonal treatment can yield such rapid and specific results. But, in spite of this, medical opinion on the point is not united, for some authorities maintain that, while the autonomic disturbances of the menopause—flushes, vertigo, headache—should be treated hormonally, the nervous complaints fall in the domain of the psychotherapist. Discussion of the matter is therefore important, for progress will not be made until the point is clear.

There are reasons for the subjective disturbances to get classed as hysterical: no one would deny that emotional factors can upset the menstrual function, nor indeed that an unstable woman will not make more fuss about climacteric discomfort than will a normal one. Yet this does not prove that climacteric fatigue and stress are not primarily caused by biochemical factors. Such subjective sensations are common in the symptomatology of other hormonal disturbances and they are described by the sufferer, of necessity, in terms suggestive of emotional upset. For example, a person overdosed with insulin may experience a most profound anxiety, yet the symptom is not primarily an emotional complaint. If such stress was psychogenically induced we should expect to find it greater in the unmarried or childless woman than in the multipara. Yet this is not the case. In one survey (Medical Women's Federation, 1933) the incidence of climacteric disorder did not greatly differ among those who had borne children and those who had not, but in women with large families—ten children or more—the incidence of symptoms was noticeably higher. It seems likely that such women had been acclimatized to high steroid balances by their many pregnancies, and on this account found greater difficulty in adjusting to the hormonal alterations. There is plenty of clinical evidence to suggest that stress appears most often when the climacteric processes occur too quickly or when the endocrine system is unduly slow to adapt. Such reactions point not to hysterical factors but to biochemical ones.

A Possible Therapeutic Rationale

Biochemical theories about the climacteric do not give much therapeutic lead. For instance, the time is past when the syndrome could be regarded as due merely to falling oestrogen levels. Although some authorities still use synthetic oestrogens, others have found that these are more safely employed combined with androgens (as in the popular portmanteau prescriptions). Some find that androgens alone give very successful results, and yet others are using progesterone, clearly on occasion with success. The practitioner, faced with such a medley of advice and advertising, is naturally bewildered. In fact, anyone who employs these three hormones has either to decide that no current theory explains their successful use, or that such results are achieved because the doctor and patient are over-suggestible.

The former deduction is surely the correct one, which means that a new concept of climacteric events must be sought.

It seems likely that in women there is an optimum balance of steroid sex hormones which makes for well-being. Hormonal conditions are continually changed by the events of the monthly cycle, such changes inducing in some women a temporary balance of real discomfort. This appears most often as premenstrual tension during the last week of the cycle, or, in relation to the menopause, it can occur for longer phases, when it can be classed as climacteric stress. The mood of such states is invariably negative, whether premenstrual or climacteric: bodily or emotional discomfort is caused, a strange endogenous misery. I have discussed this condition elsewhere (Malleon, 1953), suggesting it should be called a "negative state" balance. Such a state can usually be relieved by measures which alter the ratio between oestrogen, androgen, or progesterone; in fact, by a single hormone or a combination of hormones, which will tilt the balance in a more comfortable direction. If this postulate is correct, it would explain the success of the extraordinarily contradictory therapies now in vogue.

Whether a rational explanation for present-day therapy can be found or not, field work in the empirical approach will be in the hands of the general practitioner, for it is only he who sees cases of the sort described above. He will find little recent literature to guide him (see Bishop, 1951), but he was wisely reminded in a recent leading article (*British Medical Journal*, 1955) that the sex hormones when mixed do not necessarily lose their disadvantageous properties. One point fortunately has been clarified by Bishop and others—namely, that there is no need to fear that oestrogens, exogenously administered, will invite cancer in the human female. This unfortunate suggestion has occasionally complicated the therapeutic approach.

Experience in the use of the sex hormones brings many small points to the fore; and, although each clinician may develop an individual method, for those unaccustomed to these substances I shall describe some useful or commonly accepted techniques. Most of these points are empirical, and for the sake of brevity are stated dogmatically. And since this paper is about specific hormone therapy I shall deliberately refrain from mentioning the ordinary forms of treatment which suffice for relieving minor cases of stress. The question of psychotherapy should be raised after the hormonal balance has received attention, and not before. Where alternative treatments are likely to be adequate, obviously they will be chosen, for at present steroid substances are rather costly, and supervision is invariably required.

Practical Points in Hormone Therapy

The steroid sex hormones should usually be given intermittently whether menstruation has ceased or not. If the choice is suitable results will be positive well within two weeks: fatigue lessens, sleep deepens, and the patient realizes how unwell she has been feeling. Treatment for a few weeks often suffices, a temporary respite from symptoms allowing a better phase to be reached. Treatment is sometimes necessary for months or even years.

Oestrogen therapy should be given in the first two-thirds of a cycle, or for some 18 days if menstruation has ceased: androgen and progesterone (ethisterone) are usually given sublingually in the last 7 to 12 days, but some authorities shift these days to the middle of the month. By one or other of these measures premenstrual tension or climacteric stress may be relieved. Thyroid medication can be started in addition, or instead.

It is curious that these sex hormones act sometimes synergically, sometimes antagonistically. Thus for fatigue and emotional stress oestrogen and androgen are often but not always interchangeable; both, if the dose is too large, can even give euphoria—a condition obviously best avoided.

Both cause fluid retention in some women, so that salt and fluid restriction may be necessary. Yet their action on the breast and genital tract is totally antagonistic. Progesterone and androgen have many properties in common, and where serious menopausal bleeding occurs their combined use may make hysterectomy avoidable.

The vagaries of the negative state balance can be most clearly observed when the patient suffers from migraine or fibrositis. Here, the response tends to be most specific—oestrogen, androgen, or progesterone may immediately relieve or immediately exacerbate the symptom. Some authorities use ethisterone successfully for menopausal rheumatism.

There may be no indication of which hormone is suitable for a given case, but a feature in the history sometimes gives a lead, particularly the condition of the breast or genital tract. For mastodynia, androgen or progesterone is preferable to oestrogen, and also where there is pelvic pain, menorrhagia, or fibroids. Where there is dyspareunia due to kraurosis, oestrogen—with or without thyroid—is invariably the choice. Often there is a premenopausal phase where for some months the oestrogen level appears to be high: the breasts will be tender, there is fatigue, and sometimes a tiresome sexual tension. Oestrogen is contraindicated, but androgen will bring great relief. In the early part of the climacteric, androgen is perhaps most often the first choice; later on, usually oestrogen. Since the choice of hormone is guesswork, it is well to invite the patient's co-operation, giving no assurance that the first measure will be the satisfactory one.

Some comments on the individual hormones may be helpful:

Oestrogens.—Oestrogen is widely distributed in nature; it is found in insects and fish, and is so concentrated in some plants (hops, clover) that ingestion upsets the female oestrus cycle (Burrows, 1945). The synthetic oestrogens have quite different molecular structures, and, though some of their therapeutic properties are similar, some are different: they do not seem to control climacteric stress as adequately as the natural substance. One cannot yet guess how the well-being of some older women comes to be so strongly influenced by natural oestrone. I have seen women years past the accepted climacteric who, by minute quantities such as 0.05 mg. daily, have been relieved of exhaustion or ill-moods in a surprising manner. Synthetic oestrogens, less costly than oestrone and much more potent, are valuable for hot flushes and many other purposes. Bishop estimates oestrone as having 1/20 the strength of stilboestrol and 1/40 that of ethinyloestradiol, but as these preparations do not influence all symptoms comparably precise dosage is difficult to assess. Cameron (1947) considers that the normal output of oestrone is 0.4 mg. daily, except during menstruation, when the figure rises to 10 mg. Older women take smaller quantities of oestrogens than younger ones, and they are often intolerant of synthetic oestrogens, which then cause malaise, headache, or nausea. Overdosing is shown by mastodynia, pelvic distension, leucorrhoea; if persisted with, uterine bleeding could occur. In such cases treatment is suspended and symptoms may be treated with androgen. If oestrogens are graded in small quantities, it is possible to adjust the dose carefully and lessen it slowly. Thus natural oestrone or stilboestrol can be given in 0.1-mg. tablets: when flushes are present, the patient can safely raise the dose until they are controlled—usually from 4 to 12 tablets daily suffice: the dose, always intermittent, can be gradually lessened, and by this means slight underdosage is ideally achieved. The popular ethinyloestradiol seems unnecessarily strong for climacteric use, and no unit of comparable grading could be devised. Its effects may be mitigated if combined with androgen, as in the commercial preparations, yet a patient may remain intolerant of the substance even then, so that confusion results. Ethinyloestradiol and stilboestrol are the substances which sometimes cause hyperplasia and uterine bleeding. A patient

formerly treated by synthetic oestrogens will, if the preparation is changed, need larger doses of oestrone than normal. Where kraurosis is a prominent complaint dosage can be given locally as oestrone suppositories. Women over 60 seldom require more than 0.05 mg. daily of oestrone in any form. Oestrogen is particularly suitable for the hypothyroid type of woman.

Androgen.—Methyl testosterone sublingually can give very rapid relief in some cases of menopausal stress; it appears to "toughen up" the psyche in a truly remarkable way, 5 mg. daily generally suffices, but 10 mg. may be necessary to combat menorrhagia or pelvic pain. The substance is particularly valuable if there is pelvic discomfort, and newly developed fibroids appear to shrink under its influence. It almost invariably relieves mastodynia. Some authorities are giving it in 10-mg. doses for as long as two months at a time. Given thus, there seems to be a good deal of fluid retention—the patient considers she is putting on weight—and hirsuties may be encouraged, but is said to regress when the hormone is withdrawn. Dosage should seldom exceed 250 mg. a month and supervision is essential. When the choice is unsuitable nausea is commonly induced: some women develop acne under its influence and occasionally libido is increased.

Progesterone.—It is inconvenient to inject this substance, and ethisterone sublingually can be employed. Its value has been better appreciated since the interesting work of Greene and Dalton (1953), who have used it successfully for premenstrual tension, pregnancy toxæmia, and other allied conditions. They employ large doses, but in climacteric work a range of 15–20 mg. daily seems suitable. The indications are rather similar to those of androgen, but it does not appear quite so dependable in its action. It is less liable to cause fluid retention, in fact it is a diuretic to some women. It is valuable when acne is present in the premenstruum. Its use does not appear fraught with any danger, but in middle age, if oestrogen has been given or if the oestrogen balance is high, ethisterone may induce bleeding. Progesterone appears particularly suitable for the hyperthyroid type of woman. My experience with the substance is not great, but I have met a menopausal woman whose nervous breakdown had been much relieved by it, and have prescribed it successfully for a disturbed pre-psychotic patient, and also to another, known to have a high oestrogen level, who was suffering delusions. Under its influence she "still heard voices but no longer believed they were real." If the choice is unsuitable, malaise or nausea will be induced.

Future Research

Anyone who observes a case of climacteric stress resolve under such therapies must be left wondering what is the meaning of the whole concern. The answer will come from the biochemists. They are nearer, now, to understanding the interplay of hormones upon mental balance than they have been before. The discovery that adrenochrome—an unoxidized product of adrenaline—will cause schizophrenia-like delusions and behaviour (Hoffer *et al.*, 1954) opens up a fascinating new territory. Such work may have bearing on the problems here discussed.

There are various possibilities which might throw light on the production of a negative-state balance at the climacteric. For instance, normally oestrogen is broken down by the liver, but the process may be interfered with in certain conditions of hepatic dysfunction, or where there is a deficiency of vitamin-B complex. The ratio of oestrogen to androgen is disturbed under these conditions, a point well illustrated in men suffering from hepatitis, when the piling up of oestrogen causes gynaecomastia. Thus it is possible that the normal intake of vitamin-B complex is inadequate for the climacteric woman, with the result that a negative-state hormonal balance is caused. There may well be other such physiological conditions which upset the hormonal pitch in indirect ways. There seems some clinical evidence

that large doses of vitamin B₁ will bring relief to some climacteric women. These are purely speculative matters, but some clues to the discomfort of the climacteric might be found along lines such as these. There are some thirty million females in our country, and 80% of them are likely to experience climacteric discomfort of some sort (Medical Women's Federation, 1933), so that the scope for clinical study is virtually limitless.

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NEW UNIVERSITY TEACHING UNIT AT SHEFFIELD

[FROM A SPECIAL CORRESPONDENT]

One great change in medical education since the second world war at both the postgraduate and undergraduate levels has been the greater use of clinico-pathological conferences, seminars, and forums. This stems from the difficulty of providing for the student a reasonably balanced picture of surgical or medical illness by the traditional ward appointments alone. It is no less vital that staff members of each sub-specialty should have some centre where they can discuss their own problems and viewpoints with those of other disciplines. In addition, more and more research investigations of a physical or chemical nature are performed by clinical units, and in general laboratory space for such purposes on the hospital site is at a premium. Most of our hospitals in fact make little provision for teaching accommodation and research laboratories, and because of a long-felt lack in Sheffield the university, with financial support from the University Grants Committee, has built a new teaching block in the grounds of the Sheffield Royal Infirmary. This will house the university departments of therapeutics and surgery, both of which are provided with a suite of modern and well-equipped laboratories in close proximity to the wards and operating theatre. An elegant lecture theatre, seating approximately 150 and equipped with mechanically operated blinds, windows, and air-extraction apparatus, is again conveniently near the wards so that patients can easily be brought there for demonstrations or conferences. The whole building, which cost approximately £50,000, was formally opened on Thursday, November 29, by Professor G. W. PICKERING, Regius Professor of Medicine, Oxford, in the presence of representatives from the university, hospital, and town.

The standard of medical care in the country as a whole, said Professor Pickering in his address, was conditioned by the quality of the training in the teaching hospitals. For this to be satisfactory certain conditions must hold: there should be sympathetic and amicable co-operation between the board of governors and the university; adequate laboratory space and teaching facilities must be provided on the hospital site; and the spirit of clinical science and of experimentation should permeate the clinical teachers. Professor Pickering emphasized particularly the need for adequate laboratory and teaching-room space in the planning of any new hospital. Votes of thanks to Professor Pickering were proposed by Alderman A. BALLARD, chairman of the board of governors, and by the Vice-Chancellor, following which the new laboratories and equipment were demonstrated to the invited audience.