tions with a high mortality (about 15% according to Wagner *et al.*, 1950) it can provoke, any incidentally found Meckel's diverticulum should be removed if this procedure does not materially increase the operative risk.

Summary

The complications of Meckel's diverticulum which call for emergency surgery are infection, obstruction, intussusception, volvulus, and haemorrhage. The difficulties in diagnosis have been illustrated by five cases.

The incidentally found Meckel's diverticulum should be removed if this procedure does not materially increase the operative risk.

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In 1953 the accident section of the London Ambulance Service dealt with 90,896 emergency calls—compared with 87,691 in 1952 and 87,012 in 1951. Thirty-nine ambulances were in commission, operating from the 18 accident ambulance stations; they covered 457,514 miles, an increase of 15,246 over 1952. Fridays and Saturdays are still the busiest days of the week, with averages of 267 and 266 calls, and Sunday remains the quietest day with 188 calls. Unlike 1952, when most calls were received in December, in 1953 the highest average number of calls were received in June—280 calls a day—and May—269 calls a day. These figures reflect the record numbers reached on Coronation Day, when 650 patients were removed by the London Ambulance Service. The general section of the Service, which deals with the non-urgent removal of sick people, carried out 428,946 journeys in 1953, conveying 721,334 patients a distance of 3,625,430 miles. In 1951 550,621 patients were carried, and in 1952 660,206. The majority of these journeys were for the conveyance of out-patient cases to and from hospitals, clinics, etc.

COMPARISON OF SODIUM AND PROCAINE PENICILLIN IN TREATMENT OF EXPERIMENTAL STAPHYLOCOCCAL INFECTION IN MICE

BY

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It is remarkable that there is still a division of opinion regarding the administration of penicillin in the treatment of infections. It has often been maintained that the therapeutic benefits of penicillin depend on the time during which there is an amount of penicillin in the blood stream sufficient to kill or inhibit the growth of the infecting organism. This possibility was recognized in the early days of penicillin therapy, and the continuous administration of penicillin by intramuscular drip rather than by intermittent intramuscular injection was advocated so that a bacteriostatic level of penicillin in the blood could be maintained throughout treatment. It was, however, pointed out by Hudson *et al.* (1946) that, for the same amount of penicillin over a 24-hour period, the intermittent method of administration gave a much higher average level of penicillin in the blood than the continuous method, and they also contended that intermittent therapy would be more effective in that the high peaks of penicillin obtained in the blood after each injection would enable penetration of penicillin into the foci of infection. The intramuscular drip method was soon abandoned, largely because of technical difficulties in its application, with the result that no clear-cut comparison could be made of its value relative to the more widely used intermittent method.

The question has again been raised with the introduction of depot preparations of penicillin, which have the advantage over sodium penicillin of prolonging the absorption of penicillin from the site of injection, so that effective concentrations are maintained in the blood stream for a much longer time. It is on these grounds that the advocates of the new preparations recommend their use, but it appears that little or no evidence has been adduced to show that they are better than aqueous solutions of sodium penicillin in the treatment of infections. The experiments described here have been designed to provide such evidence so far as it applies to an experimental infection which has been used by Selbie and Simon (1952) in their investigation on the virulence of *Staph. pyogenes* to mice.

Material and Methods

The two strains of *Staph. pyogenes* used for these experiments have been described by Selbie and Simon (1952). Strain No. 221 was used for five experiments, but had to be abandoned because of a fall in virulence. Fourteen experiments were done with Strain No. 144. At the time of the experiments the growth of the strains *in vitro* was inhibited by about 0.04 unit of penicillin per ml.

In each experiment four groups of six mice of about 30 g. body weight were inoculated intramuscularly in the left thigh with 0.2 ml. of an 18-hour culture of *Staph. pyogenes* in tryptic digest broth. The first group was left untreated, and the succeeding groups were treated with an aqueous solution of the sodium salt of penicillin G, a suspension of procaine penicillin G in arachis oil containing 2% aluminium stearate ("avloprocil"), and an aqueous suspension of procaine penicillin G ("distaquaine G"). Each

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dose of penicillin preparation contained 30,000 units in 0.1 ml. and was injected subcutaneously in the right axilla so as to be as far away as possible from the site of infection and thus ensure that penicillin would reach the lesion by way of the blood stream rather than by direct diffusion through the tissues.

In two series of experiments treatment with penicillin was started three hours after inoculation, when some swelling of the thigh could already be detected. This was done on the basis of preliminary experiments which showed that earlier treatment rapidly abolished the lesions in most of the mice, whereas when treatment was started at three hours the great majority of the mice showed measurable swellings during the whole of the succeeding week, so that an opportunity could be afforded of measuring differences in response to the various penicillin preparations. In the third series treatment was not started until after 24 hours, when the lesions were first measured. Measurement of the lesions was made at 1, 2, 4, and 7 days after inoculation by determining the diameter of the left thigh by callipers to the nearest millimetre and subtracting the diameter of the normal thigh.

Results

The average effect of six experiments, in which only one dose of penicillin had been given three hours after inoculation is shown in Fig. 1. The average effects of two further series of experiments in which four daily doses of penicillin have been given, commencing at 3 hours and 24 hours after inoculation, are shown in Figs. 2 and 3 respectively. The overall mortality rate of 1% has not interfered with the analysis of the results, especially as only one mouse has died in each affected group. Progressive infection, as judged by the increasing average size of the swellings, has been obtained in the untreated mice of all the experiments except for the onset of regression after two days in one experiment, and after four days in three experiments. All three penicillin preparations reduced the size of the lesions as compared with those in the control mice, but there were great differences between experiments in response to the three penicillin preparations.

The results have been submitted to Dr. L. J. Edwards for statistical appraisal. He finds that the most suitable way of dealing with these is to express the sum of the swellings on each day in each experimental group of six mice as a percentage of the sum of the swellings in the

corresponding control group on that day. The means of the percentages for each day in each treatment have been used to construct Figs. 1 to 3. Dr. Edwards has also calculated the variances of the means, and concludes that all three penicillin preparations significantly reduce the size of the swellings on all regimes of dosage and on all days of measurement, but none of them can be said to be demonstrably better than either of the others.

Concentration of Penicillin in Blood of Mice

The concentration of penicillin in the blood serum of mice at intervals after subcutaneous injection of the three penicillin preparations in the dose of 30,000 units used for treatment was estimated by the twofold serial dilution method described by Selbie *et al.* (1945). Each estimation was made on 1 ml. of serum from the pooled blood of three mice which were bled from the heart with a Pasteur pipette immediately after they were killed.

The results are shown in the Table. It will be seen that during the first 10 minutes sodium penicillin gives a concentration in the serum five times greater than the highest level attained at any time by either of the other preparations. It can also be seen that the concentrations given by sodium penicillin are lower than those given by the other two preparations from 30 minutes onwards and are no longer detectable by the method used at 18 hours. The results obtained with the procaine penicillin preparations show a more rapid absorption from the aqueous suspension, which, however, gives detectable levels of penicillin up to at least four days, as against seven days with the oily preparation.

Discussion

The clinical use of procaine penicillin preparations in preference to sodium penicillin is based largely on the contention of Eagle *et al.* (1950) that the curative effect of penicillin depends primarily on the concentration of penicillin in the blood and the total time for which it remains at effective levels. It has, however, been shown here that equivalent doses of sodium penicillin and two preparations of procaine penicillin are equally effective in controlling the lesions of an experimental staphylococcal infection in mice. If the presence of a bacteriostatic level of penicillin in the blood were the principal factor in determining a curative effect, the blood levels shown in the Table would indicate that the dose of sodium penicillin used would become ineffective

FIG. 1.—Average effect of one dose of 30,000 units of penicillin given three hours after intramuscular inoculation of *Staph. pyogenes*. —○—○— Untreated mice. —○—○— Mice treated with sodium penicillin. ×—×— Mice treated with oily suspension of procaine penicillin. +—+— Mice treated with aqueous suspension of procaine penicillin.

FIG. 2.—Average effect of four doses of 30,000 units of penicillin given 3 hours, 1 day, 2 days, and 3 days after intramuscular inoculation of *Staph. pyogenes*. Explanation as for Fig. 1.

FIG. 3.—Average effects of four doses of 30,000 units of penicillin given 1, 2, 3, and 4 days after intramuscular inoculation of *Staph. pyogenes*. Explanation as for Fig. 1.

Penicillin in Blood Serum of Mice After Subcutaneous Injection of 30,000 Units of Penicillin in 0.1 ml.

Preparation	Units of penicillin per ml. at												
	Minutes			Hours						Days			
	5	10	30	1	3	6	12	18	24	2	4	5	7
Sodium penicillin G	800	800	2.5	1.3	5	1.3	0.64	—	—	—	—	N.D.	—
Oily suspension of procaine penicillin .. .	20	40	160	10	5	2.5	10	N.D.	5	2.5	1.3	N.D.	0.04
Aqueous suspension of procaine penicillin ..	40	40	160	160	40	40	20	N.D.	0.64	1.3	0.08	—	—

— = Less than 0.04 unit per ml. N.D. = Not done.

within 18 hours, whereas the equivalent doses of oily and aqueous procaine penicillin would remain effective for four and seven days respectively.

It is, however, obvious from Fig. 1 that the curative effect following one injection of sodium penicillin continues long after penicillin falls below a detectable level in the blood, and is as good as that obtained after an injection of procaine penicillin. This continuing effect after sodium penicillin treatment is also evident when four daily doses are given, whether the first dose is given at 3 hours or 24 hours after inoculation (Figs. 2 and 3); in both regimes the aggregate time during which effective levels of penicillin would be present in the blood is less than three days with sodium penicillin and seven days with the procaine penicillin preparations.

It would thus appear that the total duration of an effective level of penicillin in the blood is not the only factor that is of importance in determining the curative effect of penicillin in this experimental infection. Two of the factors that have to be considered are the maximum concentration of penicillin attained in the blood and the defence mechanisms of the host. The Table shows that the maximum concentration of penicillin detected in the blood after the injection of sodium penicillin is five times greater than that detected after injection of the procaine penicillin preparations. Sodium penicillin would therefore give a much higher concentration of penicillin in the staphylococcal lesions and so produce a greater therapeutic effect than procaine penicillin. This more intensive effect of sodium penicillin would, however, be maintained over a relatively short period.

The reason why such a short but intensive action of sodium penicillin should be as valuable as the prolonged maintenance of a lower therapeutic level by procaine penicillin may be found by a consideration of the part played by the natural defence mechanisms of the host. These mechanisms are constantly in operation, and are so effective that staphylococcal infections in man and the experimental infection described here are in the end usually overcome even when chemotherapy is withheld. The part played by penicillin may then be regarded as an intervention in this natural process whereby the suppression of the staphylococci by the antibacterial action of penicillin, even if it is only temporary, so tips the scales in the reactions between host and parasite that the defence mechanisms of the host become more effective. The relatively high concentrations attained immediately after an injection of sodium penicillin at an early stage of infection would thus exert a more intensive effect, and the later continuing effect would be entirely due to the operation of the natural defence mechanisms. Procaine penicillin, on the other hand, would have a less intensive initial effect, but the results of the experiments show that it largely overcomes this disadvantage by its much more prolonged intervention at a relatively low intensity.

These conclusions are at variance with the views of Eagle *et al.* (1950). They, however, have based their conclusions on a different type of experimental infection. In one of their recent publications they show that the effect of penicillin in reducing the mortality rate of a streptococcal infection in mice depends primarily on the aggregate time during which penicillin is present in the blood at or above the bactericidal level, irrespective of the dosage regime, pro-

vided that the interval between doses is not too long (Eagle *et al.*, 1953). It must, however, be borne in mind that the streptococcal infection used by Eagle and his co-workers and the staphylococcal infection used here are very different in their behaviour. Mice have little or no immunity to haemolytic streptococci, so that the experimental infection is rapidly fatal. On the other hand, mice are so much more resistant to staphylococcal infection that even the large numbers of staphylococci used for inoculation in the experiments described here produce only a local lesion with a very low mortality rate. The intense exudative response to the staphylococcal infection also appears to make the organisms less accessible to penicillin, as can be judged by the much larger doses required to control the staphylococcal lesions as compared with the streptococcal infection, in which the organisms are more directly in contact with the circulating body fluids. It is therefore not surprising that the two experimental infections should differ in their response to chemotherapy.

The application of these findings to the penicillin treatment of infections in man is difficult because of the highly artificial nature of animal experiments. It can be said that the experimental staphylococcal infection resembles conditions in man more closely than the streptococcal infection of Eagle and his colleagues because most human infections elicit some degree of response on the part of the body defences. If this view is accepted it is then apparent that penicillin treatment should be given in such a manner as to give maximum aid to the body defences. The results presented here suggest that this can be done just as well with sodium penicillin as with procaine penicillin even when doses are given infrequently. Evidence in support of this view is to be found in the report by Tompsett *et al.* (1949), who have failed to detect any difference in response between 21 cases of pneumococcal pneumonia treated with daily doses of 30,000 units of procaine penicillin in oil, and 19 similar cases treated with three 12-hourly doses followed by daily doses of 300,000 units of sodium penicillin.

Another investigation of this type is that of Griffiths *et al.* (1949), who found no significant difference in response to treatment between a group of 116 patients with acute septic infection, mainly staphylococcal, given a daily injection of 300,000 units of an oily suspension of procaine penicillin and a similar group of 116 patients given twice-daily injections of 300,000 units of sodium penicillin in saline. Both groups of authors suggest that their results warrant the conclusion that a continuous effective level of penicillin is not necessary for the control of the two respective types of infection.

The results recorded here and a search of the literature have been disappointing in that no clear evidence has been found to show whether sodium penicillin or procaine penicillin gives the better results in the treatment of infections. It is probably true that the prolonged blood levels obtained with procaine penicillin are of great value when only one dose of penicillin can be given, as in the mass treatment of syphilis and yaws. On the other hand, even when penicillin can be given only at infrequent intervals, it has yet to be proved in practice whether the prolonged low blood levels provided by procaine penicillin are more efficacious than the short-lasting but high blood levels provided by sodium penicillin in the treatment of the generality of infections amenable to penicillin therapy.

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