TABLE II.—Serum Penicillin Levels in Units per ml. at 3 p.m. on Consecutive Days. 300,000 Units of Penidural Given Six-hourly Throughout

Case No.	3 hours	27 hours	51 hours	75 hours
1	0.06	0.25	0.25	0.25
2	0.125	0.25	0.25	0.25
3	0.25	0.5	1.0	1.0
4	0.125	0.5	0.5	0.5

FIG. 1

FIG. 2

cases hourly penicillin levels were estimated and a cumulative effect was seen following a second oral dose. Fig. 2 shows one such typical example, in which there were satisfactory blood levels for six hours, but no residual level at 12 hours after a single dose. When a second dose was given at six hours, not only were the levels for the succeeding six hours higher than in the first period but there was also a residual level at 12 hours.

In Table II are shown the blood levels at 24-hour intervals in four consecutive patients of differing weights and ages to whom six-hourly penidural was being given. Blood samples were taken at the same time each afternoon, three hours after the last dose of the drug. Each shows the same increase in blood levels as is depicted in Fig. 2. There was some indication in the figures shown in Table I that better blood levels were obtained when penidural was given before meals.

Discussion

Penidural is the first oral preparation of penicillin which has in our experience been reliably absorbed in 100% of patients, irrespective of size and weight and using a standard dosage of 300,000 units. No attempt has been made to work out a graded system of dosage according to body weight, but it is possible that in the smaller children thera-

peutic blood levels might be obtained with lesser amounts of penidural. The emergence of a reliable oral penicillin seems to bring this drug into line with the newer antibiotics where penicillin-sensitive organisms are being dealt with.

In the treatment of acute infections blood levels during the first six hours with this oral penicillin alone cannot be regarded as adequate, and in five cases of acute illness in which penidural has been used therapeutically a single intramuscular injection of a large amount of crystalline penicillin has been used to augment the blood level during this period. In these cases—two of osteomyelitis and three of pneumonia—the results obtained have been as good as those which would have been anticipated had intramuscular penicillin been chosen for treatment.

A rational scheme of treatment of acute infection appears to be an initial intramuscular injection of 600,000 units of penidural (Fletcher and Knappett, 1953) and 100,000 units of crystalline penicillin, with 300,000 units of penidural orally, the treatment continuing thereafter only with oral penidural. Such a scheme will produce reliable therapeutic penicillin levels and should be adequate to treat infection by penicillin-susceptible organisms. Abuse of this new penicillin preparation is likely to enhance the growing number of strains of penicillin-resistant bacteria, and it is hoped that the growing menace of penicillin-resistant staphylococci will not be unnecessarily increased by improper dosage or dose-spacing.

We are indebted to Messrs. John Wyeth, Ltd., London, for a plentiful supply of penidural.

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COMBINED ORAL PENICILLIN AND SULPHADIMIDINE IN ACUTE MIDDLE-EAR INFECTIONS

BY

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Modern antibacterial drugs have revolutionized the treatment of acute otitis media, and the role of surgery in this condition is of rapidly diminishing importance. Before the discovery of antibiotics, sulphonamide administration was an established part of the therapy of this condition (Hall, 1948). Owing to the limitations imposed by toxicity upon the attainable blood sulphonamide level, and the diversity of the invading organisms, it is not surprising that sulphonamides alone are often unable to quell the infection.

The Literature

The commonest causal agents are *Staph. aureus* and *Str. haemolyticus*; consequently much better results follow the use of penicillin as the antibacterial agent (György *et al.*, 1946; Lierle and Paul, 1946; Robinson *et al.*, 1948; Jersild and Kiørboe, 1950). However, this still leaves the dangerous residue of insensitive Gram-negative bacilli, notably *Bact. coli* and *Proteus* strains, which are often present in varying numbers in a mixed infection. Elimination of the main infecting bacteria allows, and even stimulates, these fellow-travellers to multiply rapidly and restore the severity of the original disease condition.

Of the newer antibiotics, streptomycin carries with it a danger of vestibular damage and is unlikely to commend itself for the treatment of infections in the aural cavities. Chloramphenicol and aureomycin, with a wider antibacterial range, approach more closely to being ideal drugs for the

treatment of this condition. The cost of these antibiotics, however, is prohibitive; and, if used with penicillin, the superior bactericidal power of the latter might be prejudiced by their antagonistic action (Armstrong and Lerner, 1951). My personal impression of a very limited trial of chloramphenicol is that it is not quite so effective in a mixed infection as penicillin and a sulphonamide combined.

That such a combination results in a pronounced synergism between the two drugs has been repeatedly demonstrated in the laboratory (Bigger, 1944; Chain and Duthie, 1945; Kolmer, 1948). Further, this synergistic action extends to Gram-negative organisms such as *Bact. coli* and *Bact. typhosum* (Stewart, 1947; Thomas and Hayes, 1947; Bigger, 1950; El Borolossy and Buttle, 1950). The action of the sulphonamides in preventing destruction of penicillin by penicillinase (Cronheim and King, 1951) may be of importance when dealing with these latter organisms. On the clinical side there are very few reports of combined therapy with the two drugs, although Johnson *et al.* (1951) have described a synergistic action between oral penicillin, sulphadiazine, and sulphamerazine in the treatment of gonorrhoea. On the other hand, Nielsen and Strup (1951) found no difference between combined therapy and therapy with either drug alone in the treatment of pneumonia. I can trace no records of similar treatment in acute otitis media, although Moffett and Dalton (1949) have successfully treated acute mastoiditis with penicillin and sulphadiazine. It is the purpose of this paper to describe a number of cases treated with sulphadimidine and penicillin, with particular emphasis on the oral route for the latter drug.

There can be no doubt that, when administered on an empty stomach, penicillin is well absorbed from the first part of the duodenum in a dosage some five times in excess of that by injection (Little and Lumb, 1945; Buchanan, 1946; Husson, 1947; Markowitz and Kuttner, 1947; Reisman *et al.*, 1947; Stewart and May, 1947; Cohlan *et al.*, 1948). Hypochlorhydria, occurring as a result of severe illness, contributes to this (Buchanan, 1946; Anderson and Landsman, 1947; Bicknell, 1951). The adequate clinical effect of oral therapy in serious illnesses such as pneumonia has been amply demonstrated (Bunn *et al.*, 1945; Finland *et al.*, 1945; Suchett-Kaye and Latter, 1947; Anderson and Landsman, 1947; Eadie *et al.*, 1951). Good results have also been claimed in ear, nose, and throat infections (Robinson *et al.*, 1948; Wheatley, 1951). Oral administration is of greater convenience in general practice, where most cases of acute otitis media are likely to be seen. As this infection most commonly occurs in children, the oral route is again particularly desirable. For combination with sulphonamides, too, it is convenient to administer both drugs together by mouth, at the same dosage intervals. After some trial I adopted an eight-hourly interval for the treatment of these cases. This is a schedule which others have found to be highly effective with oral penicillin in pneumonia and scarlet fever (Bunn *et al.*, 1950; Weinstein and Perrin, 1950). Bunn and his co-workers also treated some of their cases with 12-hourly dosage, as did Austrian *et al.* (1951). Results were comparable with those following parenteral therapy.

In treating the acute middle-ear infection, the ideal procedure is to institute chemotherapy before perforation of the tympanic membrane can occur; thereby spontaneous perforation or the need for paracentesis may be avoided. The latter procedure is a difficult one to perform in general practice, and I am not convinced of its absolute necessity. Simpson (Fleming, 1950), considering this question in relation to penicillin therapy, advises paracentesis after 24 hours if there is no improvement. He rightly stresses that the object of treatment is the preservation of the function of hearing, and points out that even a sterile collection of fluid in the middle-ear may lead to resultant adhesions, and possible recurrence later. I personally feel that such a collection of fluid will naturally drain away via the Eustachian tube, without the need for paracentesis. However, in order to prevent the possibility of serious permanent disability chemotherapy must be prompt and adequate.

Results

The cases have been divided into two groups, classified as mild and severe. Mild cases were those in which there was little constitutional disturbance but inflammation and bulging of the tympanic membrane were present. Severe cases were those in which there was much pyrexia and pain, or in which perforation of the ear-drum had already occurred before they were seen. Most of the mild cases were treated with penicillin alone, sulphadimidine being held in reserve in case there was not a prompt response to treatment. The severe cases were treated mainly with combined penicillin and sulphadimidine from the onset. Chloramphenicol was substituted in three cases when the results of bacteriological examination showed an organism highly sensitive to this antibiotic. In these cases the response to combined therapy had not been as immediate as in the other cases in the series. The results are tabulated and compared with some earlier results obtained with sulphonamides alone and with parenteral penicillin. These cases do not include acute exacerbations occurring in chronic otitis media. The standard dose for adults was 0.375 g. (600,000 units) of penicillin plus 1 g. of sulphadimidine, eight-hourly by mouth; there was a proportionate reduction in amounts for children.

Comparison of Results

Treatment	Cases			Perforated Before Treatment	Perforated After Treatment	Recurrence in 3 Months	Chloramphenicol Substituted
	Mild	Severe	Total				
S.	3	4	7	3	Nil	3	Nil
Inj. P. . . .	8	9	17	3	2	1	"
Inj. P. and S. .	3	5	8	2	Nil	1	"
Oral P. . . .	23	6	29	6	"	Nil	1
Oral P. and S. .	4	28	32	13	"	1	2
Total	41	52	93*	33	2	6	3

S. = Sulphonamide. P. = Penicillin. * There were 2 separate attacks in 4 cases.

Bacteriology.—Swabs were taken from one-third of the 33 cases in which perforation had occurred before treatment was begun. The cultures gave the following results:

<i>Staph. aureus</i>	3 cases
" " and diphtheroids	1 case
" " " <i>Proteus</i>	1 "
" " " <i>Bact. coli</i>	1 "
<i>Bact. coli</i> , pneumococci, and <i>Staph. albus</i>	1 "
<i>Staph. albus</i> (48 hours after treatment)	1 "
<i>�� Str. haemolyticus</i>	1 "
<i>��</i> " " <i>Staph. albus</i> , and diphtheroids	1 "
Sterile	1 "

Late Results.—General practice offers some unique opportunities for follow-up of these cases, with particular reference to late effect on hearing. This is so because over the course of years many of these patients are seen from time to time for other ailments. About three-quarters of the cases described here have been thus observed for periods of one to three years. In none of these was there any residual hearing defect, as measured by their ability to hear the whispered voice at 15 feet (4.6 metres) with the affected ear alone. Where perforation had occurred healing took place in every instance. Sometimes a minute scar could be seen at the site of the perforation; but in many it was impossible to detect any evidence of the previous rupture of the membrane or of the original infection. The six cases in which there was a recurrence in three months resolved with further treatment. In four cases there were repeated but separate infections (often in the opposite ear). These also resolved with repeated treatment, and further attacks were prevented when infected tonsils and adenoids were removed.

Conclusions

The small numbers of cases treated with sulphonamides alone and with parenteral penicillin offer no basis for accurate comparison. However, they are useful in that they indicate that oral penicillin is no less effective than penicillin by injection. Of the seven cases treated with sulphonamides

alone there was a recurrence within three months in three. This was regarded as an unsatisfactory result. Although one case out of 32 treated with oral penicillin and sulphadimidine suffered a recurrence in three months, it must be borne in mind that this group included by far the greatest number of severe cases. The satisfactory end-results in 93 cases of acute otitis media treated with chemotherapy alone are held to obviate the necessity for surgical intervention. The results of bacteriological examination in 11 cases indicate that the majority of cases are probably due to infection with penicillin-sensitive organisms, but that non-sensitive bacteria, particularly *Bact. coli*, form an important minority. It is held that the co-administration of sulphonamides with penicillin will effectively deal with most of these infections. This is particularly important in those cases (the majority) in which perforation of the ear-drum has not occurred and, as a result, the nature of the invading micro-organism cannot be ascertained. In the occasional instance in which a more specific antibiotic is required, combined therapy will stay the infection until the result of bacteriological examination is known.

Summary

The role of chemotherapy in acute otitis media is discussed and the advantages of combining penicillin and a sulphonamide are outlined. The synergistic action of these two drugs and the desirability of co-administration in mixed infections is stressed. The literature on oral penicillin administration is surveyed, and it is concluded that this is an effective and convenient method of administering the antibiotic.

The results in 93 cases of acute middle-ear infection are described. Of these, 61 were treated with either oral penicillin alone or oral penicillin and sulphadimidine, according to severity. Out of 34 severe cases treated in this manner, perforation of the tympanic membrane had already occurred in 19 before treatment was begun. The results were uniformly good, with no permanent sequelae or after-impairment of hearing. Healing of the ear-drum occurred in all cases in which perforation had occurred. The bacteriology in 11 cases showed a preponderance of infection with *Staph. aureus* and *Str. haemolyticus*. However, the infection was usually a mixed one, with *Bact. coli* and *Proteus* as the usual co-invaders.

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THE Q-T INTERVAL IN MYOCARDIAL INFARCTION

BY

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The Q-T interval of the electrocardiogram is measured from the beginning of the Q wave to the point where the T wave ends at the isoelectric line. It is an indication of the total time occupied by ventricular excitation and recovery. Recently, great interest has been evinced in this hitherto neglected feature of the electrocardiogram, and its variations have been reported in a variety of conditions.

A statement in a leading textbook of electrocardiology (Wolff, 1950) that "abnormal Q-T occurs regularly as a result of myocardial injury. If QRS is normal, the prolonged Q-T must signify a profound disturbance in the recovery process" aroused interest in this question, and, as a search of the literature of the subject was barren in its results, this particular study was embarked on.

Clinical Material and Methods

As this study was undertaken to evaluate the significance of the Q-T interval in myocardial infarction particularly, it was decided to rule out all possible variables. For this purpose all the normals which serve as controls were selected from the ages of 40 and above. It was also made absolutely certain that all the normals had no electrocardiographic abnormality. The group of cases of myocardial infarction selected was also carefully scrutinized to exclude any which showed any changes of rhythm, of ventricular hypertrophy, of bundle-branch block, or of hypertensive heart disease, or which demonstrated either erect or inverted U waves. Also, any patient who had had digitalis (Berliner, 1931) or who had been on a regime of mercurial diuretics was discarded.

A total of 600 normal tracings (400 males and 200 females) and 800 tracings of myocardial infarction were studied. All the tracings had been taken on the standard Cambridge string-galvanometer electrocardiogram, by the same individual, with the same standardization (1 mV=1 cm.). In the examination of each tracing a strict routine was adhered to, the tracings being examined under a powerful magnifying-glass. Any tracing which showed any abnormality in the shape or the duration of the QRS complex was discarded, as were also all tracings in which the end of the T wave was not clearly definable. Each Q-T interval was measured from the point at which the Q wave (in the absence of the Q wave, the R wave) left the isoelectric line to the point where the T wave after its excursion returned to the isoelectric line. Each R-R interval was measured from the peak of the R wave of one complex to the peak of the R wave of the next complex.