(1948) using T.E.A.B. was not found. Stability of the minimal diastolic pressure suggests the relative independence of the nervous and humoral factors in hypertension. The striking difference in the ages of Groups A and C is the only factor with which the response to H.M.B. could be correlated, and it suggests the separation of elderly hypertensives into a distinct aetiological group.

Collateral evidence for this is found in the well-known differences in mortality of hypertension below and above 50 years (Bechgaard, 1946; Burgess, 1948), particularly as the incidence of hypertension increases so strikingly with age, rising from 5% in young adults to 30–40% after the age of 40, and thereafter increasing progressively with age (Master *et al.*, 1943). In contrast to the severity and frequency of changes in the renal arteries of young hypertensives, in elderly hypertensives the lesions have been shown to be mild, and only a little more severe than those seen in subjects of the same age without hypertension (Perera and Krane, 1951).

In the group which failed to respond to hexamethonium it is clear that the autonomic nervous system can play little part in the elevation of the blood pressure at rest, and in this they behave in the same way as experimental renal hypertension. It is concluded that the absence of a response in the case of coarctation of the aorta is evidence that a humoral mechanism is present in this condition.

The evolution of early labile hypertension into a sustained humoral one is not supported by the present findings, but the reverse seems possible. Subjects in the intermediate Group B and those with renal hypertension in Group A may tentatively be said to have had a nervous mechanism superimposed upon a humoral one.

Summary

Hexamethonium was used to investigate a group of 46 cases of hypertension. It was given in repeated doses to produce the maximal fall in diastolic pressure. The results show that the neurogenic component is present in elderly hypertensives and is very uncommon below the age of 50 years.

I acknowledge the co-operation of the staff of Charing Cross Hospital, Drs. R. A. Hickling, K. Shirley Smith, and E. C. Warner, who allowed me access to their cases of hypertension, and to Mr. E. A. Crook and Mr. L. A. Broster for allowing certain of their cases to act as controls. I also thank Dr. A. A. Osman for facilities to investigate cases of hypertension at the Renal Unit, Pembury Hospital, Kent, and Mr. K. Browne for checking the statistical material.

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TERRAMYCIN IN THE TREATMENT OF ACUTE OTITIS MEDIA IN CHILDREN

BY

STUART MAWSON, F.R.C.S.

Surgeon to the Ear, Nose, and Throat Department,
 King's College Hospital and the Belgrave Hospital for Children

J. D. GRAY, M.D.

Pathologist, the Belgrave Hospital for Children

AND

A. B. HEWLETT, M.R.C.S., L.R.C.P.

Clinical Assistant, the Ear, Nose, and Throat Department,
 King's College Hospital and the Belgrave Hospital for Children

It is generally agreed that procaine penicillin, in single daily injections of not less than 300,000 units, is the most reliable means of controlling acute otitis media in children with a minimum degree of supervision. Larger doses of crystalline penicillin at more frequent intervals increase the margin of certainty. Oral penicillin and sulphonamides are less reliable, but they offer advantages of administration which favour their use in certain cases. Lewis *et al.* (1952) assessed the value of chloramphenicol and aureomycin in this disease, but concluded that they were unsuitable for domiciliary treatment because, although as effective as penicillin against the organisms commonly found in acute otitis media, some children took such a strong aversion to them that it was impossible to maintain an adequate dosage.

With the advent of terramycin it was decided to review the position, as this compound appeared to offer certain advantages that might answer the need for an oral antibiotic effective in this disease. Terramycin has a wide range of antibacterial activity, and so far has been reported free from toxicity. It is reasonably stable in flavoured solutions, not unduly bitter to the taste, and can also be given in the form of sugar-coated tablets or capsules. In the absence of any published studies of the action of terramycin in otitis media and of an exact precedent for dosage, a clinical trial was made using 50 mg. of terramycin per kg. of body weight per twenty-four hours, against a control series of cases receiving penicillin.

Method

A two-page form was prepared, the first page containing the history, results of examination, type of treatment, and notes on the bacteriological investigation. The second page showed the patient's name only and a summary of daily progress. When a case of acute otitis media was accepted the necessary parts of the form were completed and the pages separated: the first was retained in the laboratory and the second in the out-patient folder. This was to ensure that the clinical observers (S. M. and A. B. H.), who saw each case from the second day onwards, had no knowledge of which antibiotic was being used for treatment and could therefore rely on the impartiality of their judgment.

All cases were first seen by the same casualty officer, well experienced in the recognition of the disease, who allocated the cases to their respective antibiotic in strict alternation. Myringotomy was performed, regardless of

antibiotic, if it was considered necessary to relieve tension. Penicillin was given in the form of "distaquaine," 1.2 ml. daily for five days; this contains 100,000 units of crystalline penicillin and 300,000 units of procaine penicillin. Terramycin was administered orally for five days in the form of a flavoured elixir, tablet, or capsule—the mode depending on the age of the patient. The daily dose was 50 mg. per kg. body weight split into three portions, one being given after each main meal. Five days was regarded as the minimum safe period of administration, for each antibiotic, to be reasonably certain of avoiding an unextinguished disease due to bacterial "persisters."

Results

Clinical.—The Table shows the effect of the terramycin treatment of acute otitis media in children in comparison with treatment with procaine penicillin. It will be seen

The Effect of Terramycin Compared with that of Procaine Penicillin in the Treatment of Acute Otitis Media in Children

Treatment Groups	Distaquaine (F)	Terramycin
No. of cases	33	35
" " ears affected	42	44
" " unilateral cases	24	26
" " bilateral cases	9	9
Average days' duration before seen	2.6	4.0
Drums intact	34	30
" " perforated	8	14
Myringotomy required	16	9
Average days for:		
Relief of—		
Pain	1.4	1.4
Discharge	2.2	3.5
Ear to return to normal—		
Ear discharge, surgical or spontaneous	8.6	8.6
Ear never discharged	7.0	5.7
Failures	4	4
Mastoidectomies	0	0

that the results are comparable, the apparent failure rate—four cases in each series—being the same. On analysing the incidence of acute otitis media in childhood in relation to age in the 68 cases it was found that it was highest in the 6-year-old group. The Chart demonstrates the age/incidence relationship. It suggests that during the first school

Chart showing incidence of acute otitis media in relation to age.

year exposure of the child to an alteration in its usual bacterial environment plays a part in the causation of this disease. The cases were equally divided between the sexes.

Bacteriological.

Two media were used, blood-agar and blood-crystal-violet agar plates, the second to suppress *Staphylococcus aureus* in order that any underlying haemolytic streptococci could be isolated. Meatal swabs taken as close as possible to the drum were inoculated on each medium.

No. of sterile swabs in presence of an intact inflamed drum	21
No. of swabs giving growth in presence of an intact inflamed drum	9
Coagulase-negative <i>Staph. albus</i>	4
Diphtheroids	1
Coagulase-positive <i>Staph. aureus</i> (1 penicillin-resistant)	4
No. of swabs giving growth in presence of a perforated drum or after myringotomy	29
Haem. strep. in pure culture	14
Coagulase-positive <i>Staph. aureus</i>	7
Haem. strep. and <i>Staph. aureus</i> mixed	5
<i>H. influenzae</i>	2
<i>Str. pneumoniae</i>	1

(1 strain of *H. influenzae* isolated was insensitive to penicillin)

All organisms isolated were tested for sensitivity to both antibiotics using the A.C.P. (1952) disk method. With the exceptions given above, all pathogens were sensitive to terramycin and penicillin.

Penicillin Failures

Case 1.—On the third day of treatment for otitis media of the left ear, acute disease set in on the other, healthy, side, and bilateral myringotomy became necessary. The course of penicillin therapy had to be extended to 10 days before the infection was brought under control.

Case 2.—This case was one of unilateral otitis, for which myringotomy was required. Haemolytic streptococci in pure culture were isolated from the exudate. Two days after the completion of treatment there was a recurrence in both ears, followed by perforation of the drums. A five-day course of terramycin was given, with return of the middle ear to normal.

Case 3.—This was a case of right otitis media with an intact drum. Five days after apparent satisfactory response to penicillin, otitis media recurred; this responded well to a course of terramycin.

Case 4.—Bilateral otitis media with perforated drums and a discharge from which haemolytic streptococci were isolated in pure culture. After five days' treatment there was still a copious discharge from the left ear (no growth obtained on culture). Terramycin therapy was then started, and led to a dry left middle ear with a small healing perforation.

Terramycin Failures

Failure in Cases A and B was due to refusal of the patient to take the antibiotic in any form, the refusals being apparently based on childish antipathy to "medicine."

Case C.—A case of unilateral otitis media requiring myringotomy. Three days after completing the terramycin course bilateral relapse occurred. *Staph. aureus* was recovered from the primary and relapse exudates. This organism was only moderately sensitive to terramycin, but was highly sensitive to penicillin. Substitution of the latter antibiotic gave satisfactory clinical response.

Case D.—A case of unilateral otitis media with a perforated drum and copious discharge from which haemolytic streptococci in pure culture were isolated, equally sensitive to terramycin and penicillin. After two days' terramycin treatment the discharge was sterile and showed signs of abatement. Fourteen days after completion of the antibiotic course there was a recurrence of exudate through the unhealed perforation. A course of penicillin then resulted in cessation of discharge in six days.

Discussion

Of the four failures in the penicillin-treated cases, three responded to terramycin. In the terramycin series, if the two which refused medicine are discounted, the balance of favour indicated by an assessment of the failures rests with terramycin. In all other respects there is little to choose between the antibiotics. We have experienced no real difficulty in administration, nor have we encountered unwelcome side-effects. Terramycin should thus prove a satisfactory antibiotic for domiciliary use, particularly in treating nervous, frightened children whose reaction to a hypodermic needle leaves one exhausted and dismayed at the future prospects, and in those cases in which daily attendance by a doctor or nurse is difficult or impracticable.

Summary

A clinical trial of terramycin in the treatment of acute otitis media in children is reported.

The results indicate that this antibiotic, at a dose of 50 mg. per kg. daily for five days, compares favourably with intramuscular procaine penicillin daily for the same period.

No real difficulty was encountered in the administration of terramycin. Toxic effects were not observed.

We are indebted to Dr. Ivor Marsh, late casualty officer, Belgrave Hospital for Children, for his interest and enthusiasm; to the Medical Research Council Antibiotic Clinical Trials (Non-tuberculous Conditions) Committee; and to Dr. R. K. Phillips, of Pfizer, Ltd., for supplies of terramycin.

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Medical Memoranda

Familial Cystinuria

Cystinuria is an inborn error of metabolism in which the amino-acid cystine, together with lysine and arginine, is excreted in greatly increased quantity in the urine. There is also evidence that some cystine is excreted as a labile precursor of unknown composition which liberates cystine on standing. (In the absence of calculi, cystinuria is a symptomless condition.) The output of cystine is not increased by feeding this amino-acid, as it is excreted as a sulphate. However, if cysteine or methionine is fed there is an increased output of cystine. High-protein diets would therefore seem inadvisable. The factors responsible for keeping cystine in solution in the urine are not yet known, but calculus formation does not seem to be directly related to the concentration of cystine in the urine. It has been reported that solution of stones will take place if the urine is kept at a pH of 7.5 by administration of sodium citrate.

The occurrence of cystinuria in families has recently been reviewed by Dent and Harris (1951). In addition to the 11 families reported in the literature they have collected a further 11. As a result of their study they have put forward the view that cystinuria occurs in three types of case: (1) in the Fanconi syndrome, associated with many other amino-acids; (2) in Wilson's disease (hepato-lenticular degeneration); and (3) "classical" cystinuria, the type considered here, in which there is also an increased excretion of lysine and arginine: several of the cases of this type in the literature were, in their opinion, examples of the Fanconi syndrome.

In the past the detection of cystinuria depended mainly on the recognition of the typical hexagonal crystals of cystine in the urine or on the qualitative cyanide nitroprusside test. Lewis (1932) examined the urine of 10,534 students by the cyanide-nitroprusside test and found an increased quantity of cystine to be present in 1 in 600. It seems likely that the use of the newer and more sensitive methods of chromatography and polarography will bring more cases to light.

FAMILY HISTORY

The family reported here was discovered initially through the finding of cystine crystals in the urine of one member. Subsequent examination of the urine of all available members of the family by the cyanide-nitroprusside test and the methods of paper chromatography and polarography brought one further case to light.

The family tree, showing ages of members and presence or absence of cystine in the urine.

Case 1.—A retired coach-driver aged 51 was operated on for removal of bladder stones at the ages of 6, 14, and 25 years. He had a right nephrectomy for "staghorn" calculus in 1943. He was admitted to St. Mary's Hospital in January, 1951, for treatment of cardiac failure following myocardial infarction in May, 1948. On routine treatment he complained of a burning pain on micturition. Microscopical examination of the urine revealed cystine crystals. The cyanide-nitroprusside test was positive and paper chromatography showed an increased excretion of cystine, lysine, and arginine. An x-ray picture of the bladder showed two stones.

Case 2.—A younger brother (aged 42) of Case 1. There is no history of renal or cystic calculus. His only symptoms are those due to a peptic ulcer. Paper chromatography showed the same abnormal pattern of amino-acid excretion as in Case 1.

In both these cases polarographic studies (Reed, 1942) suggested that the output of cystine was about 0.5 g. a day. The range of output in normal persons is 40–80 mg. in 24 hours. In cystinurics the range has been given as 0.4–1.8 g. in 24 hours.

The investigations of Dent and Harris tend to show that classical cystinuria is inherited through a simple recessive factor or is a heterozygous condition with irregular manifestation. The family history reported here would fall into either of these forms of inheritance.

I am indebted to Dr. J. W. Litchfield for permission to publish this case report, and to Dr. H. Harris and Professor F. L. Warren for examining the urine by chromatography and polarography at University College, London.

P. O. WILLIAMS, M.B., M.R.C.P.

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Blackwater Fever Treated with Cortisone

CASE REPORT

A Yoruba boy aged 19 months suddenly became ill at 11 a.m. on August 25, with a high fever, and was given an injection of quinine before admission to hospital the same day. He had been quite well, apart from having attacks of fever at varying intervals since birth, for which he had always received quinine. This treatment had apparently terminated the fever rapidly on each occasion.

On admission he was in a collapsed condition; his temperature was 104° F. (40° C.), his pulse 140 and of a poor volume, but he appeared to be well nourished. The mucous membranes were very pale and no icterus was noticed at the time. The heart was apparently normal. In the lungs scattered sibili were audible. The spleen was palpable three fingerbreadths below the costal margin, and the edge of the liver was just palpable. At 11.30 a.m. he passed 10 ml. of almost jet-black viscid urine, and methaemoglobin was demonstrated spectroscopically. The haemoglobin was 4.8 g.%, and a blood film showed large numbers of *Plasmodium falciparum* trophozoites. On August 26 he appeared to be moribund. The conjunctivae were icteric, and his general condition had deteriorated. By 3.45 p.m. only 1 oz. (28 ml.) of black urine had been passed since the last specimen was collected at 11.30 a.m. on the previous day.

Cortisone, 100 mg., was given intramuscularly, and at 8 a.m. on August 27 there was a noticeable clinical improvement: the child sat up and ate; his temperature was 97.2° F. (36.2° C.), and his pulse 94. He had taken 70 oz. (2 litres) of fluid in the past 24 hours and was known to have excreted 8½ oz. (240 ml.) although he had been incontinent since 3.45 p.m. on August 26. The first three specimens following the injection of cortisone were dark, but were lighter than previous specimens, and the next three