in generalized osteoarthritis, and if these are abnormal some other form of arthritis is present. A great excess of low-viscosity joint fluid, synovial thickening, and lesions in the bursae, tendon sheaths, and tendons are further indications of inflammatory polyarthritis.

Although some subjects with a very high erythrocyte sedimentation rate were included in our original study of patients with generalized osteoarthritis (Kellgren and Moore, 1952), subsequent experience has suggested that in uncomplicated generalized osteoarthritis the E.S.R. is not greatly elevated, and a value of over 30 mm./hour (Westergren) is now regarded as evidence of the existence of some other disease, as is the presence of anaemia. A positive sheep-cell agglutination test is also strong evidence for the presence of concomitant rheumatoid arthritis. Rheumatoid arthritis in elderly males may present as increasing pain and stiffness in a single large joint, such as the hip, which may lead to an erroneous diagnosis of osteoarthritis; but this can be avoided by routine examination of all joints, because such patients usually have definite signs of rheumatoid arthritis in other more accessible sites, especially in the feet and hands, and it should be remembered that gross erosive changes in these joints in old men are often painless. It is obviously essential to aim at a correct diagnosis in all patients with osteoarthritis in whom some other diseases, such as rheumatoid arthritis, are present, since it is the latter conditions that determine prognosis and treatment.

Finally, pain and stiffness in the limbs and back in a patient with obvious osteoarthritis may not be due to the joint disease but to some concomitant non-articular disorder, especially disease of the nervous and cardiovascular systems. For instance, patients with a stiff hip may get leg pain from a prolapsed disk, and stiffness of the legs in patients with obvious osteoarthritis of the hips may be due to a concurrent spastic paraplegia or Parkinsonism, and it is surprising to what an extent a radiograph showing gross osteoarthritis of the hip concentrates our attention on the hip-joint.

SUMMARY AND CONCLUSIONS

Osteoarthritis has been studied in population groups as well as in patients, and such studies have led to the conclusion that osteoarthritis in women is predominantly a polyarticular condition resulting from inherited constitutional factors which may also be influenced by diet and other environmental conditions. In men the same causative factors may operate; but trauma, occupational stress, and mechanical factors in the joints probably play a predominant part. Osteoarthritis as a sequel to inflammatory joint disease also contributes to the sum of osteoarthritis in both sexes. The future prospects for prevention and medical treatment of osteoarthritis may therefore be good, and further research along both epidemiological and experimental lines is urgently needed.

In the meantime a proper differential diagnosis of the type of osteoarthritis present and the true reasons for seeking medical consultation can lead to more successful palliative treatment.

Figs. 1, 3, 4, 5, and 6 are reproduced by permission from the *Annals of Rheumatic Diseases* (Kellgren *et al.*, 1953; Kellgren and Lawrence, 1958). Fig. 2 is reproduced by permission from the *British Journal of Industrial Medicine* (Kellgren and Lawrence, 1952).

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METHICILLIN

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Methicillin ("celbenin") is of proved value in the treatment of staphylococcal infections that are resistant to benzylpenicillin (penicillin G) (Douthwaite and Trafford, 1960; Stewart, Nixon, and Coles, 1960). Investigation into the problems arising from its use have continued to be made. In particular, the question of the occurrence of resistance *in vivo* of staphylococci has been studied. A method of achieving satisfactory blood levels of methicillin in combination with probenecid in a low dose regime is here described.

Clinical Material and Methods

The series consists of 46 patients, all of whom had benzylpenicillin-resistant staphylococcal infections of varying types. The types of cases treated were:

Cases			Cases		
Pneumonia	9		Bacterial endocarditis ..	4	
Empyema	1		Lung abscess	2	
Septicaemia	4		Cervical abscess	1	
Osteomyelitis	2		Neonatal pemphigus	2	
Meningitis	1		Multiple boils and abscesses	4	
Cerebral abscess	1		Urinary tract infection ..	4	
Bronchiectasis with acute exacerbations	5		Wound infections	6	

Levels of methicillin in the blood and cerebrospinal fluid were measured whenever practicable and routine haematological, radiological, and bacteriological investigations were carried out.

The dosage of methicillin was altered according to the blood levels (see below). The maximum dose was

1 g. four times daily and the minimum 750 mg. three times a day. The variation in dosage was due to the experimental use of probenecid, which was given with a view to delaying the excretion of methicillin.

Antibiotic concentrations were determined by the cup-plate biological assay method using *Sarcina lutea* ATCC 9341 as the test organism (Knudsen and Rolinson, 1960).

Results

At the time of writing no case has failed to respond to methicillin. Evidence for this statement is provided by clinical improvement supported by changes revealed by haematological, radiological, and bacteriological investigations. In six cases recrudescence of the staphylococcal infection occurred at varying intervals after the cessation of treatment. These cases are set out below. In each the dosage of methicillin was 1 g. four times a day.

Case 1: Urinary Infection.—Nine days after completion of a three-day course of methicillin and five days after a prostatectomy staphylococci were cultured for the second time from the urine. No symptoms ensued on this occasion, no further treatment was given, and staphylococci were not identified in subsequent urine cultures.

Case 2: Asthma and Bronchitis.—After a five-day course of treatment with methicillin sputum culture became negative. One week later, after a further attack of bronchitis, staphylococci were cultured from the sputum and once again were found to be sensitive to methicillin.

Case 3: Staphylococcal Pneumonia.—After a five-day course of treatment with methicillin no staphylococci were cultured from the sputum. One week later staphylococci were once again identified and were found to be sensitive to methicillin. The patient was treated with methicillin for a further seven days and subsequent sputum cultures proved negative.

Case 4: Staphylococcal Endocarditis.—Prolonged treatment with benzylpenicillin, tetracycline, chloramphenicol, erythromycin, and ristocetin ("spontin") failed to control the infection. Heart failure developed, the patient became critically ill, and methicillin was administered for 32 days. The clinical response was good; the fever abated and the signs of heart failure receded. The drug was stopped after the patient had remained afebrile for 14 days. Ten days later the fever recurred and the patient again became seriously ill. Once more cardiac failure supervened and staphylococci were cultured from the blood. The patient died 48 hours later.

Methicillin was the only antibiotic that proved to be of therapeutic value in Case 4, and control of the infection apparently had been achieved when the drug was stopped. Administration of the drug for a longer period might well have resulted in cure.

Case 5: Multiple Boils.—After a five-day course of methicillin the boils regressed but recurred one week later. It is difficult to decide in a condition such as this whether the recurrence is due to failure in elimination of the original infection or to reinoculation. Other workers (Stewart *et al.*, 1960) quote a similar recurrence of multiple boils after a course of methicillin.

Case 6: Cerebral Abscess.—The patient had a long history of staphylococcal cerebral abscess, and despite prolonged and varied antibiotic treatment infection persisted. After treatment with methicillin the abscess became sterile and the cellular reaction in the cerebrospinal fluid disappeared. After discharge from hospital the symptoms recurred and staphylococci were again found. Methicillin was readministered with an excellent clinical response. Unfortunately the *in vitro* sensitivities on this second occasion were not ascertained.

Serum and Cerebrospinal Fluid Levels of Methicillin

Knox (1960) reports that, in most naturally occurring infections investigated, the effective level of methicillin in the serum is 2 to 4 $\mu\text{g./ml.}$ The level of sensitivity *in vitro* of the staphylococci obtained from the cases reported here was between 2 and 4 $\mu\text{g./ml.}$ An exception was a coagulase-negative staphylococcal infection in which the sensitivity was 6.5 $\mu\text{g./ml.}$ (Case 7, see below). After intramuscular injection of 1 g. of methicillin the serum level of 2 to 4 $\mu\text{g./ml.}$ is maintained for only two and a half hours.

It has been shown that 75% of the dose of methicillin administered throughout one day is excreted in the urine (Douthwaite and Trafford, 1960). Knudsen and Rolinson (1960) reported similar results.

Probenecid was administered in order to judge its effect in blocking the renal tubular excretion of methicillin. If 0.5 g. of probenecid four times a day is added to the treatment the effective blood level of methicillin is maintained for six to eight hours and the peak levels obtained in the serum are increased. This observation confirms previous reports (Stevenson and Harrison, 1960). The Chart shows the effect of the addition of probenecid.

Mean results of 18 subjects given methicillin alone and of 12 given methicillin and probenecid.

One patient who was being treated with methicillin for a scalp infection was investigated with a view to exclusion of an intracranial extension, and we took advantage of this to estimate the level of methicillin in his cerebrospinal fluid. None was found. This observation was repeated in a second patient in similar circumstances. In a case of meningitis, however, the cerebrospinal fluid level of methicillin one hour after administration was found to be 2.8 $\mu\text{g./ml.}$

Toxic Effects

Injections of methicillin are painful, and we have found that the administration of lignocaine hydrochloride before injection reduces the pain considerably. The actual technique is as follows. 0.5 ml. of 1% lignocaine is injected into the patient. The needle is left *in situ* and the syringe which had contained the lignocaine is disconnected. After an interval of 15

seconds a syringe containing the methicillin is connected to the needle which has been left *in situ* and the methicillin is then injected.

Four patients to whom methicillin has been given had previously had skin rashes as a reaction to benzylpenicillin. In the first two cases antihistamine and prednisolone cover was given, and methicillin was then administered in a test dose of 50 mg. No reaction occurred. Subsequent to receiving the maximum dose of 1 g. four times daily one patient developed a generalized erythema; in the fourth patient no reaction occurred. The erythema gave rise to no discomfort, and faded within five days despite continued administration of methicillin.

In the two other patients known to be sensitive to benzylpenicillin, a test dose of 50 mg. of methicillin was given without antihistamine or prednisolone cover, and was followed by steadily increasing doses until 1 g. four times daily was being administered without reaction occurring.

It has been stated that patients sensitive to benzylpenicillin may also be sensitive to methicillin (Douthwaite and Trafford, 1960). Stewart *et al.* (1960) reported the case of a volunteer who was known to be sensitive to benzylpenicillin and who reacted severely to a test dose of methicillin. Although the patients quoted have been few in number they provide some evidence to suggest that not all patients sensitive to benzylpenicillin are also sensitive to methicillin. Caution should, however, be exercised in administering methicillin to penicillin-sensitive subjects.

It has been reported to one of us by Schurr (personal communication, 1960) that a patient who was receiving methicillin, and was responding satisfactorily, developed a fever associated with vomiting which could not be explained. After transfer to another hospital, a further course of methicillin was advised for a persisting sinus. Within 48 hours the fever and vomiting recurred. It is probable that this was a reaction to methicillin.

Occurrence of Resistance *in vivo*

It is known that staphylococci resistant to methicillin can be readily obtained *in vitro* by repeated subculture in the presence of the compound (Rolinson, 1961). Knox (1961) reports that staphylococci resistant to a level of 500 μg . of methicillin per ml. can be cultured in the laboratory. This is in contrast to the naturally occurring staphylococcal infections we have studied, in which the effective concentration in the blood appears to be between 2 and 4 μg ./ml. To our knowledge no case has been reported in which a methicillin-resistant strain has been isolated from a patient after treatment with the drug, although Jevons (1961) has recorded the finding of strains of staphylococci that are naturally resistant to methicillin.

In our own series no evidence of resistance has been encountered clinically.

Case 7.—A patient of particular interest is one who developed bacterial endocarditis after cardiac surgery. A coagulase-negative staphylococcus was isolated and proved to be sensitive *in vitro* to methicillin at a level of 6.5 μg ./100 ml. The patient was treated with methicillin 1 g. three times a day, and, although the blood levels were below the *in vitro* sensitivity for many hours of the day, he responded with excellent clinical results.

This case is reported not only for its interest from the point of view of the resistance of the organism

in vitro to methicillin, but also because it is known that coagulase-negative organisms causing endocarditis after cardiac surgery are particularly lethal.

Summary and Conclusions

The results of the use of methicillin in 46 patients emphasizes the value of this drug in the treatment of staphylococcal infections.

For most staphylococcal infections blood levels of between 2 and 4 μg ./ml. are satisfactory and may be achieved by intramuscular injection of 1 g. of methicillin. This level is maintained for only two and a half hours after injection. The addition of probenecid 0.5 g. four times a day prolongs the effective blood level of methicillin to six to eight hours.

It would appear that, like benzylpenicillin, methicillin probably gains access to the cerebrospinal fluid only when a meningeal lesion exists.

Sensitivity reactions to methicillin of patients known to be resistant to benzylpenicillin are discussed.

In each of the 46 patients treated a good response was obtained, but in six a recrudescence of the infection occurred after an initial satisfactory recovery. This never occurred while the drug was being administered.

No case has been encountered of resistance *in vivo*. In one case it is noted that *in vitro* tests of sensitivity to methicillin did not reflect accurately the degree of sensitivity which was present *in vivo*.

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PHENETHICILLIN AND BENZYLPENICILLIN IN ACUTE OTITIS MEDIA

BY

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In 1959 Batchelor *et al.* reported that the penicillin nucleus, 6-aminopenicillanic acid, had been produced by fermentation. "Broxil," the first commercially available synthetic penicillin, is the potassium salt of 6-(alpha-phenoxypionamido) penicillanic acid. Being freely soluble in water, acid-resistant, and well absorbed from the gastro-intestinal tract, it is an ideal penicillin for oral administration.

Present Trial

Objective of Clinical Trial.—The main purpose of this therapeutic trial was to compare the results of treatment of acute suppurative otitis media in two groups of patients, the first group being treated with oral phenethicillin (broxil) and the second by intramuscular benzylpenicillin (penicillin G). Also it was hoped that the investigation would throw some light on the current bacteriology of acute middle-ear infections.