GENERAL AND LOCAL ADMINISTRATION OF PENICILLIN

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PENICILLIN in earlier work (Chain et al. 1940, Abraham et al. 1941) showed promise of being a powerful weapon against the common forms of sepsis. Certain of the basic biological and chemical facts which must be known about a chemotherapeutic substance before it can be used on man were established. To ensure the greatest effect these facts must always be kept in mind when the drug is used for the treatment of patients.

A reasonably stable impure sodium salt of penicillin can be made. This substance is extremely soluble in water but is destroyed by boiling, by acids and alkalis, by certain heavy metals, by oxidising agents and by enzymes produced by air and other bacteria. Penicillin is bacteriostatic and not bactericidal, at least in concentrations likely to be used therapeutically, and reliance must therefore be placed on the body defences, both humoral and cellular, to destroy the bacteria present in a lesion while penicillin prevents their multiplication. Pus, blood, serum and tissue autolysates do not interfere with the antibacterial action of penicillin and the number of organisms present has little or no effect on its capacities. Leucocytes will live and tissue cultures will grow in the presence of a concentration many times greater than that necessary to produce bacteriostasis. Mice will tolerate without toxic symptoms a dose much in excess of that which will produce bacteriostasis in their blood, and artificially induced infections in mice can be controlled by repeated injections of penicillin.

The few therapeutic trials already reported indicated that no serious toxic symptoms need be anticipated in man. They also showed that penicillin is rapidly excreted by the kidneys in a high concentration so that large doses must be given to maintain a bacteriostatic level in the blood. A larger therapeutic trial, based on these general principles, is reported here. The investigation has called for the coördination of many separate efforts.

The production of much of the penicillin used is due to the work of Mr. G. Glister, with the assistance of Miss P. McKegney Miss R. Callow, Miss B. Cooke, Miss M. Lancaster and Miss P. Gardiner. Dr. A. G. Sanders and Mr. J. Kent have been responsible for constructing and working a laboratory large-scale extraction plant. We are also indebted to ICI (Dyestuffs) Ltd. for part of the penicillin used. The many physicians and surgeons who have placed their cases at our disposal for penicillin treatment have been responsible for the diagnosis and general care of the patients and for such surgical interventions as were necessary; their names are given in the case-records. For the bacteriological investigations which have furnished some of the essential criteria for assessing the action of penicillin we are indebted to Dr. A. M. McFarlan, Dr. Joan Taylor, Dr. R. L. Vollum, Dr. Kingsley Smith and Dr. M. A. Jennings; and for the blood examinations to Dr. R. G. Macfarlane and Dr. J. R. P. O'Brien.

Cases treated by General Administration

In this series attention has been directed to (1) methods of administration and dosage; (2) possible toxic effects, especially on the bone-marrow and kidney after long administration; (3) changes in the bacteriological content of the lesions during treatment; and (4) the course of the disease. It has been considered desirable to have at least a sufficient amount of pencillin always present in the blood to exert a complete inhibition of growth of the organism causing the disease. At first reliance was placed on the "ring" test, but this was not sufficiently sensitive and in the later cases a modification of the slide-cell technique (Wright and Colebrook 1921) was used. Dr. N. G. Heatley was responsible for the elaboration of this test.

BY MOUTH

For a course of treatment likely to extend over many days in a patient seriously ill administration by mouth would usually be the most convenient. Penicillin is absorbed from the intestinal canal, but the acid gastric juice will destroy at least part during its passage through the stomach. This might be avoided by enclosing the drug in a suitable capsule or possibly by using a duodenal tube. Some enteric capsules were prepared by coating gelatin capsules containing 10,000 or 20,000 units of penicillin with cellulose acetate phthalate (supplied by Eastman Kodak Co.), which is soluble in alkaline but not in acid media.

A normal person swallowed a capsule containing 10,000 units just before breakfast. Hourly samples of blood were taken for 3 hours and of urine for 7 hours. The plate and cylinder ring test was used for detecting bacteriostasis. The blood showed a trace of inhibition of the test staphylococcus at 1 hour and definite inhibition at 2 hours; there was none at 3 hours. In the urine, inhibition was present at the end of the first hour and penicillin was still being excreted at the end of 7 hours when observations were discontinued. When this experiment was repeated the capsule (containing 20,000 units) did not burst till 5 or 6 hours after ingestion. Urine samples up to the fifth hour were negative but at the sixth hour well-marked inhibition appeared.

In order to carry out a similar investigation over several days a patient (case 1) was chosen who was receiving no other treatment and who might benefit from penicillin.

CASE 1.—*Facial and orbital cellulitis.* (Radcliffe Infirmary. Mr. H. Whitelocke.) Male, age 42, weight about 160 lb. Pimple on nose 3 weeks before had led to cellulitis extending from alæ nasi to top of forehead and into right orbit, producing loss of sight, proptosis and immobility of eye, with some delirium. During week's observation when no penicillin was available temperature and pulse-rate fell gradually to maximum of 99·6° F. and 96 per min.

Bacteriology.—*Staphylococcus aureus* (coagulase +ve) grown from lesion on nose and pus from right orbit.

Method of penicillin treatment.—By mouth: in capsule for first 5 days; by duodenal tube on days 6 and 7.

Day	*Dose*	*Blood bacteriostasis (ring test)*
1 ..	5000 units 2-hrly. ..	Trace
2–5 ..	10,000 ,, 4-hrly. ..	Trace
6 and 7 ..	10,000 ,, 4-hrly. ..	Trace
	Total: 480,000 units.	

Progress.—Inflammation of face subsided and proptosis and œdema of right eyelids lessened. An orbital cellulitis was still present, with secondary intraocular infection and hypopyon ulcer of the cornea. Tenderness and swelling of right knee developed on 3rd day but had almost completely subsided by 7th. Patient apyrexial when penicillin discontinued but eye condition had not subsided; 16 days later pyrexia and signs of meningitis developed and *Staph. aureus* cultivated from cerebrospinal fluid. Treated with sulphathiazole and eventually recovered, eye being enucleated. No albuminuria throughout.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	3,500,000 ..	65 ..	15,000 ..	24
At end of Tt. ..	3,200,000 ..	60 ..	18,000 ..	29

Tt. = treatment.

Comment.—Little was learnt from this case owing to the inadequacy of the bacteriostatic tests on blood in use at the time. That some absorption of penicillin took place was shown by the constant presence of penicillin in the urine. The patient's condition improved during treatment but little stress can be laid on this. Though he was apyrexial at the end of treatment the staphylococci had not been eliminated as his subsequent history showed. No toxic effects were noted.

CASE 2.—*Actinomycosis of lungs and possibly of gastro-intestinal tract.* (Radcliffe Infirmary. Dr. F. G. Hobson.) Male, age 36, weight 117 lb. Attacks of abdominal pain for 13 months. Swelling of left loin, pleural effusion, and cough with sputum which was ameliorated by potassium iodide and postural drainage. Apyrexial when admitted for penicillin treatment but complained of cough and weakness. Swelling in loin and pleural effusion had subsided some time previously.

Bacteriology.—Actinomyces often found in sputum and present in fæces. Organism was sensitive to penicillin.

Method of penicillin treatment.—In solution by duodenal tube passed through nose and kept in position continuously. The 4-hourly dose was 10,000 units on days 1–4 and 20,000 units on days 5 and 6; total 480,000 units. Blood bacteriostasis (ring test) was slight at 1 hr. only with both dosages.

Progress.—During treatment patient developed constant running of nose, loss of appetite, diarrhœa and colic. Sputum still contained actinomyces a week after end of treatment. Diarrhœa persisted. No albuminuria throughout.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	3,300,000	54	10,000	25
At end of Tt.	3,400,000	58	14,000	40

Comment.—Administration by duodenal tube was here a failure. Using the ring test no well-marked inhibition could be demonstrated in the blood, though penicillin was constantly present in the urine. There was evidence of gastro-intestinal irritation but as the nose was also running it is not clear that this was due to the penicillin. The drug had no effect on the course of the illness.

INTRAVENOUS AND INTRAMUSCULAR

After case 2 it was decided to abandon for the time being further attempts to give penicillin by mouth.

CASE 3.—*Osteomyelitis.* (Radcliffe Infirmary. Dr. Leonard Findlay.) Male, age 2 months, weight 7½ lb., weight at birth 6 lb. Osteomyelitis of 2nd and 3rd lumbar vertebræ with sinus formation developed after unsuccessful lumbar puncture. After 3 weeks secondary foci appeared successively in L. femur, L. index finger and nape of neck, latter accompanied by rigidity and head-retraction. X rays showed progressive bony lesions of lumbar vertebræ and periostitis of femur, with dislocation of femur from acetabulum. Finger showed some bony involvement but nothing abnormal seen radiologically in cervical vertebræ. Apathetic, very thin, gaining weight at 3½ oz. a week. Sulphapyridine proved ineffective; 6 days' administration of sulphathiazole lowered evening temperature to 100° F. from previous 103° F., but pyogenic lesions continued to progress.

Bacteriology.—*Staph. aureus* in pure culture obtained from lumbar and cervical lesions and finger.

Method of penicillin treatment.—Intramuscular injection. Two intravenous doses given into sagittal sinus. Local treatment of abscesses carried out by aspirating pus and injecting penicillin solution. Dosage: 1st–5th days, 250 units in 1 c.cm. 4-hourly; 6th–9th days, 500 units in 1 c.cm. 4-hourly; 10th–20th days, 1000 units in 1 c.cm. 4-hourly. In addition, 2000 and 3000 units were given intravenously on the 10th and 11th days and from the 3rd to the 8th day a solution of 250 units per c.cm. was injected into the abscesses in the neck and finger, after aspiration of the pus. Total: 100,800 units.

Progress.—Slight improvement in first 9 days; rapid improvement when dose raised to 1000 units 4-hourly. After 8 days (5 days of local treatment) no pus could be withdrawn from neck or finger. At end of 20 days' treatment neck swelling had disappeared, finger swelling was much reduced and soft-tissue swelling in lumbar region had subsided. Limited voluntary movement had returned in L. hip. X ray showed no evidence of further spread of bony lesions. Gaining 10 oz. a week and lively.

Three months after end of treatment baby's condition excellent. At 6 months of age weighed 14 lb.; lumbar deformity considerably less; no swelling or stiffness in neck and moved L. thigh as well as R. X ray showed bony consolidation in spine and resolution of periostitis in femur. At 9 months no visible deformity except for flattening of normal lumbar curve; X rays revealed still further progress in bone formation; looked healthy and active.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	2,960,000	56	17,000	..
4 days after end of Tt.	3,400,000	66	13,000	32
14 days after end of Tt.	3,860,000	72	14,000	..
4 months after end of Tt.	..	..	..	32

Urine.—High concentration of penicillin constantly present during treatment. No albuminuria.

Comment.—This case showed the practicability of the intramuscular route. A widespread staphylococcal infection, involving bone, was controlled and no toxic symptoms were noted from the drug.

CASE 4.—*Pelvic abscess.* (Radcliffe Infirmary. Prof. Chassar Moir.) Female, age 23, weight about 100 lb. Admitted 3 weeks earlier with pelvic pain, vaginal hæmorrhage and pyrexia after self-induced abortion. Condition had steadily deteriorated and abscess in pouch of Douglas opened 4 days before penicillin treatment started. When treatment began had great abdominal distension and was extremely exhausted, able to speak only few words in a whisper. Temperature erratic, mainly between 99° and 102° F. Pulse weak, fast and variable. Had received repeated blood-transfusion—6 pints in all—and 2 courses of sulphapyridine.

Bacteriology.—Pus aspirated from pelvic abscess grew actinomyces and anaerobic streptococci.

Method of penicillin treatment.—Intravenously for 4 days, at first into blood-transfusion tube and later directly into a vein. Intramuscularly for 2 days.

Day	*Dose*	*Blood bacteriostasis (ring test)*
1–4	35,000–40,000 units in 10 c.cm. intraven. 12-hrly.	Present at 2 hr.; absent at 7 hr.
5 and 6	17,500 in 10 c.cm. intramus. t.d.s.	
	Total: 412,000 units.	

Continuous duodenal drainage established to relieve distension.

Progress.—No effect on pulse, temperature or respiration. Nine days after discontinuing penicillin another abscess discharged into vagina; culture still showed actinomyces and anaerobic streptococci as well as *Strept. fœcalis* and *Bact. coli.* Made slow recovery and discharged convalescent in 10 weeks.

Comment.—This case showed that doses as large as 40,000 units could safely be given intravenously but that such doses given twice daily did not maintain constant bacteriostasis in the blood. It is therefore not surprising that no effect was produced on the bacterial cause of the illness. The evacuation of pus from the pelvis was enough to account for the patient's recovery. No toxic symptoms were noted.

INTRAMUSCULAR ONLY

The next case was treated by more frequent injections.

CASE 5.—*Chronic osteomyelitis of ischium and femoral neck; infection of urinary tract.* (Radcliffe Infirmary. Mr. Abernethy). Male, age 6½ years, weight 36 lb. Eleven months earlier developed osteomyelitis of R. ischium with subsequent sequestrum formation associated with abscess in R. buttock. Sinus formed and still discharging after 7 months. A week before penicillin treatment begun second sinus appeared and urine contained blood and pus cells. No radiological evidence that destruction of bone had progressed during past 7 months but head of R. femur was subluxated and could only be kept in joint cavity by abduction frame. Considerable soft swelling of thigh. Temperature usually normal for several months but pulse fluctuated daily between 84, 120 and 130 per min. Thin and pale.

Had received three 3-day courses of sulphanilamide—8, 6 and 8·5 g. during 3 weeks, without obvious immediate effect. Abscess of buttock incised and sequestrum removed.

Bacteriology.—*Staph. aureus* and *Strept. pyogenes* grown from sinuses and *Staph. aureus* from urine.

Method of penicillin treatment.—For 21 days given 9000 units in 1 c.cm. 6-hourly intramuscularly. Total: 755,000 units.

Progress.—Hyperæmia round sinus mouths diminished by 3rd day of treatment; fresh sinus closed within a week and old sinus in 2 weeks. After beginning of treatment temperature never rose above 98·4° F. and pulse-rate though variable remained between 80 and 90 for several days at a time. Urine still contained pus cells though they were fewer. Urine cultures sterile 2 days after penicillin was discontinued; thereafter weekly cultures of non-catheter specimens produced only *Bact. coli* or *Staph. albus.* Splints left off 6 weeks after penicillin first given and 9 weeks later dislocation had not recurred; considerable movement in joint though flexion limited. Not supposed to walk without crutches but often seen kneeling up in bed or walking with support of furniture. Soft swelling of thigh remained and not satisfactorily explained. Boy gained 16 oz. during 4 weeks after first administration of penicillin and thereafter at rate of 5½ oz. a week for remaining 2½ months in hospital. Urine sterile on discharge. General appearance greatly improved.

Walking 4 months after treatment began, mobility of hip-joint showing continuous improvement.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
Before Tt.	3,500,000	66	7000	26
7th day of Tt.	4,200,000	70	9000	24
At end of Tt.	4,400,000	74	7000	30

Comment.—It was not thought justifiable to trouble this child by blood sampling, but the clinical recovery showed that the 6-hourly injections maintained sufficient bacteriostasis in the blood. The practicability of long continued intramuscular injection was shown, since no local disturbance was experienced at the site of injection. No toxic effects were noted from the drug. Since the only other treatment given besides the penicillin was splinting, which had been in use before, it is reasonable to attribute the satisfactory clinical result to the drug.

CASE 6.—*Acute osteomyelitis of tibia.* (Wingfield-Morris Hospital. Mr. Scott, Mr. Trueta.) Female, age 6 years, weight 36 lb. Had had pain and swelling of L. leg and pyrexia for 3 days. No radiological evidence of bony lesion yet, but diffuse tender swelling of lower third of L. leg extending to below malleoli, with some redness over external malleolus. No fluctuation. Child flushed with hot dry skin; restless and plaintive. Temperature steady around 102° F. Had received 6 g. sulphanilamide followed by 4 g. sulphathiazole, discontinued 8 hours before penicillin begun.

Bacteriology.—On 3rd day of penicillin treatment *Staph. aureus* (coagulase + ve) grown from few c.cm. turbid fluid aspirated from L. ankle-joint. Blood-culture negative.

Method of penicillin treatment.—All doses given intramuscularly.

Day	*Dose*	*Blood bacteriostasis (ring test)*
1–4	20,000 units in 1 c.cm. 6-hrly.	None at 6th hr.
5–8	10,000 ,, 0·5 c.cm. 3-hrly.	..
9–14½	15,000 ,, 0·75 c.cm. 4-hrly.	..
	Total: 1,100,000 units.	

Progress.—During first 4 days fever changed from continued to irregular swinging course. Swelling of L. leg extended during first 24 hours almost up to tibial tuberosity and later down over dorsum of foot. On 5th day, after X ray had shown definite rarefaction on metaphyseal side of internal malleolus, child was examined under anæsthetic. No definite fluctuation or area of redness over tibia but well-defined red patch over external malleolus. This was incised down to periosteum and bone drilled. No pus found and cultures from bone were sterile. Dried penicillin placed in wound, 'Vaseline' gauze dressing applied, and limb put up in plaster. Temperature rose to only 100° F. instead of 102° F. that evening and settled to below 99° F. in 4 days—i.e., 10 days after beginning of penicillin treatment. Child made steady recovery from 5th day and able to take part in "school on 9th day. Three days after plaster cast had been applied it was demonstrably loose and œdema of foot had disappeared. On removal of plaster 7 days later no œdema of limb and cultures from wound sterile; some bony thickening remained above ankle.

X rays showed extension of rarefaction of lower end of tibia till 16th day after beginning of penicillin treatment but at 4, 6 and 8 weeks progressive calcification and well-marked periosteal reaction were seen. At 8 weeks child was running about, ankle showed only very slight bony thickening and wound which had at no time been infected was completely epithelialised. No albuminuria throughout.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*
At beginning of Tt.	4,000,000	76	10,000
2 days after end of Tt.	4,000,000	78	9000

Comment.—Here blood sampling was done and it appeared both from this and from the clinical state that 6-hourly injections were not adequate, so after the 5th day the same total dose was given at 3-hourly and later 4-hourly intervals. This undoubted case of acute staphylococcal osteomyelitis was treated early. The lack of any initial dramatic fall of temperature and a rise in the white count led to surgical intervention, but, fortunately for the assessment of the case, no pus was found and the incision remained sterile throughout. The application of a plaster instead of a backsplint may have had some influence on the fall of temperature but it is reasonable to attribute the abolition of infection and rapid recovery of complete function to the penicillin. No toxic symptoms from the drug were noted.

INTRAVENOUS AND INTRAMUSCULAR

CASE 7.—*Pyæmia.* (An RAF Hospital. Wing-Commander L. M. Crooks.) Male, age 51, weight 147 lb. Severe accident 20 years earlier fractured both legs and L. thigh; femur plated at that time. Since then sequestra removed at intervals. During present illness had been in hospital for 5 weeks with pain in sacral region and L. thigh, and pyrexia. No radiological evidence of active bony disease, but abscesses had formed in both regions and been opened down to bone. General condition had steadily deteriorated and penicillin asked for after 5th week because, all other treatment having failed, outlook considered hopeless. Irregular pyrexia, much purulent sputum but no radiological evidence of lung abscess; blood and pus cells in urine. Emaciated, mentally confused and looked extremely ill.

Previous treatment.—Repeated blood-transfusion, including 2 pints just before penicillin was begun. Sulphathiazole, 25 g. in 6 days, and later 100,000 units antistaphylococcal serum during 13 days. Just before penicillin treatment was started three screws were removed from plate on femur exposed in bottom of thigh wound.

Bacteriology.—*Staph. aureus* (coagulase +ve) grown from both abscesses and from urine, sputum and blood.

Method of penicillin treatment.—All doses given 3-hourly; 1st day intravenously, thereafter intramuscularly. Single dose: 1st day, 20,000 units in 5 c.cm.; 2nd and 3rd days 25,000 units in 4 c.cm.; 4th to 9th day 20,000 units in 4 c.cm.; 10th to 13th day 10,000 units in 2 c.cm. Total: 1,580,000 units.

Progress.—Temperature subsided to 99° F. within 24 hours and did not rise higher than that again; after 3 weeks remained normal. General physical and mental state steadily improved. After 7 days wounds were sterile but staphylococci returned 5 days after end of treatment. Wounds then dressed with penicillin powder every second day; and sacrum completely healed in 4 and thigh in 7 weeks. Urine remained free from pathogens after beginning of penicillin treatment; cells disappeared after fortnight. Staphylococci could almost always be grown from sputum, but he had difficulty in coughing anything up after 3 weeks. Walking with sticks 5 weeks after beginning of treatment and alone in 6 weeks. Left hospital after 7 weeks still needing to put on weight but looking and feeling well though weak.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning * of Tt.	4,130,000	80	38,400	24·8
11th day of Tt.	4,640,000	96	18,600	
4 days after end of Tt.	5,149,000	100	9000	29·6

* After transfusion of 2 pints of blood.

Comment.—Since all other treatment had been accompanied by a steady deterioration it is reasonable to attribute the patient's recovery, which dated from the beginning of penicillin administration, to the drug. It is remarkable that even the wound over the exposed plate in the femur healed. There were no toxic symptoms.

INTRAPLEURAL AND INTRAMUSCULAR

CASE 8.—*Empyema.* (Radcliffe Infirmary. Mr. Whitelocke; Mr. Holmes Sellors). Male, age 64, weight 153 lb. Had had cough and pain in L. side of chest for a month. On admission looked ill and was in respiratory discomfort. Temperature swinging between 98° and 100° or 101° F. Aspiration produced 560 c.cm. creamy foul-smelling pus from L. pleural cavity.

Previous treatment.—Course of sulphapyridine (22 g.) given outside hospital without improvement. After admission 9 g. given in 32 hours.

Bacteriology.—Pus grew a streptothrix and streptococci (anaerobic). Sputum grew pneumococci, *Strep. viridans*, a streptothrix and *B. proteus.*

Method of penicillin treatment.—During first 3 weeks, by aspiration of pus from pleural cavity and replacement by penicillin. During next 2 weeks, by intramuscular injection.

Day	*Dose (daily)*	*Route*	*Blood bacteriostasis (ring test)*
1–20	10,000	Intrapl.	..
21–22	10,000	Intrapl.	..
	5000	Intramus.	..
23	10,000	Intrapl.	..
24	10,000	Intrapl.	Complete for 2 hr.;
	20,000	Intramus.	absent in 3rd hr.
25–34	20,000 3-hrly.	Intramus.	..

Total: local, 213,000; general, 1,440,000 = 1,653,000 units.

Progress.—During local administration patient's appearance improved considerably; respiration-rate fell from 35 to 25 per min. in 4 days and appetite was greater than hospital menu could satisfy. Perpetually asking to get up. Evening pyrexia of 99°–100° F. continued and pus of variable, though less, amount aspirated daily. Bronchoscopy and bronchograms revealed no definite lung lesion, but because sputum contained a streptothrix with *Strep. viridans*, pneumococci and *B. proteus*, intramuscular injection begun. Chest then aspirated weekly. Fever continued till end of general treatment when ceased abruptly. General administration stopped after 9 days, mainly on account of short supplies. Pus from chest free of streptothrix after first 10 days of local treatment and of streptococci from 24th day till 12 days after treatment was stopped. Sputum contained no streptothrix after 4th day of general treatment.

In 7 weeks after general administration patient gained stone in weight and looked fit and cheerful. Doing small jobs about home and garden. Pleural pus decreased to nothing and radiography showed gradual clearing in lung. After 8 weeks a little pus found again in pleural cavity and surgery under local anaesthesia advised. Pleura removed at operation showed streptococci but no streptothrix. Convalescence complicated by carbuncles but patient has remained apyrexial. No streptothrix found in sputum or carbuncles up to 4½ months after treatment.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	3,100,000	62	20,000	33
At beginning of G. Tt.	3,200,000	62	13,000	34
At end of G. Tt.	3,400,000	62	16,000	32
6 days later	3,700,000	74	11,000	..
3 weeks later	3,900,000	80	8000	..

G. Tt. = general treatment.

Comment.—The recurrence of the infection suggests that the penicillin was not continued long enough. Nevertheless the treatment was associated with considerable clinical improvement.

INTRAVENOUS AND INTRAMUSCULAR

CASE 9.—*Cavernous sinus thrombosis.* (A military hospital and the Head Injuries Hospital. Lieut.-Colonel J. Mason Brown and Brigadier Hugh Cairns.) Male, age 28, usual weight 152 lb. Six days before beginning of penicillin treatment noticed boil inside L. nostril. Two days later was feverish and had an "inflamed" nose and swelling of L. eyelids; fainted. At start of penicillin treatment temperature 101°–106° F., and pulse-rate 100–120. Patient lay on his back in bed, breathing stertorously through clenched teeth. Could be roused enough to grunt in reply to questions but resented interference. Whole neck and face swollen and suffused. L. frontal veins indurated. Both eyelids swollen, L. more than R.; on lifting closed lids eyes seen to be proptosed and conjunctivæ œdematous. No purulent discharge. L. eye almost blind; pupil reacted sluggishly to light; movements of eyeball impaired (outward movement completely and upward movement partly lost). R. eye, acuity, pupillary reactions and movements of eyeball normal. Discs could not be seen clearly. Retention of urine.

Previous treatment.—7 g. sulphapyridine in 24 hours, then 12·5 g. sulphathiazole in next 24 hours. Patient vomited the sulphathiazole.

Bacteriology.—*Staph. aureus* (coagulase +ve) grown from blood just before start of penicillin.

Day	*Dosage of penicillin*
1	20,000 units 3-hrly. intraven.
2	6666 ,, hrly. ,,
3	20,000 ,, 3-hrly. intramus.
4	6666 ,, hrly. intraven.
5	10,000 ,, ,, ,,
6	6666 ,, ,, ,,
7	13,300 ,, 2-hrly. intramus.
8, 9 and 10	10,000 ,, 2-hrly. ,,

Total: 1,693,000 units.

Intravenous glucose saline given with the intravenous penicillin, because patient was unable to drink.

Progress.—No improvement till 3rd day of treatment when less dull and could talk and drink a little. Local appearance unchanged. On 4th day seemed moribund, and could not swallow; again given intravenous saline and afterwards improved considerably. On 5th day signs of bronchopneumonia and pleurisy, but continuously improved from this time and penicillin stopped at end of 10th day. Temperature then did not rise above 99° F.; pulse-rate 84–96 per min. Had regained control of bladder. Appetite good. Some of oculomotor palsies increased after general condition improved: right external rectus paralysis appeared on 10th day of treatment, was complete 3 days later and fully recovered in another 6 weeks. While right 6th nerve paralysis increasing right 3rd nerve paralysis diminishing. Infected clot seems to have involved left 6th nerve and to lesser extent, left 3rd nerve; the later and fleeting involvement of right 3rd and 6th nerves was probably due to non-infective clot covering main focus.

Temperature rose irregularly to 99°–100° F. for 5 weeks after treatment due to patch of pleuropneumonia in L. lung, followed radiologically until discharge from hospital. After 4 weeks was walking steadily and ocular palsies gradually diminishing. Eight weeks after initial injection became apyrexial and remained so till discharged a month later. Since regained normal weight and able to go for long walks. Four months from beginning of treatment vision, pupillary reactions and external ocular movements all normal, except for impairment of outward movement of left eye. Two months later X ray of chest showed some basal thickening of pleura only. Outward movement of left eye possible to 18°. Returned to duty.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	..	..	8200	..
4th day of Tt.	..	..	17,000	42
5th day of Tt.	3,090,000	74	12,100	..
At end of Tt. (10th day)	..	..	7800	..
4 weeks later	4,260,000	72	8600	28

Comment.—This undoubted cavernous sinus thrombosis had a particularly acute onset, the patient being semi-comatose on the 4th day of the illness. It was justly described as a "fulminating" case. The only treatment apart from 48 hours of sulphonamides was penicillin and glucose saline. Penicillin was begun early and as far as the infecting organism is concerned recovery appears to be complete. Since the eye movements continue to improve it is reasonable to hope that the patient will recover completely.

CASE 10.—*Osteomyelitis.* (A military hospital and Wingfield-Morris Hospital. Lieut.-Colonel J. Mason Brown and Professor Seddon.) Male, age 34, weight 150 lb. Illness began 7 weeks before penicillin treatment with boil on back which developed into small carbuncle. As this healed abscess formed in R. thigh. Five weeks before penicillin treatment abscess was opened but thereafter temperature swung daily from 98° to 103° F. with occasional rigors. Fluid which on aspiration was not purulent formed in R. knee. Later inflammatory area developed in L. calf. Few days before penicillin treatment, X ray showed considerable rarefaction of upper half of shaft and neck, both condyles and intercondylar notch of femur; patient extremely ill and wasted, too weak to talk except in short low-voiced phrases; infrequent cough.

Previous treatment.—Limb had been fixed on Braun's splint and 30 g. sulphathiazole given in 4 days with staphylococcal antitoxin 20,000 units daily; no obvious effect on temperature, pulse-rate or general condition. Leg put in closed plaster with small window over thigh wound. Blood-transfusion of 1 pint given. Three days later temperature, which had dropped, again registered 102° F. and staphylococci cultivated from blood. Penicillin therefore begun.

Bacteriology.—*Staph. aureus* grew in pure culture from abscess in thigh, fluid in knee-joint and from blood. Immediately before start of penicillin same organism (coagulase +ve) obtained from urine, sputum, blood and thigh wound.

Method of penicillin treatment.—During first 3 days intravenously into continuous saline drip and thereafter intramuscularly.

Day	*Dose*	*Blood bacteriostasis*
1–3	10,000 units 2-hrly.	Complete for 2 hr. after 10,000 unit dose, intraven. or intramus. (confirmed 3 times).
4–12 (day)	10,000 ,, ..	..
8–14 (night)	20,000 ,, ..	..
13–14 (day)	15,000 ,, 3-hrly.	..

Total: 1,680,000 units.

Progress.—No obvious effect on pulse, respiration or temperature for 4 days but thereafter general and local conditions began to improve. Tender lump in L. calf regressed. Granulations round sinus in thigh epithelialised while cocci in discharge from sinus decreased and many became intracellular. Two days after end of treatment no staphylococci could be grown from sinus, urine sterile and no sputum obtained.

Evening temperature had not been above 99° F. for a week. Next day when plaster removed knee swollen and painful on movement; much pus expressed from depth of sinus, gave good growth of staphylococci. X rays showed rarefaction of whole length of femur; limb therefore enclosed again in plaster, and patient transferred to orthopædic hospital. No albuminuria throughout treatment.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt. (after transfusion)	3,422,000	65	14,700	33
At end of Tt.	3,800,000	72	10,800	50
2 days later	..	..	..	27
3 weeks later	4,200,000	80	13,000	..

Comment.—This patient was severely ill with a generalised staphylococcal infection. His general condition improved steadily during penicillin treatment. The closed plaster, considered essential for orthopædic reasons, hampered the assessment of progress of the local condition and prevented a representative sample of pus from being obtained from the sinus. The patient was left with a localised infection of the femur which has been dealt with by orthodox methods. Had it been possible to watch the local lesion in the thigh a second course of penicillin might have been tried in the hope of eliminating the staphylococci altogether. The blood-urea was higher than is usual at the end of treatment but fell promptly. There was no albuminuria. The urinary frequency may have been due to the penicillin as it stopped soon after the drug was discontinued. There was thus no indication of any serious toxic effect.

INTRAMUSCULAR ONLY

CASE 11.—*Pyæmia.* (A RAF hospital. Wing-Commander D. M. Anderson.) Male, age 34, weight 147 lb. (about). Illness began 3½ weeks earlier with boil behind R. ear, followed by carbuncle on back of neck, spreading over scapulæ. Signs of pneumonia developed, and pain and swelling appeared on inner side of L. knee; no radiological evidence of bony lesion. Fever present from beginning and for last week had swung between 98° and 103° F. or over; pulse and respirations erratic: 80–120 and 20–40 per min.

At beginning of penicillin injections patient, who had just been transferred 40 miles by ambulance, was fairly well-nourished, pale and sweating profusely; exhausting coughing attack every few minutes. Speech difficult on account of cough and rapid breathing, but quite rational. Carbuncle extended from base of neck into both scapular fossæ over area 5½ by 9 in. On L. side of neck were 17 areas of ulceration with undermined edges containing sloughs and exuding pus. R. side had reached stage of discoloration, swelling and induration only. Chest expanded poorly; signs of diffuse bronchopneumonia. L. knee tender over inner aspect of tibial head and small effusion into joint. Tender swelling in R. calf. L. forearm and hand swollen, without localised tenderness.

Previous treatment.—Sulphapyridine, 6½ g. in 3 days followed by sulphathiazole, 48 g. in 7 days. Temperature fell for short time but rose again while course was still in progress.

Bacteriology.—*Staph. aureus* (coagulase +ve) grown from blood. Carbuncle and sputum gave heavy growth of same organism. Urine sterile.

Method of penicillin treatment.—All doses given intramuscularly.

Progress.—During first 6 days temperature peak fell a little lower each day till down to 99·4° F.; after 36 hours pulse ceased wide excursions and kept between 110 and 120. Dramatic steadying of respiration-rate at about 30 in spite of persistent cough. Sputum 15–20 oz. daily at first; after 5th day steadily diminished. Swelling of carbuncle going down by 3rd day; sloughs smaller and granulations bright red. By end of 9 days all induration gone from R. side; on L. a few ulcers had coalesced, others dry, edges no longer undermined and epithelium growing in. Pus grew diminishing numbers of *Staph. aureus* till healing complete. Three days after large initial dose had been reduced, when blood-culture was sterile, temperature, pulse- and respiration-rate began to rise again; maxima 101° F., 120 and 35. Because 2-hourly injections were exhausting and batch of penicillin in use might have pyrogenic properties, treatment stopped on 16th day. All but 7 ulcers had then epithelialised completely and rest were beginning to do so. L. knee had no detectable fluid in it and all soft-tissue swellings gone. Paroxysms of coughing much fewer and sputum at most 10 oz. daily. Considerably greater air entry in chest than during first week of treatment.

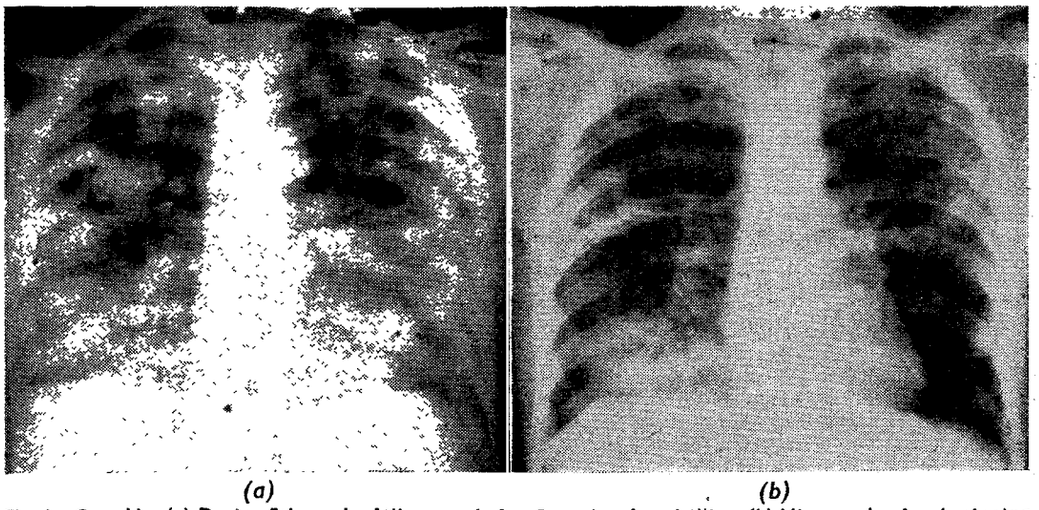
Day	*Dose*	*Blood bacteriostasis (slide test)*
1–4	20,000 units 2-hrly.	Complete for 3 hr. up to dilution of serum of ½; partial up to ⅛.
5–9	10,000 ,, 2-hrly. by day	Complete for 2 hr. (undiluted).
	20,000 ,, 3-hrly. by night	..
10–13	10,000 ,, 2-hrly. by day	..
	20,000 ,, 4-hrly. by night	..
14–16	15,000 ,, 2-hrly. by day	Complete for 3 hr. (undiluted).
	20,000 ,, 4-hrly. by night	..

Total: 2,590,000 units.

At end of treatment there was no immediate alteration in TPR, but in another 10 days, during which transfusion given, temperature subsided to normal and remained there, pulse steadied round 100 and then began to drop lower and respirations suddenly fell to 20–25. Sputum lessened and 6 weeks later was very slight. Patient walking about 7 weeks after start of penicillin. No X ray taken at beginning of treatment for fear of disturbing patient. At end of treatment first radiogram (fig. 1, *a*) showed multiple cavitation at both apices and consolidation of both lower lobes and part of R. middle lobe. Subsequent weekly X rays showed steady clearing, passing through patchy stage indistinguishable from multiple abscess formation. Nine weeks after treatment began there was still some opacity at the base of the R. middle and lower lobes (fig. 1, *b*). By 3 months after treatment last remaining cavity had almost disappeared, and bronchogram showed normal filling of the R. middle and lower lobes.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	3,430,000	70	12,300	31
6th day of Tt.	3,810,000	70	20,000	20·8
14th day of Tt.	..	..	..	71
At end of Tt.	3,500,000	74	18,000	22·8
After transfusion	5,300,000	80	14,400	..
2 months from start of penicillin	4,700,000	92	8000	..

Comment.—The carbuncle started to clear up from the time of penicillin administration though at no time were the staphylococci absent from his lungs. As he had no other treatment till well on the way to convalescence his recovery from the very severe infection with lung abscesses may reasonably be attributed to penicillin.



(*a*) (*b*)

Fig. 1—Case 11. (*a*) During 5th week of illness and after 2 weeks of penicillin. (*b*) Nine weeks after beginning of penicillin.

INTRAMUSCULAR AND INTRATHECAL

CASE 12.—*Streptococcal meningitis.* (St. Mary's Hospital, Paddington. Prof. Alexander Fleming.*) Male, age 52. Seven weeks earlier patient became febrile, without localising signs. After 3 weeks, vomiting, drowsiness and frontal headache began and in next week further clinical signs of meningitis developed. CSF pressure 300 mm.; 500 cells (mostly polymorphs) per c.mm.; globulin and total protein increased. Except while sulphapyridine was being administered, temperature 97°–102° F. and pulse-rate 96–128. Condition deteriorated and when seen with view to penicillin treatment was drowsy and at times comatose, with intervals of extreme restlessness. Had had uncontrollable hiccough for last 10 days; incontinence of urine and fæces for a week. Night before treatment started oxygen administered; man believed to be dying.

Previous treatment.—Sulphapyridine, 1 g. 4-hourly for 8 days, lowered temperature but it rose again promptly at end of course, illness not otherwise influenced. Later, sulphathiazole given for 13 days without effect.

Bacteriology.—No organisms could be cultivated from CSF by ordinary methods, but 6 days before treatment began a non-hæmolytic streptococcus was isolated by shaking 3 c.cm. of CSF in 10 c.cm. of sloppy (0·2%) glucose agar. Culture by this method was repeated. Organism was sulphathiazole-resistant but penicillin-sensitive; about half as sensitive as test staphylococcus. Agglutination of organism by patient's serum complete at 1 in 80 and partial up to 1 in 320; none of 12 normal sera gave any agglutination at dilutions of 1 in 10 or more.

Method of penicillin treatment.—Intramuscularly, with 5 doses intrathecally. For first 8 days injections given 2-hourly for whole 24 hours; thereafter 2-hourly from 8 AM to 8 PM, with 20,000 units at 10 PM.

Day	*Units intramuscular*		*Units intrathecal*
	Single dose	*Total*	
1 (part)	10,000	30,000	..
2 and 3	10,000	120,000	..
4	10,000 or 20,000	190,000	..
5	20,000	240,000	..
6	15,000	180,000	..
7	10,000 or 15,000	160,000	5000
8	10,000 or 7500	105,000	5000
9	7500	90,000	2500
10	10,000 or 20,000	100,000	5000
11–13	10,000 or 20,000	90,000	..
14	..	..	5000

Grand total: intramuscular, 1,305,000; intrathecal, 22,500 = 1,327,500 units.

Progress.—Uninterrupted. Temperature did not rise above 98·6° F. after 7th day of treatment. Discharged from hospital 5 weeks from beginning of treatment with no abnormal signs or symptoms.

Blood examinations	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	85	15,000	30
At end of Tt.	84	8300	30

White-cell count dropped steadily during treatment.

Bacteriostasis complete in 9 of 11 samples of blood, partial in 1 (slide-cell and other techniques). After intramuscular injection CSF was less bacteriostatic than blood, but after intrathecal injection it was many times more so, even 24 hours later. From this it is clear that penicillin does not pass freely between CSF and blood.

Comment.—Other medication had failed and the patient's condition appeared to be hopeless. Recovery began with penicillin treatment and was uninterrupted. This was the first patient to have penicillin intrathecally, and there appeared to be no ill effects.

INTRAMUSCULAR ONLY

CASE 13.—*Staphylococcus aureus septicæmia.* (Radcliffe Infirmary. Mr. Stallworthy.) Female, age 37, weight in health about 120 lb. After a delivery with considerable hæmorrhage given blood-transfusion into R. saphenous vein; 4 days later temperature rose to 105° F. and felt pain behind R. knee. On 7th day signs of lung involvement. Temperature remained between 102° and 105° F. and pulse about 140 till it became too weak and irregular to count. Penicillin treatment started on 9th day. Then extremely pale with heavy shadows under eyes and round nose; breathing, interrupted by a short cough, very shallow and accompanied by loose rattle in throat which she seemed incapable of clearing. Could answer questions in few whispered words and seemed rational during day but wandered at night. R. leg considerably swollen from foot to thigh with induration of subcutaneous tissues along inner side of leg. Well-marked œdema of dependent parts of body.

Previous treatment.—Sulphonamides given but frequently vomited and as white-cell count fell from 12,000 to 5000 in 3 days they were stopped. Just before penicillin treatment packed cells from a pint of blood were transfused.

Bacteriology.—*Staph. aureus* (coagulase +ve) grown from blood (8 colonies per c.cm. and 4 days later 70 colonies per c.cm.), and from sputum before penicillin started, and later from abscess which developed in leg. Urine sterile.

Method of penicillin treatment.—For 20 days received 15,000 units 3-hourly intramuscularly; total 2,400,000 units. Bacteriostasis complete for 3 hours and partial in 4th hour after injection of 15,000 units on 9th day of treatment.

Progress.—In first 24 hours only change was slight drop in temperature. Next day pulse began to improve, but attacks of dyspnœa accompanied by pain in chest started, with clinical signs of multiple emboli; cough looser. On 4th day patient began to look better and blood-culture was sterile. After 6th day attacks of dyspnœa stopped. Temperature fell irregularly; by 14th day was normal, respirations below 30, pulse regular though still fast (100–110), little cough and no sputum. Packed cells from 4 pints of blood transfused on 15th day; no immediate reaction but 36 hours later sudden and very severe attack of dyspnœa with fear, cyanosis and almost imperceptible pulse; patient gradually recovered.

On 9th day radiogram of chest showed consolidation of both bases and partial collapse of both lower lobes. On 16th day, after the severe attack, areas of consolidation were smaller but fluid found in L. pleural cavity; on aspiration found to be amber-coloured, slightly turbid, free of cells and sterile. At no time was there evidence of abscesses in lungs, in spite of clear clinical history of pulmonary emboli. Weekly radiograms showed steady clearing of lung shadows. R. chest clear 4½ weeks after first administration of penicillin; L., where fluid had collected, by 8th week. Swelling of leg steadily decreased after 3rd day. Staphylococcal abscess found on inner side of leg on 6th day treated by aspiration; pus decreased daily till dry on 14th day.

Penicillin stopped on 20th day. Apart from mild cystitis due to *B. proteus*, which followed repeated catheterisation, patient made uninterrupted recovery. Cough completely gone 3 days after penicillin stopped.

Patient was losing profuse bright red lochia throughout treatment.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning * of Tt.	..	38	5000	46
2nd day of Tt.	2,700,000	40	9000	..
4th ,,	..	..	16,000	..
10th ,,	2,200,000	40	10,000	..
14th ,,	2,700,000	49	6000	32
At end of Tt. (20th day)	..	..	..	53
5 days after end of Tt.	..	..	..	35

* Before transfusion of cells from 1 pint of blood.

	Red cells per c.mm.	*Hb. %*	*White cells per c.mm.*
After transfusion on 17th day	4,800,000	74	16,000
14 days after end of Tt.	4,200,000	80	8000
28 days after end of Tt.	5,000,000	76	8000

Comment.—In spite of the patient's very low hæmoglobin no transfusion was given after the initial pint of packed cells for the first 16 days. With the mastery of the infection the hæmoglobin rose although a profuse lochia continued. Only after the disappearance of embolic phenomena in the lungs for 10 days was the patient again transfused. Evidence of the lodgment of emboli in the lungs followed, but no lung abscesses developed and the fluid aspirated from the chest was sterile. It is reasonable to attribute the very satisfactory clinical result to the penicillin.

CASE 14.—*Osteomyelitis with pyœmia.* (Wingfield-Morris Hospital. Mr. Trueta.) Male, age 8 years, weight 53 lb. "Chronic bronchitis" for previous 3 years; treated in sana-

* This case was treated with penicillin supplied from Oxford. We are indebted to Professor Fleming for permission to include an abstract of his notes in this series.

torium and later in open-air school. Present illness began as undiagnosed fever 3 weeks before beginning of penicillin treatment. After few days, vague pains started in joints; eventually abscesses pointed and were incised below R. knee and L. ankle. After 2 weeks, signs of consolidation in both lungs and rusty sputum. For 10 days before treatment started temperature, irregular at first, had swung between 99° and 103° or 104° F.; pulse-rate had steadily mounted to 120–140 and respirations to 30–40.

Extremely thin, very pale, especially round the mouth and nose, rational but listless, querulous when roused. Breathing shallow and rapid; little cough; tongue dry and dirty. Considerable areas of consolidation and pleural rubs on both sides of chest; osteomyelitis with abscess formation in upper end of shaft of R. tibia, lower ends of R. fibula and L. tibia, with some involvement of L. ankle-joint. Drains present in both tibiæ; thick blood-stained pus aspirated from R. fibula. Fullness and tenderness of L. loin; psoas spasm and tenderness under L. ischium; reddened tender area over one metacarpal head; some stiffness of R. elbow; and tenderness over one sternoclavicular joint.

Previous treatment.—At onset of illness 2·5 g. sulphapyridine given in 24 hours, followed for some days by salicylates which favourably affected TPR. Appearance of pus led to further 2 days' sulphapyridine (12 g.) before admission to Wingfield-Morris Orthopædic Hospital.

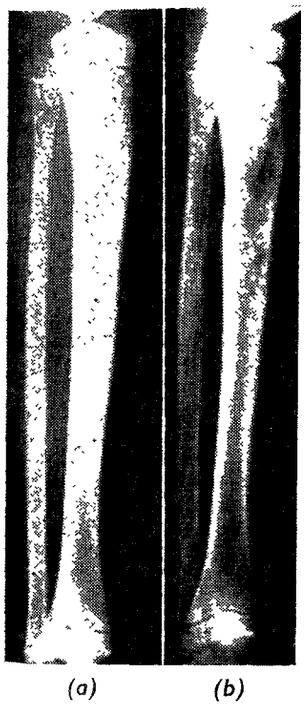
Day	*Dose*	*Blood bacteriostasis (slide test)*
1–6 ..	7500 units 3-hrly. ..	Present for 2 hr. after injection.
7–12 ..	10,000 ,, ..	Present for 1st hr. only.
13–22 ..	15,000 ,, ..	Present for all 3 hr.

Total: 1,987,500 units.

Bacteriology.—Heavy growth of *Staph. aureus* (coagulase +ve) obtained from sinuses and abscesses aspirated in legs. *Staph. aureus* of the same serological type isolated from blood and urine. Sputum could not be obtained for culture.

Treatment.—Child allowed to lie in bed in position found most comfortable. Limbs dressed every 2 or 3 days with dry dressings. No splinting except for week in middle of treatment when abduction frame used to overcome continued psoas spasm. Abscess over R. fibula treated by repeated aspiration. Sedatives were only drugs used beside penicillin; no transfusions. All penicillin given intramuscularly.

Progress.—After drop of 2°–3° in first 24 hours temperature swung regularly every day from 98° to 102° F. for over a week, increased dose having no effect on it. Then fell irregularly to region of 99° F. when penicillin was discontinued after 3 weeks. Pulse-rate remained at 100–120 throughout. Respirations showed earliest definite improvement; regular between 20 and 25 by 9th day. Temperature finally remained normal 26 days after treatment began. Anæmia showed progressive and rapid diminution throughout treatment. Listlessness disappeared early and child became very restless. Improvement in appearance even while temperature still swinging. Appetite prodigious by 14th day, and taking part in school on 18th day. Clinical and X ray examination demonstrated progressive clearing of consolidation in lungs, though resolution not complete by end of treatment. Elbow swollen and painful on movement on 6th day, but subsided. Sinuses dry by 9th day, L. ankle swelled more during second week; aspiration produced no fluid. R. fibula abscess aspirated several times and showed progressive diminution in *Staph. aureus*; both this abscess and some fluid which had collected in old R. tibial abscess' cavity sterile at end of 3 weeks.



(*a*) (*b*)

Fig. 2—Case 14. (*a*) Right tibia and fibula before penicillin was begun. (*b*) Three weeks later, at the end of penicillin treatment; note extensive rarefaction in both fibula and tibia. (*a*) is a somewhat softer plate than (*b*).

Radiograms, as in other cases, showed progressive rarefaction of affected bones at first (fig. 2*a* and *b*). By end of treatment whole of R. fibula, half R. tibia, lower third of L. tibia, and astragalus involved; some indication of osteomyelitis in descending ramus of L. pubis. Evidence of subperiosteal bone formation in some places. No further rarefaction had taken place when radiograms were taken 1 and 2 months after end of treatment.

No explanation of tenderness in L. loin forthcoming until 5 days after penicillin stopped, during which time he was very cheerful, sitting up and playing in bed, and free from fever. Then developed high temperature and renal colic. Pyelogram showed stones in pelvis of L. kidney and in L. ureter. Urine contained some pus cells and grew *B. coli*. At no time were staphylococci grown from urine. After 9 days, during which passed a stone and much gravel, temperature fell to normal and boy became lively and active, with no residual disability except stiff L. ankle. During next 6 weeks remained apyrexial. Movement in all joints except L. ankle became full and free. Looked very well and had returned to same weight as before illness.

Blood examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*
At beginning of Tt.	2,000,000 ..	38 ..	22,000 ..	45
8th day of Tt.	2,400,000 ..	42 ..	14,000 ..	25
14th ,, ..	2,980,000 ..	60 ..	12,800 ..	20
3 days after end of Tt.	3,400,000 ..	60 ..	10,000 ..	25
6 weeks later ..	3,900,000 ..	74 ..	10,000 ..	40

Comment.—This case, a boy very seriously ill, demonstrated that with adequate doses of penicillin widespread osteomyelitis could be controlled without surgical intervention. No toxic effects were seen from the penicillin and the anæmia steadily decreased during treatment.

INTRAMUSCULAR AND INTRAVENOUS

CASE 15.—*Subacute bacterial endocarditis.* (Radcliffe Infirmary. Dr. Cooke.) Male, age 24, weight about 98 lb. (112 lb. in health). Pyrexia with daily range of 100°–103° for 2 months; onset accompanied by headache only. Known to have a congenital heart lesion, probably a septal defect, since a child. Now had aortic murmurs, probably due to endocarditis. When penicillin treatment began he looked ill, flushed, worried and very thin; rather rapid shallow respirations interfered somewhat with conversation. Skin very moist. No demonstrable lesions other than cardiac murmurs, moderate enlargement of heart to left, and Osler's nodes on great toe and right index finger.

Previous treatment.—First 'Dimol' and sodium salicylate, then 33 g. sulphanilamide in a week and later 'Soluseptasine,' 4 ampoules daily for 3 days. None of these drugs affected TPR or symptoms.

Bacteriology.—Month after illness began *Strep. viridans* cultivated from blood. Positive blood-culture also obtained before beginning of penicillin administration. Streptococcus isolated from the blood 3 weeks after end of treatment found to be only a quarter as sensitive to penicillin as the one originally isolated.

Day	*Dose and route of penicillin*	*Blood bacteriostasis (slide test)*
1–18 ..	15,000 units 3-hrly. intramus. ..	Complete for 2 hr. in 1st week; only for 1 hr. in 2nd week.
19–21 ..	20,000 ,, ,, ,, ..	Complete for 1 hr. only.
22–25 ..	30,000 ,, ,, ,, ..	Complete for 2 hr.
26–29 ..	10,000 ,, hrly. intraven. ..	..
30 ..	15,000 ,, 3-hrly. intramus. ..	..

Total: 4,670,000 units.

Progress.—During first week appetite improved rapidly and remained of surprising proportions throughout treatment; temperature dropped steadily till between 98° and 99° F., pulse-rate fell a little and respiration-rate from 30 to 25. Temperature then became more erratic and condition obviously not improving. Blood-culture negative after a week but *Strep. viridans* isolated again at end of second week. Dose of penicillin increased but temperature only transiently improved and rose again after 2 days. On further raising dose temperature again dropped; blood-culture at this stage negative.

Bacteriostatic tests at all dosages up to date had shown absent or incomplete inhibition in third hour, so it was decided to give hourly injections of 10,000 units—i.e., same total

daily dose but given more often by means of blood, and later saline, drip transfusion. This was kept up for 5 days. In spite of rigorous treatment patient obviously put on flesh and appetite remained prodigious. At end of treatment looked much better; very bright and anxious to get up. Temperature started mounting 4 days after penicillin discontinued; within a week curve resumed original height, and patient lost his appetite and looked ill and anxious as before. Little change in heart signs; some indefinite abdominal pain and tight sensation across chest; no other added symptoms and no embolic phenomena. Three weeks after administration ceased heart had appreciably enlarged; there was greater thoracic discomfort and blood-cultures were again positive; he was sent home, and died 3 weeks later.

Blood and urine examinations	*Red cells per c.mm.*	*Hb. %*	*White cells per c.mm.*	*Blood-urea: mg. per 100 c.cm.*	*Urea clearance %*
At beginning of Tt. ..	3,400,000	54	10,000	31	85 normal
End of 1st week ..	3,700,000	52	18,000	32	..
End of 2nd week ..	3,300,000	52	12,000	32	..
End of 3rd week ..	3,400,000	54	8800	35	..
End of 4th week *	4,200,000	80	19,000	29	..
3 weeks after end of Tt...	4,000,000	52	9000	25	115 normal

* Five days after transfusion of 1¾ pints of blood.

No albuminuria throughout administration.

Comment.—This patient had by present standards a very large dose of penicillin continued for a month. He showed no toxic signs and his appetite remained extraordinarily good throughout. Even these doses produced only temporary effects. The causative organism developed a considerable resistance to penicillin. It would probably have been better to give very large doses initially but it must be admitted that this case does not give grounds for the belief that penicillin will cure subacute bacterial endocarditis.

COMMENT ON GENERAL TREATMENT

From these observations the most practicable method for the administration of penicillin seems to be by intramuscular injection. Owing to the great ease with which penicillin is excreted by the kidney injections must be repeated frequently. In general a 3-hourly interval, especially in the most acute stages of the illness, is desirable. A dose of at least 15,000 units should be given and careful examination made of the serum to see that at the end of the 3-hour period after injection it is still fully bacteriostatic; if it is not the dose must be increased until it is. As penicillin at present is so difficult to make in quantity one has been tempted to find the minimum effective instead of the optimal dose. It is quite possible that some good results will be obtained with less dosage than is recommended above, but if penicillin ever becomes available in quantity the above dosage will probably be considered small. In estimating clinical progress the temperature chart seems to be a poor guide, and for those used to the sharp falls often associated with sulphonamide administration this is somewhat disconcerting. Other criteria, such as bacteriological examinations, diminution of pain, and improvement of appetite and general condition, rank high. In the cases treated the temperature has come down by lysis over as long as 14–20 days. Penicillin should be continued till this result has been obtained and for a few days longer.

In many hundreds of intramuscular injections there has been no suggestion of serious damage at the site of injection, even in a baby. The impure preparations employed have contained no more than 10% of penicillin and it can be counted extremely fortunate that the impurities are non-toxic. Even with the greatest dosage (case 15) no toxic effects of the drug were noted. There was a rise in blood-urea in some of the patients; this fell promptly on discontinuing the drug and such a rise probably does not indicate kidney damage. In some of the most severe cases we were fortunate in being able to avoid blood-transfusions so that a clear-cut picture was obtained of the effect of penicillin on the blood. In nearly all cases there was an improvement in the red

SENSITIVITY OF ORGANISM TO PENICILLIN BEFORE TREATMENT COMPARED WITH THAT DURING OR AFTER TREATMENT

Case	Organism	Source of organism	Days since start of treatment when 2nd culture taken	Comparative amounts of penicillin required for complete inhibition at 2nd and 1st culture	Notes
10	*Staph. aureus* (coag. + ve)	Wound	10	No change	
11	,,	Carbuncle	15	4 times as much	Both compared with original culture from carbuncle.
11	,,	Sputum	15	No change	
14	,,	Abscess L. ankle	7	No change	Organism from the original blood-culture had the same titre.
13	,,	Blood-culture; abscess	12	No change	Abscess aspirated during treatment compared with original blood-culture.
15	*Strep. viridans*	Blood-culture	51	4 times as much	Second culture taken 21 days after end of treatment.

count and hæmoglobin level during treatment. Any fall in white cells was associated with a diminution of infection and in no case was there any suspicion that a leucopenia was produced. The fact that in certain cases blood-transfusion was withheld does not mean that it is undesirable. Improvement in the hæmoglobin level by transfusion would possibly have accelerated clinical improvement.

With two exceptions the staphylococcal cases were only referred to us because they were considered hopeless, after other forms of treatment, including sulphonamides, had been tried without effect. They have all recovered, and, where dosage was adequate, without surgical interference. The cases with bony lesions were particularly interesting, for rarefaction of the bone increased simultaneously with the general improvement, so that at the end of treatment the bones looked a good deal worse radiologically than at the beginning. Nevertheless, when left alone they gradually recalcified. The extensive rarefaction should be interpreted not as an extension of the disease process but rather as evidence that the diseased bone is being rapidly cleaned up (? by macrophages) when the staphylococcal infection is overcome. The evidence is that with adequate dosage it is possible to eliminate all infection, and one may look forward to the time when osteomyelitis treated early will no longer be a surgical condition. In certain cases of staphylococcal infection it has been possible to follow the sterilisation of unopened abscesses during general administration only. Abscesses already present before treatment should be dealt with by aspiration, if possible, rather than incision; there is every indication that they will then heal. When the dose of penicillin is adequate we have not seen abscesses form de novo during treatment.

In 5 cases the sensitivity of the infecting organism to penicillin before and during or after treatment was compared by Dr. M. A. Jennings (see table). In 2 cases some resistance had developed and in 3 the titre was unchanged. There are therefore reasons for believing that organisms will sometimes develop resistance to penicillin during its administration. It has previously been shown that this can occur in vitro (Abraham et al. 1941). Even on this ground alone fully adequate dosage must be given at the beginning of treatment.

Cases treated by Local Application

While the large amounts of penicillin needed for parenteral injection are not likely to be widely available for some time, the relatively small amounts needed for local application could possibly be made available much sooner. When the properties of penicillin are considered—for instance, its unimpaired activity in the presence of pus and autolytic products, and its low

toxicity to leucocytes—its suitability for local application is beyond doubt, and it is indeed a reasonable view that if a good result is not obtained in an infection with a penicillin-sensitive organism the penicillin is, for one reason or another, not being adequately applied.

For some cases in the present series the hygroscopic sodium salt of penicillin was used. The calcium salt, which is not hygroscopic, is much more conveniently handled and has proved satisfactory for local application in either powder or solution; it is to be preferred to the sodium salt. The calcium salt should in no circumstances, however, be injected in strong solutions intramuscularly or intravenously.

In essence, the problem of using penicillin locally is that of devising some means to apply a very soluble and diffusible substance so that a bacteriostatic concentration is constantly maintained at every point where there are infecting organisms. It is useless to apply penicillin unless the whole infected area can be reached, and local application must therefore be accompanied by suitable surgery. For this purpose "suitable surgery" may not be orthodox surgery; free drainage is undesirable because the penicillin drains away with the exudate. In our view it is best to establish a closed cavity when possible into which penicillin can be instilled and from which exudate can be sucked away periodically if necessary. We are particularly indebted to Mr. R. G. Macbeth and Mr. G. H. Livingstone who have modified their usual mastoidectomy operation to fulfil this condition. This type of infected cavity may be considered as a model for other situations.

MASTOID INFECTIONS

Of the 22 cases of mastoid infection treated with penicillin, 16 had a history of from 4 days to 4 weeks and the other 6 were chronic cases with acute exacerbations. Pus was found in 18, mucoid or mucopurulent material in the remaining 4.

The patient's ages ranged from 10 months to 76 years, this last being a diabetic.

Bacteriology.—Hæmolytic streptococci were found in 8 cases, pneumococci in 6 and *Staph. aureus* in 2; 4 cases were sterile and in 2 no bacteriological examination was made.

Method of treatment.—After an orthodox Schwartze mastoidectomy the wound was sewn up completely from below and a fine rubber tube, with no side holes, was inserted through the upper end of the wound down to the base of the cavity and sutured into position. Penicillin dissolved in distilled water, sufficient to fill the cavity, was injected and the tube closed with a spigot. Penicillin in vaseline was smeared along the suture line. Exudate was aspirated and fresh penicillin injected 6-hourly for 5 days, when the sutures were removed, and twice daily for 2 more days, after which the tube was removed. The strength of the penicillin solution varied from 250 to 500 units per c.cm. The amount used for one case varied from 5000 to 35,000 units; average 17,300 units.

Results.—Primary healing of the wound took place in 14 of the acute and 5 of the chronic cases. The ear was dry either at the first dressing (at 5 days) or within 10 days of operation in 19 cases. Two of the failures (acute cases) occurred early in the series and could reasonably be attributed to inexperience in the technique. In no case was any serious complication met with.

Comment.—It is likely that treatment every 6 hours was excessive, as the material aspirated just before an injection was several times found to be strongly bacteriostatic—i.e., penicillin was still present. Probably 12-hourly treatment would have been adequate. It is also uncertain whether 7 days' treatment was necessary, but to get complete information about variations in the treatment would have needed a far larger series. The present small series shows at least that the principle of instillation and aspiration after surgical cleaning and closure should be given a further trial.

EYE INFECTIONS

We are indebted to Miss Ida Mann for the diagnosis and advice on the cases and to Mr. H. E. Hobbs for his help. Of the 89 eye infections treated with penicillin, 46 were cases of blepharitis, 18 of acute conjunctivitis (with corneal ulcers 6, with infected eye-socket 1, with infected meibomian cyst 1, with hypopyon 1), 19 of chronic conjunctivitis, and 6 of dacryocystitis.

Blepharitis.—The 46 cases treated had scaling, redness of the lids, swelling, ulceration and soreness. The duration of symptoms ranged from 2 months to 32 years; 35 cases had had symptoms for over a year. Swabs were taken from ulcers on the lids before treatment with penicillin and plated on blood agar. *Staph. aureus* (coagulase +ve) was found in 35 cases; *Staph. aureus* and *Staph. albus* (coagulase +ve) in 1 case; *Staph. aureus* and pneumococci in 1 case; *Staph. albus* alone in 4 cases; and *Sarcina lutea* in 1 case; in 4 cases no cultures were made.

Penicillin ointment was made by dissolving the powder in distilled water and incorporating it in vaseline in a strength of 600–800 units per g. The patients were told to bathe the lids to soften and remove the scales, and then to rub the ointment into the lid margins two or three times a day with a glass rod or wooden probe. The length of treatment varied from 2 to 12 weeks, the time appearing to depend less on the severity or chronicity of the condition than on the intelligence and persistence with which the treatment was carried out. Evacuee children were almost invariably long in recovering; the children of obviously diligent mothers recovered within a few weeks.

A complete report on the bacteriology of the eyes after treatment is unfortunately impossible, as many patients would not report in person once they considered themselves cured. Clinical cure was obtained in 37 cases; of these, sterile or pathogen-free cultures were obtained at the completion of treatment in 24 cases. Improvement without complete recovery before the patients ceased attending was recorded in 7 cases, and no improvement after 2 weeks' treatment in 2 cases. Recurrences appeared in 10 cases, all but 3 within a month of the end of treatment. Except for 4, these recurrences were associated with staphylococcal infections of the skin, conjunctivitis from foreign bodies, colds or allergic manifestations. The recurrences were not severe and were all easily cleared in the 7 patients who persevered with treatment. In two cases *Staph. aureus* returned without producing symptoms. Of the 2 cases reporting no improvement, one may have had a chemical blepharitis, as a corneal ulcer had previously been treated with various preparations. No pathogenic organisms were isolated from this case. The other only carried out her treatment for 2 weeks.

Acute conjunctivitis.—The 18 cases include 4 of simple conjunctivitis infected with *Staph. aureus*, 1 growing a hæmolytic streptococcus as well; 6 cases with corneal ulcers, 4 being infected with *Staph. aureus* and 1 each with *Staph. albus* and *Bacterium coli*; 1 case with hypopyon which gave a growth of non-pathogens only; 1 case with meibomian cyst, infected with *Staph. aureus* and a hæmolytic streptococcus; 1 case of infected eye-socket, in which an achromobacterium only was found; and 5 cases of ophthalmia neonatorum, 2 infected with *Staph. aureus* and 1 each with *Bact. coli*, *Gonococcus* and an unknown organism.

The penicillin was applied in vaseline or distilled water, 600–800 units per g. or c.cm. The ointment was preferred as ensuring less waste, but when patients, as they occasionally did, complained of a burning sensation from the ointment, the drops were substituted. Treatment was given hourly by day and 2-hourly by night at first in the most severe cases, the frequency lessening as progress was noted. It was continued in all cases till cultures taken after 24 hours without treatment were sterile or grew only non-pathogens. No other treatment was given except in cases with a corneal ulcer, which received atropine or hyoscine when necessary.

Some of the cases, particularly those with ulcers, had had various antiseptics applied before penicillin, so that a pathogenic organism was not always found. All cases were free of pathogens after treatment. Improvement was felt or seen (except in 2 cases, the hypopyon and the *Bact. coli* ring ulcer) in 1–3 days. The ulcers healed in 5–7 days, including the staphylococcal ring ulcer which extended round two-thirds of the cornea. The conjunctivitis recovered in 1–5 weeks according to the severity of the case. The hypopyon, in a woman of 80, had cleared completely in a month. Treatment after a week was discontinued in the second ring ulcer when *Bact. coli* was the only organism found and no improvement could be seen; the patient had rheumatoid arthritis.

The gonococcal case of ophthalmia neonatorum had shown no response to 3½ weeks' sulphapyridine and irrigation. The discharge was profuse even under ¼-hourly irrigations. Penicillin (1200 units/c.cm.) was dropped into the eye hourly. In 12 hours the pus had much diminished and in 2 days it had gone; the eyes were open and the conjunctivæ white. No gonococci were seen in films made 8 days later, after penicillin

had been discontinued for 48 hours. No recurrence was reported. The other ophthalmias were treated with drops (600 units/c.cm.) and all cleared within a week. A mild recurrence which occurred in one was easily dealt with.

The infected eye-socket had received various local applications for 2½ weeks without improvement. The discharge, which was extremely copious, lessened considerably by the 4th day of penicillin treatment and within 2 weeks the socket looked healthy and cultures were sterile.

Chronic conjunctivitis.—These include all cases of conjunctivitis which had not responded to other treatment for from one month to several years. Of the 19 cases, 17 were simple, infected with *Staph. aureus* (7), *Staph. albus* (4), *Staph. albus* and *Achromobacterium* (1), *Staph. albus* and *Pneumococcus* (1), *Strep. viridans* (1), *Staph. aureus* and *Neisseria catarrhalis* (2), and an unknown organism (1); 1 case was associated with a corneal ulcer, infected with an unknown organism; and 1 with recurrent corneal ulceration, infected with *Staph. aureus*.

Penicillin drops or ointment, 400–800 units per g. or c.cm., were applied t.d.s. or 4-hourly according to the convenience of the patient and in all but 3 cases were continued for a week after cultures grew no pathogens, whether symptoms were present or not. All but one case recovered in 1–5 weeks, the average being 2½ weeks. Lacrimation persisted in some cases but usually responded to ephedrine. In the one case which did not respond the *Staph. aureus* disappeared but *N. catarrhalis* persisted, the clinical picture being typical of "spring catarrh." Recurrences were reported in 3, all of which responded to further penicillin treatment. *Staph. aureus* was cultured also from 3 cases which were symptom free a month or more after the end of treatment.

Dacryocystitis.—All except one of these 6 cases were of several years' duration. The organisms grown were: *Staph. aureus* 2 cases, *Staph. aureus* and *albus* (coagulase +ve) 1 case, and *Pneumococcus* 3 cases.

The sac was injected with a solution of penicillin in distilled water (800 units/c.cm.) five times in a week. Cultures were taken on the 8th day. Where probing of the duct was necessary, penicillin in vaseline was applied to the conjunctival sac.

Cultures invariably became sterile but clinical recovery occurred only in 3 cases. Two of the pneumococcal cases improved during treatment but did not persist with it. The third who failed to recover had lupus of his face. There was no appreciable lessening of the discharge. The 3 who recovered completely had treatment for 1–3 weeks; one of these was a boy of 8 years who had suffered from this complaint since birth.

CHRONIC WOUND SINUSES

The 11 chronic wound sinuses treated were under the care of Professor Seddon, Mr. Scott, Mr. Elliot Smith, Dr. Cooke, Mr. Whitelocke, Mr. Livingstone or Dr. Findlay at either the Wingfield-Morris Orthopædic Hospital or the Radcliffe Infirmary, Oxford. The source of the sinus was old osteomyelitis about the hip, 3 cases (duration 4 months to 12 years); old nephrectomy, 2 cases (duration 1 year and 5 years); ear and mastoid, 2 cases (duration 3 months and 2 years); old empyemas, 4 cases (duration 3 months to 1 year).

	Organisms	Cases
Old osteomyelitis ..	*Staph. aureus*	1
	Staph. aureus and *Strep. hæmolyticus*	2
Nephrectomy	*Strep. hæmolyticus*	2
Ear and mastoid ..	*Staph. aureus*	1
	Staph. aureus and *Strep. hæmolyticus*	1
Empyemas	*Staph. aureus*	2
	Staph. aureus and *Strep. hæmolyticus*	2

Method of treatment.—(*a*) For long and tortuous sinuses, injection of penicillin solution (200–500 units/c.cm.) under pressure through a catheter inserted to the furthest possible point, the sinus being closed by a rubber bung immediately after withdrawal of the catheter. Treatment repeated twice daily for from 10 days to 3 weeks.

(*b*) For short sinuses, insertion of penicillin powder.

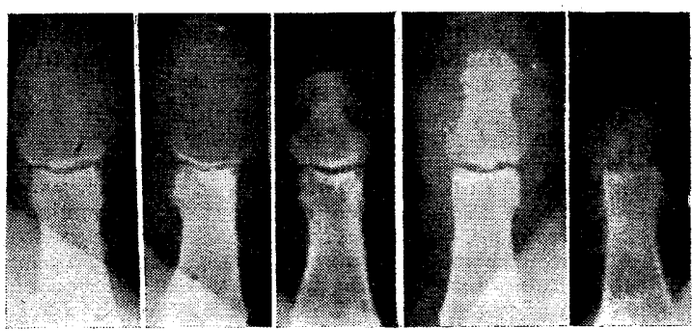
(*c*) For empyemas, injection of solution, 5–20 c.cm., twice daily with closure of the opening for all but an hour before the next injection.

Results.—Apart from 2 empyemas, all but 2 sinuses healed in from 10 days to 4 weeks. Treatment was continued till they became sterile on culture or grew only non-pathogens, *Pseudomonas pyocyanea* and *Bact. coli*. The shortest period in which sterilisation took place was 5 days. One sinus reopened after 3 months and discharged some pus—sterile on culture—and closed again quickly, another exudes a little watery fluid occasionally, while a third situated in the centre of much scar tissue, has not yet completely epithelialised. The others have shown no sign of recurrence in periods which range from 5 weeks to 18 months. In the 2 empyemas where healing was delayed a rib sequestrum and thickened pleura in the first and an epithelialised bronchopleural fistula in the second had to be dealt with surgically. The general health, as judged by weight, colour, blood-count and the patients' own feelings, improved noticeably in all patients who showed signs of debility.

MISCELLANEOUS INFECTIONS

A number of other infected cases (50 in all) have been treated locally. They include infected fingers, empyemata, wounds, carbuncles and dermatitis. They demonstrated repeatedly the ability of penicillin to remove staphylococci, streptococci and pneumococci when applied locally. In the majority of cases, chronic and acute, complete healing occurred without other treatment. In a few, surgical procedures were necessary to effect better access or to remove already sterilised abscesses. One case of meningitis following an infected lumbar puncture (*Staph. aureus*) appeared to be cured by repeated cisternal injection of penicillin (see also case 8 in "General" series). Further work is in progress on comparable cases of these types.

One case of staphylococcal infection in the terminal phalanx of first the right and then the left thumb provided an unplanned controlled experiment. Fig. 3*a* shows the condition of the right thumb 6 weeks after the onset of infection and



(*a*) (*b*) (*c*) (*d*) (*e*)

Fig. 3—Local treatment of infected thumbs (*Staphylococcus*), with and without penicillin treatment. (*a*) Right thumb, before penicillin, 6th week of infection; (*b*) at end of penicillin applications, 8th week of infection; (*c*) 4 weeks later. (*d*) Left thumb, 5th week of infection; (*e*) 17th week of infection. In the thumb treated with penicillin rarefaction accompanies cure of the infection, but 4 weeks later new bone has been laid down. In the thumb not treated with penicillin there is progressive necrosis of the terminal phalanx.

before penicillin treatment was started. Fig. 3*b* is 18 days later, at the end of a course of local applications of penicillin; note the increase in bone absorption. Fig. 3*c* is 6 weeks later and shows satisfactory calcification of the phalanx. While the left thumb was improving a similar condition appeared in the right. Fig. 3*d* shows the right thumb 5 weeks after the onset of infection; penicillin was not used in this case, and fig. 3*e* shows the end-result twelve weeks later.

COMMENT ON LOCAL APPLICATION

In this series of cases an attempt has been made to find means of applying penicillin locally so that susceptible infecting organisms are overcome. There is clear evidence that in a large number of the cases, both acute and chronic, the organisms were quickly eliminated, whereupon healing took place. A few general points can be emphasised. It is necessary to repeat the penicillin application at short intervals in an endeavour to keep up continuously a bacteriostatic concentration of the drug. It is necessary to continue till no organisms can be cultivated, and when treating eye lesions for some time after an apparent clinical cure. Relapses will occur if treatment is stopped too soon or is not pursued with sufficient assiduity and care. It cannot be emphasised too much that penicillin is not an antiseptic which kills organisms and it is therefore unlikely that one application will prove effective. It is no use expecting to sterilise a cavity, for example, by one

injection. It will be seen from a perusal of the cases reported that many applications are usually necessary but that when these are carried out properly there is every reason to expect a satisfactory result.

SUMMARY

Methods of using penicillin for the cure of infections by both general and local administration have been explored.

Of 15 cases of serious illness treated with penicillin by mouth or by intravenous or intramuscular injection, in 10 there was a staphylococcal infection, in 1 a sulphonamide-resistant streptococcal meningitis, in 3 infection with actinomyces or streptothrix plus an anaerobic streptococcus, and in 1 a subacute bacterial endocarditis due to *Strep. viridans*. The staphlococcal cases comprised 1 of orbital infection, 4 of acute or subacute osteomyelitis, 3 of pyæmia or septicæmia, 1 of fulminating cavernous sinus thrombosis and 1 of chronic osteomyelitis; all recovered, as also did the case of streptococcal meningitis. The 2 cases with actinomyces infection were not informative because the dosage was probably inadequate; in 1 case a streptothrix appeared to be eliminated. The subacute bacterial endocarditis improved during treatment but relapsed immediately it was stopped.

It is clear from this series that a generalised staphylococcal infection can be cured by penicillin and that local lesions heal during parenteral administration. The healing of bony lesions is particularly striking. In 4 staphylococcal cases the sensitivity of the organism to penicillin was tested before and after treatment; in 1 there was evidence of increased resistance.

The most practicable method of administration of the drug is by the intramuscular route at 3-hourly intervals. An endeavour has been made so to regulate the dose that the blood at all times contains at least enough penicillin to inhibit the growth of the infecting organism. This dose is about 15,000 Oxford units, but it varies from case to case.

In assessing progress attention should not be too sharply focused on the temperature chart, since other features, such as lessening of pain and improvement in appetite and sense of well-being are often more important. In staphylococcal osteomyelitis, X-ray examination shows increasing rarefaction of the affected bones during treatment, although the infection is being overcome. The radiological appearances should be interpreted in the light of this knowledge.

No toxic symptoms due to the drug have been met with.

Local penicillin treatment has been used in 172 infections of the eye and mastoid process, chronic wound sinuses and miscellaneous local septic conditions. In most cases after adequate treatment staphylococci and streptococci were eliminated with subsequent healing. While the supplies of penicillin will not permit the treatment of more than a few cases by general administration the uses of local application are being further explored.

Penicillin is as yet available in only the smallest quantities; no applications for it should be made either to the authors of this paper or to ICI (Dyestuffs) Ltd. for supplies.

We are indebted to the Medical Research Council and the Rockefeller Foundation for grants towards the manufacture of penicillin in the Sir William Dunn School of Pathology, Oxford.

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RUBBER GLOVES.—The Ministry of Supply have for sale rubber gloves of a good household quality suitable for many tasks for which surgical gloves are normally used. The Ministry are prepared to supply these in reasonable numbers to hospitals, clinics and mortuaries. Application should be made to the Secretary, Ministry of Supply (Rubber Control), Empire House, St. Martin's-le-Grand, London, E.C.1, who will give the names of firms from which the gloves may be obtained.

SORE AND BLEEDING GUMS
IN NAVAL PERSONNEL
VITAMIN C AND NICOTINIC ACID INTAKES

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THIS investigation forms part of an inquiry into the cause of sore and bleeding gums in Naval personnel, noted in 1940, and suspected on clinical grounds alone to be possibly due to vitamin-C deficiency. Between October and March 51 patients exhibiting the lesion were admitted to hospital, 38 from trawler-minesweepers and other small ships, 2 from larger ships and 11 from shore establishments. Our investigations included a search for clinical and other evidence of nutritional deficiency; clinical and bacteriological examination of the mouth and throat; estimation of vitamin-C intake; vitamin-C saturation tests; and finally controlled therapeutic tests in which both doctor and dentist took part.

INTAKE AND EXCRETION OF VITAMIN C

Dietary studies aimed to determine whether vitamin-C intake had been deficient during the 6 months before the onset or exacerbation of symptoms. The history of an average week's diet was taken with the help of food models and checked with weighed helpings* and investigation of victualling and cooking in small ships. "Typical" values for ascorbic acid content of raw, cooked and canned foods were adopted from food tables (Fixsen and Roscoe 1938 and 1940, Fixsen 1938, Olliver 1940); many were later replaced by lower values based on estimations by Dr. C. P. Stewart of Edinburgh, in another part of the investigation, of foods cooked and consumed on small ships. According to such data, which allowed merely an approximate estimate, the average daily intake in 49 cases ranged from 16 to 80 mg., as follows: 10–19 mg. (4 cases), 20–29 mg. (14 cases), 30–39 mg. (12 cases), 40–49 mg. (10 cases), 50–59 mg. (4 cases), 60–69 mg. (2 cases), 70 mg. or over (3 cases).

Men in small ships were seldom at sea longer than 3 weeks and usually in port every day or few days. They received the standard ration and a messing or victualling allowance, but did not appear to stint themselves of food containing vitamin C for the sake of mess savings; the average intake of vitamin C in 36 ratings from small ships was not significantly less than that of 10 ratings from shore establishments. Levels were highest in men who took large helpings of vegetables or who bought fruit ashore. Low levels were sometimes related to food fads.

The main source of vitamin C was potatoes. Usually the daily allowance of 1 lb. per head was peeled and kept in cold water until boiled. In some ships, freshly cooked potatoes were available twice daily. Usual helpings were 5–13 oz.; average 8 oz. Greens were cooked unconservatively and often kept hot. Dislike of cabbage was common. Vegetables in soups were cooked many hours—not added just before serving. Although plentiful, turnip was seldom eaten more than 3–4 times a week; canned beetroot even less often. Carrots and canned peas (even the non-processed variety) were not rich in vitamin C; the juice was usually discarded. Canned tomatoes, a useful source, were avoided by some. Compared with canned grapefruit, the usual canned fruits—peaches, pears, apricots, pineapple—were not good sources of vitamin C. In amounts consumed, liver, fresh milk and jams, apart from richer kinds (e.g., blackcurrant, strawberry) contributed little.

Patients were described as saturated, nearly saturated, or unsaturated to varying degrees according to whether an excretion of 100 mg. or more was obtained after the first, second, third, fourth, fifth or sixth test dose of 700 mg. of ascorbic acid.† In the few instances in which

* Food models represented weighed helpings of foodstuffs—e.g., 4 oz. cooked cabbage, as used by Miss Pybus, dietetic sister, Royal Infirmary, Edinburgh. In the case of potatoes and other important sources of vitamin C, patients helped themselves with quantities they normally consumed aboard ship and these amounts were weighed.

† Urine, collected for 24-hour periods in dark bottles kept cool and containing concentrated glacial acetic acid, was tested by rapid titration against 2 : 6 dichlorophenolindophenol. Results checked well with those of C. P. Stewart, and of McNee and Reid.