PHENETHICILLIN AND PENICILLIN G IN ACUTE SUPPURATIVE OTITIS MEDIA IN CHILDHOOD

BY

RONALD ALASTAIR McNEILL, M.B., B.Ch.
F.R.C.S.

E.N.T. Registrar, Royal Victoria Hospital, Belfast

Acute suppurative otitis media is one of the more common acute infections from which children suffer during the winter months. The administration of antibiotics to children has presented practical problems. The intramuscular injection of penicillin to young patients is both painful and unpopular, and is often not a practical proposition in a busy practice. The tetracyclines can be taken orally, but may produce irritation of the gastro-intestinal tract. For these reasons oral penicillin is a popular substitute outside hospital practice. However, the blood levels achieved by oral penicillins V and G are much lower than those achieved by parenteral administration of penicillin G, and many doctors think that adequate blood levels of penicillin cannot be achieved by oral therapy after 2 years of age.

Phenethicillin ("broxil"), which is the potassium salt of 6-(α -phenoxypropionamido)-penicillanic acid, has recently become available. Knudsen and Rolinson (1959) showed that blood levels after the oral administration of phenethicillin were twice as high as those following an equivalent dose of potassium penicillin V, and at least equal to those following an equivalent amount, by weight, of intramuscular penicillin G. Garrod (1960) compared the antibacterial activity of phenethicillin with other penicillins available, and found it was more active than penicillin G against staphylococci but less active against pneumococci and streptococci.

In view of the favourable reports published regarding phenethicillin, it was decided to treat some cases of acute suppurative otitis media with phenethicillin or intramuscular penicillin G, and to compare the results obtained.

Present Trial

All patients included in this trial had been referred to hospital by their general practitioner and were found to be suffering from acute suppurative otitis media. History was taken from a parent or relative on the patient's admission to hospital, and questions were asked regarding previous deafness and otitis media. Only cases of untreated acute otitis media with no previous history of deafness were included in the trial.

In an attempt to obtain uniformity, each case was examined, diagnosed, and classified according to the severity of the infection by one person. On admission, cases were placed alternately on phenethicillin and on penicillin G, irrespective of the severity of the infection. Thus almost equal numbers of cases in each age-group were treated by each antibiotic.

Age Distribution of Patients.—The ages of the children varied from 4 months to 12 years. Altogether 48 patients were treated and their age distribution is shown in Table I: 34 suffered from unilateral and 14 from bilateral acute suppurative otitis media, making a total of 62 ears treated. Of the 48 patients, 26 received phenethicillin and 22 penicillin G. Of the 26 patients

receiving phenethicillin, six had bilateral otitis media, making a total of 32 ears so treated, and of the 22 cases receiving penicillin G, eight were bilateral, making a total of 30 ears so treated.

Clinical Classification.—The 62 ears were classified according to the severity of the infection as follows: group I, tympanic membrane intact, inflamed, but not bulging (18 ears); group II, tympanic membrane intact, but bulging (14 ears); and group III, tympanic membrane perforated, with discharge (30 ears). There were no cases of mastoiditis. The numbers of ears in each group treated with penicillin G and with phenethicillin are given in Table II. A swab was taken of the discharge from each ear in group III and cultured for organisms, and the sensitivity of the organism isolated was tested against phenethicillin, penicillin G, sulphon-

TABLE I.—Age Distribution of Patients Treated

Age in Years:	0-1	2-3	4-5	6-7	8-9	10-11	12
Phenethicillin (26)	2	5	7	5	3	3	1
Penicillin G (22)	1	4	6	6	3	1	1

TABLE II.—Number of Ears in Trial Classified in Treatment Groups

Group	Total	Phenethicillin	Penicillin G
I	18	10	8
II	14	8	6
III	30	14	16

amides, and streptomycin, using the standard disk method. No patient was discharged from hospital until the ear had been dry and the temperature normal for 48 hours. All patients were asked to return for review at the hospital out-patient department one week after discharge from hospital.

Treatment.—Phenethicillin was given in tablet form or as a syrup, in doses of 125 mg. every six hours. Penicillin G was given by intramuscular injection in the following dosage: children up to 5 years, 500,000 units of the crystalline form followed by 300,000 units of the procaine salt twice daily; children of 6-12 years, 1,000,000 units of the crystalline form followed by 300,000 units of the procaine salt twice daily. Each patient was also given penicillin and ephedrine 0.5% nose drops. Treatment was given for six days to each patient.

Results of Treatment

The immediate response of each case was determined by the return of the temperature to normal, the return of the tympanic membrane to normal, and the cessation of pain and discharge.

Temperature.—The response to both antibiotics was rapid, but the temperature settled to normal more quickly in those cases treated with penicillin G. The return of the temperature to normal in terms of days is given in Table III.

TABLE III.—Return of Temperature to Normal in Terms of Days of Treatment

Day:	2	3	4	5
Phenethicillin (26)	2 (7.7%)	8 (30.8%)	12 (46.1%)	4 (15.4%)
Penicillin G (22)	3 (13.6%)	10 (45.4%)	8 (36.3%)	1 (4.5%)

Pain and Discharge.—All patients were free of pain within 48 hours of the beginning of treatment. Most of the ears were dry in 72 hours, and all were dry when the patient was discharged from hospital.

Tympanic Membrane.—The tympanic membrane had returned to within normal limits in all but four cases on discharge from hospital. In two of these, which had been treated with penicillin G, a perforation in the tympanic membrane was present but the ear was dry and painless. On examination in the out-patient department one week later the perforation had healed. In the remaining two cases, which received phenethicillin, the tympanic membrane was indrawn when the patients left hospital.

Follow-up

Assessment of Results.—An attempt was made to review all cases at least three months and not later than six months from the time of discharge from hospital. Each ear was examined for normality of the tympanic membrane, and investigation of hearing function, consisting of whispered-voice tests and pure-tone audiometry, was carried out. For very young children distraction tests were made. The whispered-voice tests were all performed by one person, using the technique described, in an attempt to obtain uniformity. The child was positioned with his back to the examiner to prevent lip-reading, and the ear not being tested was occluded. The examiner then produced a whisper by forced expiration following a normal expiration. Accurate answering at 25 feet (7.6 metres) was regarded as normal. In children who gave variable or inconclusive answers, pure-tone audiometry was performed.

Forty patients attended hospital for review. The remaining eight failed to attend: four of these had been treated by phenethicillin and four by penicillin G. The 40 patients represented 51 ears which had been affected with acute suppurative otitis media. Of these, 27 had been treated by phenethicillin and 24 by penicillin G. One case, which responded satisfactorily to a six-day course of phenethicillin in hospital, developed a further attack of acute suppurative otitis media in the same ear six weeks after discharge from hospital. The patient responded to a further six-day course of phenethicillin.

Out of the 51 ears treated, only two were found abnormal. The histories of these two cases are given in detail.

Case 1.—A 7-year-old girl with group I acute otitis media in her left ear responded satisfactorily to a six-day course of phenethicillin and was afebrile in three days. When discharged from hospital her left tympanic membrane was indrawn, and she had a negative Rinne test on the same side. When reviewed one week later her left tympanic membrane was dull but not indrawn, and her Rinne test was positive. At follow-up four months later the left tympanic membrane was again indrawn, but the Rinne test was positive, Weber's test was not lateralized, and she could hear a whispered voice at 25 feet (7.6 metres). Pure-tone audiometry showed no abnormality.

Case 2.—A 9-year-old girl had group I acute suppurative otitis media in her right ear, and was treated with penicillin G. She responded to treatment which was continued for six days. When she was discharged from hospital her right tympanic membrane was normal in appearance and the hearing tests were within normal limits. One week after her discharge the clinical picture was unchanged. She was next seen three months later, when her right tympanic membrane was found to be indrawn, dull, and scarred. The Rinne test was negative and she could hear a whispered voice only at 15 feet (4.5 metres). A pure-tone audiogram showed a mild conductive deafness. Politzerization was performed, after which a whispered voice could be heard at 25 feet (7.6 metres), and an audiogram was within normal limits; the Rinne test became positive.

Bacteriology

Thirty of the ears with acute suppurative otitis media presented with a perforation and discharge. Swabs were taken of the discharge and the sensitivity of the organisms isolated was determined. The results obtained are classified in Table IV. Sixteen of these ears were treated with penicillin G and 14 with phenethicillin.

TABLE IV.—Organisms and Their Sensitivities, Cultured from Ears with a Perforated Tympanic Membrane and with Discharge

Organisms	No. of Ears	Phenethicillin		Penicillin G		Streptomycin		Sulphonamide	
		Sen.	Res.	Sen.	Res.	Sen.	Res.	Sen.	Res.
<i>Staph. aureus</i> ..	21	20	1	15	6	20	1	13	8
<i>E. coli</i> ..	1	—	1	—	1	—	—	1	—
<i>Pneumococcus</i> ..	2	—	—	2	—	1	—	2	—
<i>Str. viridans</i> ..	1	1	—	1	—	1	—	—	1
<i>Haem. streptococcus</i> ..	5	5	—	5	—	5	—	5	—

Sen. = Sensitive. Res. = Resistant.

The organisms causing the infection in the 16 ears treated with penicillin G were *Staphylococcus aureus* (11 ears), *Streptococcus viridans* (1 ear), *Haemolytic streptococcus* (3 ears), and *Escherichia coli* (1 ear). Of the 11 infections due to *Staph. aureus*, three were resistant on culture while that due to *E. coli* was also resistant. The remaining organisms were sensitive to penicillin G.

Staph. aureus was the responsible organism in 10 of the ears treated with phenethicillin. The pneumococcus and the haemolytic streptococcus accounted equally for the remaining four cases.

Discussion

Numerous reports have appeared in the literature concerning the response of acute suppurative otitis media to a number of antibiotics. Asay and Hartman (1956) treated a series of cases with dibenzylethylinediaminedipenicillin G, a single injection of which is claimed to give therapeutic blood levels for 15 days. They found that 23% of their cases so treated did not respond adequately. Walker (1954) carried out a trial with the same antibiotic but had a 100% response. The disadvantage of this type of therapy in children is the severe and persistent pain experienced at the site of the injection.

Mawson *et al.* (1953) compared the response of acute suppurative otitis media to oxytetracycline ("terramycin") and to intramuscular penicillin G. They found two failures to each antibiotic, but the response was regarded as adequate in each group. No side-effects were observed.

The present investigation was undertaken to compare the clinical response of acute suppurative otitis media to phenethicillin and to penicillin G. From the results obtained it would appear that phenethicillin adequately controls acute suppurative otitis media and has the added advantage over parenteral penicillin G in that no injections are necessary. This is of considerable importance in treating children at home and in hospital, and is of great assistance to general practitioners, who often find that repeated daily injections add greatly to the toils of general practice.

No adverse reaction to either antibiotic was observed during the trial. Those children who were treated with phenethicillin suspension found it palatable, and no

nausea, vomiting, or diarrhoea was observed. This is of particular importance because the tetracycline group of antibiotics, when taken orally, may cause diarrhoea.

It is worth noting that 14 ears had bulging tympanic membranes yet no myringotomy was found necessary during the entire series. Furthermore, no defect of hearing was detected in these ears when reviewed some months after treatment was completed.

Staph. aureus was isolated from the discharge of 70% of those cases presenting with a perforated tympanic membrane. This agrees with the experience of Morrison (1961), who found that the pyogenic staphylococcus was responsible for 66% of the discharging ears in his series. Of the 30 ears in which the offending organism was isolated, five recovered in spite of the fact that the organisms were resistant, by *in vitro* studies, to the antibiotic given. Treatment was continued in spite of the adverse bacteriological report, as the clinical response of the patient was regarded as adequate. This raises the question of the need to give antibiotics in every case of acute suppurative otitis media. Fry (1958) believes that most cases of otitis media will recover without antibiotic therapy. An alternative explanation is that *in vitro* studies may not give conclusive evidence of the sensitivity of the infecting organism in the human body.

The response of the patients, judged by the return of the temperature to normal and by the disappearance of pain and discharge, was somewhat slower to phenethicillin than to penicillin G. However, all cases treated were afebrile and free from otorrhoea and earache after five days' treatment.

The impression gained from observing the response of these patients to phenethicillin is a most favourable one. It would appear to be the treatment of choice in acute otitis media in childhood because it includes the advantages of adequate blood levels obtained by oral administration, with none of the side-effects on the intestinal tract common to other oral antibiotics. Penicillin G would appear to be preferable to phenethicillin in acute suppurative otitis media with mastoiditis because it produces a slightly quicker response.

Summary

A therapeutic trial was conducted to compare the response of children with acute suppurative otitis media to treatment with phenethicillin and with penicillin G.

All cases responded adequately except for two who had indrawn tympanic membranes, but both had normal hearing after treatment was completed.

The response to phenethicillin in the dosage given would appear to be slower than to parenteral penicillin G, but it has the advantage over penicillin G in that oral administration gives satisfactory blood levels without side-effects on the intestinal tract.

I am indebted to Mr. D. H. Craig and to Mr. R. S. McCrae for permission to carry out this trial on their patients, and to Mr. McCrae for much help in conducting the trial and in the preparation of the paper. My thanks are also due to Sister Lavelle for her co-operation in the care of these young patients. The phenethicillin was kindly supplied by Beecham Research Laboratories Ltd.

BIBLIOGRAPHY

- Asay, L. D., and Hartman, G. L. (1956). *J. Pediat.*, **49**, 565.
Daggett, W. I. (1942). *J. Laryng.*, **57**, 427.
Friedman, I. (1957). *Proc. roy. Soc. Med.*, **50**, 406.
Fry, J. (1958). *Brit. med. J.*, **2**, 883.

- Garrod, L. P. (1945). *Ibid.*, **1**, 107.
— (1952). *Lancet*, **1**, 400.
— (1960). *Brit. med. J.*, **1**, 527.
Hodgkin, K. (1957). *Lancet*, **2**, 514.
Johnston, C. M. (1960). *Brit. med. J.*, **1**, 1493.
Knudsen, E. T., and Rolinson, G. N. (1959). *Lancet*, **2**, 1105.
Lewis, R. S., Gray, J. D., and Hewlett, A. B. (1952). *J. Laryng.*, **66**, 142.
Mawson, S., Gray, J. D., and Hewlett, A. B. (1953). *Brit. med. J.*, **1**, 817.
Morrison, A. W. (1961). *Ibid.*, **2**, 8.
Walker, S. H. (1954). *J. Pediat.*, **44**, 50.
Young, A., and Hall, I. S. (1948). *J. Laryng.*, **62**, 551.

DIAGNOSIS OF AMOEBIC COLITIS ON ROUTINE BIOPSIES FROM RECTUM AND SIGMOID COLON

BY

T. A. McALLISTER, M.B., Ch.B.

Senior House Officer (now Registrar), University Department
of Pathology, Western Infirmary, Glasgow

[WITH SPECIAL PLATE]

In the United Kingdom idiopathic ulcerative colitis is one of the commonest causes of recurrent diarrhoea with the passage of blood and mucus in the stools. It can be firmly diagnosed only after exclusion of other conditions such as carcinoma of the colon and the specific dysenteries. Clinicians and bacteriologists are only too well aware of the prevalence of the bacillary dysenteries, and accordingly thorough bacteriological examination is the rule in all suspected cases. Amoebic dysentery is relatively rare, and consequently there is always a danger that the exacting procedures needed for its diagnosis, requiring the co-operation of clinician, nursing staff, and bacteriologist, will not be carried out efficiently. The present paper shows that in a general hospital the routine parasitological investigation of patients with this syndrome is sometimes inadequate to distinguish cases of amoebiasis from non-specific ulceration. The following three cases demonstrate that the histopathologist can on occasion identify or strongly suspect intestinal amoebiasis by examining fixed biopsy specimens from the rectum or sigmoid colon in patients thought to have idiopathic ulcerative colitis.

Case Reports

Case 1

A man aged 53 presented in May, 1960, with a two-months history of severe diarrhoea accompanied by rectal pain and the passage of blood and mucus. He had a poor appetite and had lost 2 stones (12.7 kg.) in weight. Neither he nor his wife had ever travelled outside the West of Scotland; at a later date he recalled that they had both drunk from a horse-trough at Lanark while walking in the country in October, 1959.

He was pale, thin (weight 111 lb. or 50.4 kg.), and slightly febrile, and apart from slight tenderness over the sigmoid colon there was no other physical abnormality. Haematological examination revealed: Hb 11 g. per 100 ml.; W.B.C. 26,700 per c.mm. (neutrophil polymorphs 82%); E.S.R. 62 mm. The stools were unformed and contained blood, mucus, and pus, but repeated bacteriological examination failed to demonstrate any pathogenic intestinal bacteria. Sigmoidoscopy revealed an oedematous mucosa with small bleeding ulcers, but biopsy on two occasions showed a normal mucosa. Barium-enema examination suggested ulcerative colitis of the sigmoid colon, and accordingly treatment with penicillin, succinylsulphathiazole,