Summary

It has been shown that sodium penicillin is as effective as either oily or aqueous procaine penicillin in the treatment of an experimental staphylococcal infection in mice.

It is concluded that the curative effects of penicillin depend not so much on the aggregate time that an effective level of penicillin is present in the blood as on other factors, of which the most important is the co-operation of the defence mechanisms of the host.

The application of these findings to the treatment of human infections is discussed.

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THE MALE CLIMACTERIC: IS IT AN ENTITY?

BY

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In Dorland's *Medical Dictionary* the climacteric is defined as "a particular epoch of the ordinary term of life at which the body is believed to undergo a radical change," and the male climacteric as "the phenomena attending the normal decrease in sexual function in the male." In an annotation entitled "The Middle-aged Man," in the *British Medical Journal* (1953), the following statements appear: "Claims have been made, and denied, that there is a rare syndrome properly described as the male climacteric. The symptoms of the presumed syndrome, briefly, are depression, irritability, lack of concentration, palpitation, weakness, and sexual impotence. . . . These claims, however, have been refuted by other workers unable to corroborate them. The so-called syndrome, they assert, is a psychiatric illness. . . . No one has described a condition in men with disturbance of hormone secretion as the only symptom of the so-called male climacteric. . . . Until an occult deficiency of testicular androgen—provided this can be estimated—is shown to bear a direct causal relation to the multiplicity of symptoms embraced by the term male climacteric, we have no ground for accepting the concept." These statements were repeated in *Prescribers' Notes* (1953), issued by the Ministry of Health. It is my endeavour in this article to demonstrate that the male climacteric exists as a clinical entity.

Female Climacteric

Before the problem of the male climacteric is discussed it is pertinent to refer to the complexities of the female counterpart, the existence of which, so far as I am aware, has not been denied. Although the climacteric is defined in a modern British medical dictionary as "the menopause," this definition needs correction, for the two terms should not be confused. Menopause simply means "cessation of menstruation" brought about by physiological failure of

ovarian function. All women have a menopause—if they live long enough—but not all women have symptoms of the climacteric; in fact, many women pass through this period of life with few or no disturbances.

As the critics of the existence of the male climacteric have insisted that its alleged symptoms must be shown to be caused by deficiency of testicular androgen, the cause of the symptoms of the female climacteric must be considered. At the time of the menopause the level of oestrogen in the blood falls as a result of the ovarian changes, and at the same time the titre of gonadotrophin (follicle-stimulating hormone, F.S.H.) rises through removal of the inhibiting influence of oestrogen on the anterior lobe of the pituitary gland. Climacteric symptoms may be directly due to oestrogen deficiency, to excessive gonadotrophin, or to some other factor. The improvement which may be effected by the administration of oestrogen is no proof that oestrogen deficiency is the direct cause of the symptoms, for their amelioration may be due to the fall in the level of gonadotrophin which the administered oestrogen produces. On the other hand, there are observations which suggest that neither of these two factors is responsible—namely: (1) many women do not have climacteric symptoms although their oestrogen level is low and their gonadotrophin titre high; (2) climacteric symptoms may appear before menstruation ceases—that is, when the oestrogen level is within normal limits; and (3) they do not occur in oestrogen deficiency due to hypopituitarism or (4) in ovarian infantilism. In fact, on grounds such as these Pratt (1950) concluded that a hormonal basis alone does not explain the symptoms of the female climacteric.

From this very brief and cursory survey it will be seen that the aetiology of the symptoms of the female climacteric is by no means established and that arguments similar to those brought forward against the existence of the male climacteric, such as those mentioned in the first paragraph of this paper, could well be advanced to deny the existence of the female climacteric.

Male Climacteric

Landau (1951), discussing the concept of the male climacteric, has stated that the period of life during which "climacteric" symptoms are presumed to occur is also the time at which the emotional and intellectual adjustment of the shift from maturity to old age must begin to be made, and that some men at that time develop neurotic reactions such as impotence and general subjective disturbances. This statement is undoubtedly true, and in my experience these patients are not improved by the administration of androgens. However, similar emotional and neurotic upsets occur in menopausal women and are not benefited by the administration of oestrogen, but this is not sound evidence that the female climacteric does not exist.

In discussing the problem of the existence of a male climacteric and whether it is due to or associated with testicular deficiency the following observations should be considered.

(1) Comparison of Symptoms of Male Climacteric with Those of Post-pubertal Castration

In post-pubertal castration libido and potency are generally diminished or absent, but this does not happen in all cases. Similarly, potency and libido may or may not be affected in the male climacteric. After castration has been performed in the adult he may experience hot flushes and sweats and suffer from generalized weakness, lack of mental drive and energy, diminished power of concentration, a sense of inferiority, emotional instability, and fits of depression. The same symptoms occur in the male climacteric. The argument, however, has been produced that in the middle-aged man they are primarily of psychological origin and that any improvement that may be obtained by the administration of testosterone is due to suggestion; yet I have had referred to me by psychiatrists castrated and eunuchoid patients with such symptoms which have disappeared or have been greatly improved with

androgen therapy. Should one assume that the improvement in these cases of known testicular deficiency is also the result of suggestion? This is unlikely, although it must be borne in mind that the improvement in these "neurotic" and "psychoneurotic" symptoms may be secondary and due to the attainment of potency (but see (3) below concerning the anabolic action of androgens).

(2) 17-Ketosteroid Excretion

The urinary excretion of 17-ketosteroids is an index of the amount of androgens produced by the Leydig cells of the testicular interstitial tissue and by the adrenal cortex. Because of the production of adrenal androgens it is often impossible by estimation of the urinary 17-ketosteroids alone to distinguish a eunuch from a normal man. Callow *et al.* (1940) found that normal adult men excreted 3.5 to 15 mg. of 17-ketosteroids in 24 hours and that eunuchs excreted 3.1 to 10.9 mg. in 24 hours. By this investigation, therefore, it is difficult to demonstrate androgen deficiency in the male climacteric. However, on the whole in men of middle age the excretion of 17-ketosteroids begins to decline: at the age of 40 the mean is 14 mg. and in old age 3.4 mg. in 24 hours (Dorfman, 1948). Howard *et al.* (1950) observed that in six patients whom they considered to be suffering from the male climacteric the urinary 17-ketosteroids "tended to be low," the values ranging from 3.9 to 10.2 mg. in 24 hours.

(3) Anabolic Action of Androgens

What is often overlooked or not fully appreciated is that in addition to their effect on the sexual organs androgens have a powerful anabolic action. They promote the anabolism of protein and increase muscular bulk and strength: thus are explained the weakness and early fatigue of the eunuch. One does not therefore have to search for a psychological cause to explain these symptoms in the middle-aged man with testicular failure. The effect of androgens on the central nervous system is not yet known. The psychological symptoms which may occur in the eunuch or in the male climacteric may be secondary phenomena resulting from sexual inferiority, or, on the other hand, they may even be primary, arising through deficiency of whatever action testosterone may have on the higher centres. In this connexion it should be noted that the administration of testosterone to women with panhypopituitarism improves their psychological disturbances and gives them a sense of well-being.

(4) Titre of Gonadotrophin

It is well recognized that high levels of F.S.H. of the anterior pituitary gland are present in the urine of men with primary hypogonadism. Heller and Myers (1944) found that in 15 men with psychoneuroses or psychogenic impotence the titre was normal, whereas in 23 men whom they considered to be suffering from the male climacteric the titre was unequivocally higher. Sniffen *et al.* (1951), who have made a careful and extensive study of testicular abnormalities, have stated that it is unusual for elderly men to have raised urinary gonadotrophin, although it is the rule in post-menopausal women, but that some men do suffer from symptoms similar to those experienced by women at the time of the menopause: in these men they found that the urinary gonadotrophin was significantly raised.

McCullagh and Hruby (1949) observed that in cases of severe hypogonadism in the male the titres of urinary F.S.H. were not reduced to normal levels by the administration of testosterone in amounts sufficient to create normal titres of urinary 17-ketosteroids and clinical signs of masculinization. This failure of testosterone to inhibit pituitary activity in doses sufficient to overcome androgen deficiency they cite as evidence in favour of the theory that a second testicular hormone (inhibin) exists normally and that it is this substance which has the power to inhibit the secretion of F.S.H. Howard *et al.* (1950) have also produced evidence in support of the existence of a second

testicular hormone, which they prefer to call "X" hormone: thus, in bilateral mumps orchitis the tubules are destroyed and the titre of F.S.H. is raised, while the appearance of the Leydig cells (which secrete testosterone), virilization, and excretion of 17-ketosteroids are all normal. These authors have brought forward arguments which suggest that the Sertoli cells are the source of X hormone and that F.S.H. stimulates its production. According to this view it is damage not of the Leydig cells but of the Sertoli cells which causes the increase in titre of F.S.H. These observations lead us to a consideration of testicular histology.

(5) Testicular Histology

Heller and Myers (1944) performed testicular biopsy on 8 of their 23 cases of the male climacteric. In five they found reduction in size and in activity of the seminiferous tubules and reduction in size and number of the Leydig cells of the interstitial tissue, and in three hyaline degeneration of the tubules. Nelson (1948), in cases which he classified as the male climacteric, observed essentially normal seminiferous tubules but decreased numbers of Leydig cells with abnormal cytological characteristics. Howard *et al.* (1950) and Sniffen *et al.* (1951), on the other hand, found normal testicular histology in their patients, although the excretion of F.S.H. was raised in all.

Howard and his colleagues divide the climacteric in both sexes into two stages: (a) compensated, and (b) decompensated. They state: "In the compensated stage there is a tendency to decreased production of one of the gonadal hormones (oestrogen in the female and X hormone in the male); this tendency is met by overproduction of F.S.H., so that the gonadal function remains essentially intact. In the decompensated stage this tendency to gonadal hormone failure is not counterbalanced in spite of increased production of F.S.H., and gonadal failure becomes clinically demonstrable. In the female the compensated stage lasts a very short time; in the male, on the other hand, one seldom meets the decompensated stage. In the compensated stage in the male, therefore, one would anticipate that the Sertoli cells would be normal microscopically, as indeed they appeared to be."

(6) Effect of Treatment

It has been mentioned above that the improvement obtained in the so-called male climacteric by the administration of testosterone has been imputed to suggestion. Heller and Myers (1944), however, have reported that the injection of an inert oil without the patient's knowledge or any substitution resulted in a relapse.

Conclusion

From these observations and from my own clinical experience I find it difficult to deny the existence of the male climacteric. Heller and Myers (1944) have stated that whereas the climacteric in females is a physiological process, in males it is rare and pathological. Bauer (1944) asserted that on these grounds the syndrome should be termed "testicular insufficiency" rather than male climacteric; he maintained that if the term climacteric is used, as it should be, to designate the cessation of gonadal activity, then there is little justification for using the term male climacteric, for although the functional activity of the testes declines with advancing years there is no definite age at which they stop functioning as do the ovaries. In this respect it would appear that decline of sexual function in the middle-aged and post-middle-aged man is not denied and that the problem is one of terminology. If we adhere to the definition of climacteric as given at the beginning of this paper I do not understand why application of the term to the male should be abandoned merely because cessation of gonadal activity occurs between the ages of 45 and 55 in women whereas in men it occurs between the ages of 50 and 70 or not at all. Further, why should decline in gonadal activity of elderly men be pathological, whereas in elderly women it is physiological? As

Abarbanel (1945) has pointed out, the process of ageing can become manifest in various organs at varying times, and just because the testis may be one of the last to succumb does not mean that it has now become the site of a pathological process while a similar state in the ovary is merely physiological.

Summary

It is considered that the male climacteric is a definite clinical entity, for the following reasons: (1) Similar symptoms occasionally occur in post-pubertal castrates and eunuchoids and are improved by androgen therapy. (2) The 17-ketosteroid secretion, while by no means diagnostic of testicular insufficiency, tends to be low. (3) Some of the symptoms can be explained by lack of the anabolic action of testosterone. (4) The urinary excretion of gonadotrophin is raised—indicative of testicular, but not necessarily of androgen, insufficiency. (5) The testicular histology may show structural changes. (6) The symptoms are improved with androgen therapy, but relapse when an inert substance is substituted. (7) Arguments similar to those advanced against the concept of a male climacteric could be raised against the existence of a female climacteric, which, however, has never been questioned.

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Can better use of the domiciliary services provided by local authorities help to relieve the pressure on the hospitals? This was one of the questions put by the Minister of Health, Mr. IAIN MACLEOD, when he addressed the annual meeting of the County Councils' Association in London on May 26. Mr. Macleod made a plea not only for closer co-operation between those responsible for the operation of the health and welfare services and the general practitioners, but also for the fullest opportunity to be given for voluntary effort to make this contribution, especially in helping to solve the growing problem of the care of old people. "We know," he said, "that it is possible to relieve the hospitals of some part at least of the burden now falling on them if better and perhaps more intelligent use can be made of the services provided by the local health authorities. It is not only a question of cost. There are many types of patient who, provided always that there is no clinical reason to the contrary, are better cared for in their own homes than in hospital. This applies particularly to many children and old people, and to the majority of maternity cases, and it is even more true that the vast majority of healthy old people and children are far better if they can be enabled to continue living in their own homes and families and to receive there proper care and supervision." The home nursing of sickness, he continued, was entirely dependent on a sufficient number of home nurses and home helps. Local health authorities should carefully watch to make sure that there were enough of them in their areas. He would also like to see local health authorities consulting general practitioners in their areas, through either executive councils or local medical committees, to find out to what extent doctors felt themselves compelled, owing to the shortage of home nurses and home helps, to refer patients to hospital who might otherwise have stayed at home.

ISONIAZID IN TREATMENT OF BONE AND JOINT TUBERCULOSIS

A REVIEW OF 20 CASES

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The Medical Research Council's (1952) interim report on the use of isoniazid (isonicotinic acid hydrazide) alone in 173 patients with pulmonary tuberculosis and of streptomycin combined with *p*-aminosalicylic acid (P.A.S.) in 158 others, concluded that, "judging wholly from short-term results," isoniazid is "a very effective drug" in that condition. It therefore seemed necessary to us to make an immediate study of its short-term effects in bone and joint tuberculosis in circumstances in which the drug would be used as the sole chemotherapeutic substance in the patients under consideration. There have already been reports on the use of the drug with and after streptomycin in bone and joint disease, and especially in "advanced" cases with sinuses and other complications, but we are not aware of any reports of its planned use alone in reasonably early uncomplicated cases.

To study such effects means denying our patients the known and very real benefits of streptomycin, and to obtain many suitable cases of bone and joint disease takes a long time. We therefore planned a small short-term study, designed purely as a pilot experiment, to tell us whether or not anything unexpected would occur in the course of the disease under treatment with this drug alone. We decided that six months was as long as we might deny streptomycin to our patients, and, though this is a very short time in the evolution of skeletal disease, we regarded it as probably adequate for a pilot investigation. All we sought was the answer to one simple question, Does anything unusual occur in the early evolution of the disease under the influence of isoniazid?

The Investigation

To give the drug every chance we selected "good" cases, not failures after other measures. Our 20 patients all had short histories of hitherto untreated new tuberculous lesions of bones and joints. We carefully excluded any case which could have been a recrudescence of an old lesion, and any patient who had had previous chemotherapy. The details of the patients are summarized in the Table. All 20 were admitted to the Robert Jones and Agnes Hunt Orthopaedic Hospital. In all save six spinal cases the diagnosis was or had been proved by biopsy or by recovery of the bacillus by aspiration of abscesses and recovery of *M. tuberculosis* therefrom, and in one of these six, all of which were clinically and radiologically typical, we accepted the presence of a proved active tuberculous lesion elsewhere in the body as adequate evidence that the spinal lesion was in fact tuberculous. The patients' ages ranged from 5 to 45 years. Ten were aged 20 or under. There were 13 males and 7 females. The sites of the lesions were: lumbar spine, 6; hip, 5;