was small (60 mg. daily). More important was an intrinsic defect in our method of assessment, which resulted in the apparent superiority of the placebo to the drug. We think that the explanation lies in the stimulant effect of the drug (equivalent to Feldman's observation of "turbulence"), which made the patient's mental disturbance more obvious in the interview situation. That this can also be true of reserpine we can confirm from personal experience. But, even allowing for these criticisms of our method, our results do suggest that azacyclonol is unlikely to be a very useful drug in the treatment of chronic schizophrenia.

The results of our clinical trial seem promising enough to warrant a more extensive trial of the drug in cases of acute schizophrenia and alcoholic hallucinosis. One difficulty in evaluating drug therapy of such acute cases is that a proportion remit spontaneously and no precise criteria are yet available for indicating which patients should have azacyclonol. Some later American papers—for example, Cohen and Parlour (1956)—suggested that azacyclonol had very little anti-hallucinatory effect. Our experience suggests that hallucinatory experience of recent onset, whether schizophrenic or toxic, is an indication for treatment with azacyclonol.

The only report of any toxic side-effect of azacyclonol is contained in the paper by Forster and Henderson (1957). They found elevation of the non-protein nitrogen in 11 out of 18 patients treated with azacyclonol. We have found similar changes in two patients. One of these was later shown to have signs indicative of chronic nephritis. However, the blood urea nitrogen did fall later to near normal levels when the dose of azacyclonol was reduced.

Summary

We have described a controlled trial of azacyclonol in 40 chronic schizophrenic patients. The results suggest that azacyclonol is not going to be of great value in the treatment of this type of patient.

We subsequently treated 18 patients (16 schizophrenics, 2 toxic hallucinatory states) with azacyclonol. The illness was of more recent onset in these patients than in those involved in the controlled trial: 13 patients improved and 6 have since left hospital.

Our clinical impression is that azacyclonol has a central stimulant action and that part of the poor result of the drug in the controlled trial was due to the masking effects of excitement and overactivity.

The only toxic effect observed was a rise of blood urea nitrogen in two patients out of a group of four who were subjected to detailed study. In one patient the elevation was not of significant degree, and in the other patient evidence of chronic nephritis was later established.

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Plans of the new building for the National Library of Medicine, Washington, provide for a five-story building with accommodation for 1,290,000 volumes (a little more than double the present number).

TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH ORAL PHENOXYMETHYLPENICILLIN

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With the preparation of phenoxymethylpenicillin in 1947 by Behrens and his co-workers an important stable oral form of penicillin was introduced. Effective absorption and therapeutic blood levels have been reported by many observers (Wright *et al.*, 1955; Martin *et al.*, 1955; Rinsler and Cunliffe, 1956; Holborrow *et al.*, 1956). A number of diseases have been successfully treated with the drug, including pulmonary infections (Hart *et al.*, 1956), beta-haemolytic streptococcal infections (Breese and Disney, 1956), dental abscesses (Hermann, 1955), and gonorrhoeal urethritis (Marmell and Prigot, 1956; Love and Weir, 1956). In subacute bacterial endocarditis clinical experience with phenoxymethylpenicillin is more limited. A cautious approach is necessary in treating a condition which a relatively short time ago was associated with such a high mortality, and which responds so favourably in most cases to parenteral penicillin. This disease can be successfully treated by oral phenoxymethylpenicillin, however, as is shown by the two cases described, in one of which it was the sole form of antibiotic therapy.

Case 1

A female domestic worker aged 37 presented with a two-weeks history of headache, malaise, loss of energy, sore throat, joint pains, anorexia, vomiting, and fever. She gave a past history of acute rheumatic fever at the age of 24, when she was confined to bed for four months.

On examination she was pyrexial and had dental caries. Her fingers were clubbed. She had a sinus tachycardia, the characteristic murmurs of mitral stenosis and regurgitation, and moderate cardiomegaly, but no evidence of congestive cardiac failure. Her spleen was not palpable.

Investigations.—Haemoglobin, 8.1 g./100 ml.; leucocyte count, 12,000/c.mm.; E.S.R. (Westergren), 65 mm. in the first hour; microscopy of the urine showed red blood cells; x-ray examination of the chest showed a mitral cardiac configuration with increased pulmonary vascular markings; electrocardiogram showed notched P waves. Six blood cultures were negative, and this may have been due to a three-day course of sulphonamides just before admission to hospital, but the seventh yielded a growth of *Streptococcus viridans*.

Treatment was begun with intramuscular injections of crystalline penicillin, 500,000 units six-hourly, and this dose was gradually increased over two weeks to 3,000,000 units six-hourly in view of the persistence of pyrexia and elevation of the E.S.R.

Soon after parenteral therapy was started local pain and tenderness occurred at the injection sites, and was associated with progressively increasing bruising and oedema. The temperature remained high and a two-weeks course of streptomycin, 1 g. intramuscularly daily, was given, but with no effect on the raised temperature. At this time, because

of the severity of the local reactions to the injections, all parenteral therapy had to be stopped and oral penicillin started instead.

The potassium salt of phenoxymethylpenicillin was given, 399 mg. four-hourly by mouth, together with probenecid, 0.5 g. six-hourly. The potassium salt was given in preference to the free acid, as it produces higher peak concentrations (Colquhoun *et al.*, 1957). The temperature and

Chart showing antibiotic therapy and temperature in Case 1.

E.S.R. began to fall. Two weeks later the dose of potassium phenoxymethylpenicillin was increased to 1,064 mg. six-hourly, the probenecid being discontinued, and an uneventful convalescence ensued (see Chart). In spite of the very large doses of oral penicillin used, no gastro-intestinal or other toxic side-effects occurred. During the latter part of her convalescence dental treatment was successfully carried out. The patient was discharged after two months, and phenoxymethylpenicillin-free acid, 500 mg. four-hourly, was continued for the subsequent six months, during which the patient was kept under observation in the out-patient department.

Case 2

A housewife aged 46 was first seen complaining of a persistent attack of "bronchitis" for five months, associated with a productive cough, loss of energy, headaches, and shivering attacks. She had lost 12.7 kg. (28 lb.) in weight over the previous three months. She had rheumatic fever at the age of 19 years and was then in bed for three months.

On examination she was febrile, very emaciated, weighing only 28.6 kg. (63 lb.), and had marked pallor of her face and mucous membranes. Her fingers were clubbed and she had a typical Osler node in the pulp of her left middle finger. Her teeth were carious. She had a sinus tachycardia and a loud, blowing systolic murmur, maximal at the apex of the heart, with moderate cardiomegaly. There was no definite evidence of mitral stenosis, or any signs of congestive cardiac failure. Examination of her lungs indicated bilateral basal consolidation. The spleen was not palpable.

Investigations.—Haemoglobin, 12.7 g./100 ml.; leucocyte count, 12,000/c.mm. (76% polymorphonuclears); E.S.R. (Westergren), 70 mm. in the first hour; microscopy of the urine showed many red cells; x-ray examination of her chest showed bilateral basal shadowing consistent with partial collapse or consolidation; the electrocardiogram was normal; blood culture at the time of admission yielded a growth of *Strep. viridans*.

Treatment was begun with phenoxymethylpenicillin-free acid, 240 mg. two-hourly by mouth. Ten days later her temperature had become normal and her clinical condition was improving. The dose was then increased to 0.5 g. two-hourly, and two days later probenecid, 0.5 g. six-hourly, was added. Treatment was continued for a further six weeks, during which time rapid progress was made. The patient was discharged to continue phenoxymethylpenicillin, 240 mg. four-hourly. During the latter phase of convalescence,

dental treatment was successfully carried out. Just before discharge from hospital the typical murmur of mitral stenosis became audible.

Serum Penicillin Levels

The estimation of serum penicillin levels was done by dilutions in phenol-red-glucose serum medium (May *et al.*, 1947).

In Case 1 the infecting *Strep. viridans* was sensitive to 0.06 unit of penicillin per ml. The Table shows the serum penicillin levels attained with parenteral penicillin and with different doses of oral phenoxymethylpenicillin with and without probenecid. It will be seen that the intramuscular dose of 3 mega units of crystalline penicillin produced a level of 64 units after one hour, which was more than adequate to deal with the invading streptococcus, but the temperature still remained elevated. Increasing doses of phenoxymethylpenicillin were given to assess whether the serum penicillin levels produced would be adequate therapeutically. With doses of 60 to 500 mg. the half-hour levels of 0.03 to 0.06 unit/ml. were barely adequate, although in every case the two-hour level was sufficient. With a 1-g. dose a half-hour level of 8 units/ml. was produced and a two-hour level of 2 units/ml. In view of these results it was considered advisable to maintain treatment with a dose of potassium phenoxymethylpenicillin of 1,064 mg., rather than with the initial dose of 399 mg. With the addition of probenecid, however, high blood levels of 16

Serum Penicillin Levels

Type of Penicillin	Route	Dose	Dose of Pro-benecid	Serum Penicillin Levels (units/ml.)			
				½ hr.	1 hr.	2 hr.	4 hr.
Case 1							
Benzylpenicillin G ..	Intra-muscularly	3 mega units	0	—	64	—	—
Phenoxymethylpenicillin potassium salt ..	Oral	399 mg.	2 g. daily	—	16	—	4
Phenoxymethylpenicillin-free acid ..	Oral	60 mg.	0	0.03	—	1.0	—
		120 "	0	0.06	—	2.0	—
		250 "	0	0.03	—	2.0	—
		500 "	0	0.06	—	2.0	—
		1 g.	0	8.0	—	2.0	—
Case 2							
Phenoxymethylpenicillin-free acid ..	Oral	60 mg.	0	0.03	—	0.5	—
		120 "	0	0.25	—	0.25	—
		240 "	0	0.5	1.0	0.5	—
		240 "	2 g. daily	—	1.5	—	—
		500 "	0	0.5	3.0	0.06	—
		500 "	2 g. daily	—	4.0	—	—
		1 g.	0	4.0	4.0	—	—

units/ml. and 4 units/ml. at one and four hours respectively could be produced with this latter dose.

The Table shows the serum penicillin levels in Case 2 with increasing doses of phenoxymethylpenicillin-free acid and also the effect of adding probenecid in two instances. The infecting *Strep. viridans* was sensitive to 0.15 unit of penicillin per ml. The 60-mg. dose produced inadequate, and the 120-mg. dose produced barely adequate, blood levels. With larger doses the penicillin levels showed a progressive increase and a greater persistence, and the addition of probenecid raised the levels, from a one-hour level of 1 to 1.5 units/ml. with a 240-mg. dose and from 3 to 4 units/ml. with a 500-mg. dose. This patient, therefore, was given a maintenance dose of phenoxymethylpenicillin-free acid of 500 mg. two-hourly, together with probenecid 2 g. daily in view of the satisfactory blood levels produced by this regime.

It will be seen from the Table that effective therapeutic blood levels can be easily attained and maintained by adjustment of the dose of oral penicillin, given with the addition of probenecid if necessary, provided the sensitivity of the infecting organism to penicillin is high.

Discussion

There are reports of successful treatment of subacute bacterial endocarditis with phenoxymethylpenicillin. Quinn *et al.* (1956) describe four cases, in two of which a *Strep. viridans* infection was treated successfully with 7.2 g. daily for six weeks. In the third patient the infection was due to a species of *Neisseria*, and treatment comprised oral phenoxymethylpenicillin together with parenteral streptomycin and dihydrostreptomycin. The fourth case was less successful owing to a penicillin-resistant *Micrococcus pyogenes*. Martin *et al.* (1956) treated two cases successfully with doses of 12,000,000 units daily, supplemented with intramuscular streptomycin.

In the two cases reported here the use of oral penicillin was indicated by the difficulties associated with parenteral therapy. The first patient was beginning to respond favourably when intramuscular penicillin had to be abandoned owing to local reactions following the mechanical trauma of injections. The persistence of pyrexia in this patient, when the infecting organisms showed such a marked sensitivity to penicillin and the penicillin blood levels seemed quite adequate therapeutically, was thought to be due to the extensive tissue destruction associated with these local reactions. The rapid fall of temperature on withdrawal of injections tended to confirm this. In Case 2 parenteral therapy was not used at all, as the severe emaciation and loss of muscle tissue, especially of the buttocks, contra-indicated a prolonged course of frequent injections. The high sensitivity of the infecting organism to penicillin and the therapeutic blood levels attainable with phenoxymethylpenicillin (see Table) were additional indications for this form of therapy. Though the use of phenoxymethylpenicillin may be associated with gastro-intestinal side-effects, they did not occur in these two patients, even with a prolonged course of treatment.

The two important considerations in the treatment of subacute bacterial endocarditis are the production of frequent high peaks of penicillin concentration in the blood (Finland, 1954; *Lancet*, 1954) and a prolonged course of therapy lasting at least four to six weeks (Bloomfield, 1950; Cates and Christie, 1951; Hunter, 1951), although satisfactory results have been claimed with shorter courses of penicillin (Hamburger and Stein, 1950). Among the factors predisposing to relapse is a short course of treatment (Cates and Christie, 1951). Whereas phenoxymethylpenicillin cannot produce penicillin blood concentrations comparable to those of parenteral penicillin, it does offer an easy and effective method of continuing therapy after discharge from hospital, and consequently of reducing the risk of relapse. With parenteral penicillin the difficulties associated with a prolonged course of out-patient treatment are self-evident.

Whereas the immediate results of therapy in both these patients have been completely satisfactory, long-term observation is required to see that these results are maintained. The first patient has been under observation for six months with no recrudescence of infection while on a prophylactic dose of 240 mg. four-hourly. The second patient is on the same prophylactic dose and has been followed up for two months after discharge from hospital.

Summary

The use of oral phenoxymethylpenicillin in two cases of subacute bacterial endocarditis due to a penicillin-sensitive *Streptococcus viridans* is described. In one case treatment was initiated with parenteral crystalline penicillin and maintained with phenoxymethylpenicillin for nine months, and in the other the oral preparation was used alone for three months. No gastro-intestinal or other side-effects occurred. The importance of penicillin blood concentrations and duration of treatment is considered.

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DETERMINATION OF PEROXIDASE IN URINE

SIMPLE METHOD FOR ROUTINE EXAMINATION OF URINE FOR ERYTHROCYTES AND LEUCOCYTES

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In diseases characterized by the presence of pathological amounts of erythrocytes and leucocytes in the urine (infections of urinary tract, tumours, calculi, nephritis, renal infarction, etc.) the correct diagnosis is generally easy if these cells or other protein are found in such quantity that a routine protein test is positive, indicating need for further examinations. If the number of cells is so small that the routine test is negative, microscopy of the centrifuged deposit will prove necessary for the diagnosis. When the symptoms do not suggest the diseases in question, however, this examination is often overlooked in routine consultation work, to the detriment of correct diagnosis. Unfortunately the local symptoms indicating the answer are fairly often absent. Infections of the urinary tract constitute an example in point, and they rank first among the diseases in question in regard to incidence.

At the Third Medical Clinic of the University of Helsinki an accurate routine examination was made of the urine of every female patient admitted. Infection of the urinary tract was diagnosed in 147 (13.1%) of 1,141 patients; symptoms suggestive of the disease were felt by only 35.4% of the patients in whom it was diagnosed (Halonen and Halonen, 1950). However, a routine examination calling for the centrifugation and microscopy of the urine is a fairly laborious task for the practising physician to perform for each patient. There should be a simpler method of determining the pathological erythrocyte and leucocyte count of urine.