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 bacteriological and chemical facts which were then 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.

As early as 1944 preliminary studies were made to determine the limits of penicillin can be made. This substance is extremely soluble in water but is destroyed by boiling, by acids and alkalies, 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. Pasteur, 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 coordination of many separate elements.

The production of much of the penicillin used is due to the work of Mr. G. Glaister, with the assistance of Miss P. McKegney, Miss B. C. Callow, Miss B. Cook, Miss M. Lancaster and Miss P. Gardiner. Dr. A. G. Sanders and Mr. J. Kent have been responsible for the maintenance of the laboratory large-scale extraction plant. We are indebted to 1CF (Dyesuffs) 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 decision regarding the need 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 penicillin 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 "bactericidal" effect, but it 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 technique.

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 100,000 or 200,000 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 but 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. Dr. H. White, late Mr. A. M. Frankland.) Mr. H. J. J. O'Brien, M. R. C. Oph. S. age 24 years, weight 160 lb. Pimples on nose 3 weeks before had led to cellulitis extending from ala 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 given, temporal tenderness 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: 1 capsule for first 5 days; by duodenal tube on days 6 and 7.

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
<th>Blood bacteriostasis (cylinder test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5000 units 2-hour.</td>
<td>Trace</td>
</tr>
<tr>
<td>2–5</td>
<td>10,000 4-hour.</td>
<td>Trace</td>
</tr>
<tr>
<td>6 and 7</td>
<td>10,000 4-hour.</td>
<td>Trace</td>
</tr>
</tbody>
</table>

Total: 480 units.

Progress.—Inflammation of face subsided and proptosis and oedema of right eyelids lessened. An orbital cellulitis was still present, with secondary intracocular 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 apprised when penicillin discontinued but eye condition had not subsided; 18 days later papilloedema and signs of raised pressure. Cultures cultivated from cerebrospinal fluid. Treated with sulpha-thiazole and eventually recovered, eye being enucleated. No albuminuria throughout.

Blood examinations 

---

<table>
<thead>
<tr>
<th>Blood examination</th>
<th>Red cells</th>
<th>White cells</th>
<th>Blood-stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>per cm³</td>
<td>per cm³</td>
<td>mg. per 100 c.mm.</td>
</tr>
<tr>
<td>At beginning of Tt.</td>
<td>3,350,000</td>
<td>65</td>
<td>18,000</td>
</tr>
<tr>
<td>At end of Tt.</td>
<td>3,290,000</td>
<td>80</td>
<td>16,000</td>
</tr>
</tbody>
</table>

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 apprised at the end of treatment the staphylococcus had not been eliminated as his subsequent history showed. No toxic effects were noted. |

Case 2.—Actinomyces of lungs and possibly of gastrointestinal tract. (Radcliffe Infirmary. Dr. F. G. Hobsom.) Male, age 36, weight 117 lb. Attacks of abdominal pain for 15 months. Swelling of left loin, pleural effusion, and cough with a sputum that was ameliorated by potassium iodide and postural drainage. Appreixal when admitted for penicillin treatment but complained of cough and weakness. Swelling in loin and pleural effusion had subsided some time before penicillin was given.

Bacteriology.—Actinomyces often found in sputum and present in faeces. 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, diarrhoea and colic. Sputum still contained actinomyces a week after end of treatment. Diarrhoea persisted. No albuminuria throughout.

Blood examinations

<table>
<thead>
<tr>
<th>Red cells</th>
<th>Hb. %</th>
<th>White cells</th>
<th>Blood-pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of treatment</td>
<td>2,300,000</td>
<td>54</td>
<td>10,000</td>
</tr>
<tr>
<td>At end of treatment</td>
<td>3,400,000</td>
<td>58</td>
<td>14,000</td>
</tr>
</tbody>
</table>

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 no recto-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 vertebrae 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 destruction of 3rd vertebra with soft-tissue swelling, with dislocation of femur from acetabulum. Finger showed some bony involvement but nothing abnormal seen radiologically in cervical vertebrae. Apathetic, very thin, gaining weight at ½ oz. a week. Sulphapyridine proved ineffective; 61st administration of sulphanilamide 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 lumbar 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 the abscesses. By 20th day's treatment neck of 20 day's treatment neck of 3rd vertebrae 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 only.

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 arm. X rays showed complete fusion of cervical and lumbar spines with solidification 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 | Hb. % | White cells | Blood-area :
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of treatment</td>
<td>2,900,000</td>
<td>56</td>
<td>17,000</td>
</tr>
<tr>
<td>4 days after end of Tt.</td>
<td>3,400,000</td>
<td>66</td>
<td>13,000</td>
</tr>
<tr>
<td>14 days after end of Tt.</td>
<td>3,800,000</td>
<td>72</td>
<td>14,000</td>
</tr>
<tr>
<td>4 months after end of Tt.</td>
<td>3,800,000</td>
<td>56</td>
<td>17,000</td>
</tr>
</tbody>
</table>

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 haemorrhage and pyrexia after self-induced abortion. Consultation advised and a pelvic paracentesis 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 96° and 105° 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 B. coli, anaerobic and 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 bacteriodes (ring test) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>35,000-40,000 units in 10 c.cm.</td>
<td>Present at 2 hr. intraven. 12–hrly.</td>
</tr>
<tr>
<td>5 and 6</td>
<td>17,000 in 10 c.cm. intramus.</td>
<td>absent at 7 hr.</td>
</tr>
</tbody>
</table>

Total: 412,000 units.

Continuous duodenal drainage established to relieve distension.

Comment.—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. fecalis and Bact. coli. Made slow recovery and discharged convalescent in 10 days.

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 ischiium 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. ischiium with subsequent sequestrum formation associated with abscess in R. buttock. Sinus formed and still discharging after 7 months. A week before admission patient's condition had become much worse; 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 developed. At this time the patient was 100 lb. and had a temperature of 103° F. Continuous daily urography showed left ureteric dilatation. One month after admission the urine contained blood and pus cells. Local redness of right thigh noticed.

Method of penicillin treatment.—For 21 days given 9000 units in 1 c.cm. 6-hourly intramuscularly. Total: 765,000 units.

Progress.—Hyperaemia 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° F., and pulse-rate though variable generally remained between 80 and 90 for the rest of the 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. Splint 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 for 5 months. Made slow recovery and left hospital at a time. Urine sterile on discharge. General appearance greatly improved.
Walking 4 months after treatment began, mobility of hip joint improves significantly. Continued improvement.

<table>
<thead>
<tr>
<th>Blood examinations</th>
<th>Red cells</th>
<th>Hb. %</th>
<th>White cells</th>
<th>Blood-urea</th>
<th>mg. per 100 c.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Tt.</td>
<td>200,000</td>
<td>66</td>
<td>10,000</td>
<td>100 c.c.</td>
<td></td>
</tr>
<tr>
<td>7th day of Tt.</td>
<td>4,200,000</td>
<td>70</td>
<td>9000</td>
<td>100 c.c.</td>
<td></td>
</tr>
<tr>
<td>At end of Tt.</td>
<td>4,400,000</td>
<td>74</td>
<td>7000</td>
<td>100 c.c.</td>
<td></td>
</tr>
</tbody>
</table>

**Comment.**—It was not thought justifiable to trouble this child with abdominal needle injection, as the clinical picture showed that the 6-hourly injections maintained sufficient bacteriostasis in the blood. The practicability of long continued intramuscular treatment was shown, since no local disturbance was experienced at the site of injection. No serious side effects were found from the drug. Since the only other treatment given besides the penicillin was splitting, 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 38 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 malleolus, with some redness over external malleolus. No fluctuation. Child flushed with hot dry skin; restless and unsteady. Temperature and pulse 102° F. Had received 6 g. sulphanalumide made by 4 g. sulphathiazole, discontinued 8 hours before penicillin begun.

**Bacteriology.**—On 3rd day of penicillin treatment Staph. aureus was grown from few c.mm. turbid fluid aspirated from L. ankle joint. Blood culture negative.

**Method of penicillin treatment.**—All doses given intramuscularly.

<p>| Blood bacteriostasis (ring test) |</p>
<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>20,000 units in 1 c.cm. 8-hrly.</td>
</tr>
<tr>
<td>5-7</td>
<td>10,000 units in 0.5 c.cm. 4-hrly.</td>
</tr>
<tr>
<td>8-14</td>
<td>15,000 units in 0.75 c.cm. 4-hrly.</td>
</tr>
<tr>
<td>Total:</td>
<td>1,100,000 units.</td>
</tr>
</tbody>
</table>

**Progress.**—During first 4 days fever changed from continued to irregular swelling course. Swelling of L. leg extended for 3 hours, reached to tibial tuberosity and later down over dorsum of foot. On 5th day, after X ray had shown definite rarefaction on metaphysal side of internal malleolus, child was examined under anaesthetic. 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 1° F. higher than before and settled to 99°F. in 4 days—i.e., 10 days after beginning of penicillin treatment. Child made steady recovery from 6th day and able to take part in "school on 9th day. Three days after plaster cast had been applied it was removed and child had not had difficulty. On removal of plaster 7 days later no oedema 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 18th 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 been at time from infant was completely epithelialised. No albuminuria throughout.

<table>
<thead>
<tr>
<th>Blood examinations</th>
<th>Red cells</th>
<th>Hb. %</th>
<th>White cells</th>
<th>Blood-urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of Tt.</td>
<td>4,000,000</td>
<td>78</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>2 days after end of Tt.</td>
<td>4,000,000</td>
<td>78</td>
<td>9000</td>
<td></td>
</tr>
</tbody>
</table>

**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 dose was increased to 8-hourly and later 4-hourly intervals. This undoubtedly was the case. In the writer's opinion the effect of penicillin was due to surgical intervention, but, unfortunately, for the assessment of the case, no pus was found and the incision remained sterile throughout. When the application of a plaster instead of a backslip may have had some influence on the fall of temperature but it is reasonable to attribute the alleviation of infection and rapid recovery of complete function to the penicillin. No toxic symptoms from the drug were noted.

**INTRAVENTRICAL AND INTRAMUSCULAR**

**Case 7.—Pyemia.** (An R.A.F. 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 last week ill was in hospital for 8 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. Ceci in condition to be steadily deteriorating. Penicillin asked for after 6th week because all other treatment having failed, outlook considered hopeless. Irregular pyrexia, much purulent spustum 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: 1,550,000 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.

<table>
<thead>
<tr>
<th>Blood examinations</th>
<th>Red cells</th>
<th>Hb. %</th>
<th>White cells</th>
<th>Blood-urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of Tt.</td>
<td>4,100,000</td>
<td>50</td>
<td>38,400</td>
<td>21.8</td>
</tr>
<tr>
<td>1st day of Tt.</td>
<td>4,000,000</td>
<td>40</td>
<td>36,000</td>
<td>21.8</td>
</tr>
<tr>
<td>4 days after end of Tt.</td>
<td>5,140,000</td>
<td>100</td>
<td>9000</td>
<td>29.6</td>
</tr>
</tbody>
</table>

**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.

**INTRAVENTRILEAL AND INTRAMUSCULAR**

**Case 8.—Empyema.** (Radcliffe Infirmary, Mr. White- lockdown, Holme, London.) Male, age 64, weight 153 lb. 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 500 c.cm. creamy foul-smelling pus from 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 streptococcii (anaerobic). Spumia grew pneumo cocci, Spiro. 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.
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 afford. First 7 days of local treatment and of streptococci from 24th day till 12 days after treatment was stopped. Sputum contained no streptococci 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 streptococci. Convalescence complicated by carbuncles but patient had regained apyrexia. No streptococci found in sputum or carbuncles up to 43 months after treatment.

Blood examinations

<table>
<thead>
<tr>
<th>Blood examinations</th>
<th>Red cells</th>
<th>Hb%</th>
<th>White cells</th>
<th>Blood-pressure</th>
<th>mg. per 100 c.c.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of G. Tr.</td>
<td>3,109,000</td>
<td>62</td>
<td>20,000</td>
<td>G. Tr.</td>
<td>100 c.c.m.</td>
</tr>
<tr>
<td>At beginning of G. Tr.</td>
<td>3,200,000</td>
<td>62</td>
<td>13,000</td>
<td>100 c.c.m.</td>
<td></td>
</tr>
<tr>
<td>6 days later</td>
<td>3,700,000</td>
<td>74</td>
<td>11,000</td>
<td>100 c.c.m.</td>
<td></td>
</tr>
<tr>
<td>3 weeks later</td>
<td>3,900,000</td>
<td>74</td>
<td>11,000</td>
<td>100 c.c.m.</td>
<td></td>
</tr>
<tr>
<td>G. Tr.</td>
<td>general treatment.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 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 abscesses after 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.—A 7 g. sulphapyridine in 24 hours, then 12 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 i.m. intraven.
2 | 6666
3 | 20,000
4 | 6666
5 | 10,000
6 | 6666
7 | 13,000
8, 9 and 10 | 10,000
Total | 1,893,000 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 except some crusts on sinus and good movement of right eye, vision, pupillary reactions and movements of eyeball normal. Discs could not be seen clearly. Retention of urine.

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On 4th day 48 hours after penicillin the temperature then did not rise above 99° F.; pulse-rate 84—96 per min. Had regained control of bladder. Appetite good. Some of ocular motor 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 3rd and 6th nerves were paralyzed, 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. Eleven weeks after initial infection 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 movements of right eye, vision, pupillary reactions and movements of eyeball normal. X-ray showed considerable rarefaction 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

<table>
<thead>
<tr>
<th>Blood examinations</th>
<th>Red cells</th>
<th>Hb%</th>
<th>White cells</th>
<th>Blood-pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of G. Tr.</td>
<td>3,109,000</td>
<td>62</td>
<td>20,000</td>
<td>G. Tr.</td>
</tr>
<tr>
<td>10th day</td>
<td>3,000,000</td>
<td>14</td>
<td>12,100</td>
<td></td>
</tr>
<tr>
<td>At end of (10th day)</td>
<td>4,200,000</td>
<td>72</td>
<td>7,800</td>
<td></td>
</tr>
</tbody>
</table>

Comment.—This undescribed 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 was a 48 hours of sulphathiazole and 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 82, weight 152 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 abscesses after 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 L. knee, 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-hr. | Complete for 2 hr. after 10,000 unit dose, in- (continued 3 times)
4—12 (day) | 10,000 |
8—14 (night) | 20,000 |
13—14 (day) | 15,000 | 3-hr. |

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 coed in discharge from sinus decreased and sputum became thinner.

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 film of staphylococci. X-rays showed rarefaction and whole length of femur; limb therefore enclosed again in plaster, and patient transferred to orthopedic hospital. No albuminuria throughout treatment.

Blood examinations

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
<th>Blood bacteriostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>20,000 units 2-hrly.</td>
<td>Complete for 3 hr. up to dilution of serum of 1: partial up to 1:</td>
</tr>
<tr>
<td>5-9</td>
<td>10,000</td>
<td>2-hrly. by day</td>
</tr>
<tr>
<td>10-13</td>
<td>10,000</td>
<td>2-hrly. by night</td>
</tr>
<tr>
<td>14-16</td>
<td>15,000</td>
<td>2-hrly. by day</td>
</tr>
</tbody>
</table>

Total: 2,590,000 units.

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 orthopaedic 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.—Pyelonephritis, A RAF hospital. Wing-Commander D. M. Anderson.) Male, aged 34, weight 147 lb. (about). Illness began 3 weeks earlier with boil behind R. ear, followed by carbuncle on back of neck, spreading over scapula. Signs of pneumonia developed, and pain and swelling appeared on inner side of L. arm.图标

At beginning of Tt. (after transfusion) 3,422,000 65 14,790 32
After 1 day 3,890,000 72 10,800 59
After 2 days later 4,200,000 89 13,000 27

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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 comatoso, with intervals of extreme restlessness. Had uncontrolled hiccup for past 10 days; incontinence of urine and faeces for a week. Night before treatment started oxygen administered; man believed to be dying. Previous treatment.—Sulphonamides, 1 g. 4-hourly for 3 days, lowered temperature but it rose again promptly at end of course 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-hemolytic streptococcus was isolated by shaking 3 c.c.m. of CSF in 10 c.c.m. of slopp 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 was 100 fold at parting up to 1320; 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 A.M. to 8 P.M., with 20,000 units at 10 A.M. 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

<table>
<thead>
<tr>
<th>Hb. %</th>
<th>White cells per c.mm.</th>
<th>Blood-urea</th>
<th>per c.mm.</th>
<th>mg. per 100 c.c.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of Tt.</td>
<td>85</td>
<td>8300</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>At end of Tt.</td>
<td>84</td>
<td>8300</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

White-cell count dropped steadily during treatment.

Bacteriostasis complete in 9 of 11 samples of blood, partial in 1 (side-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 had become inoperable. 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.

Case 13.—Staphylococcus aureus septicemia. (Radcliffe Infirmary. Mr. Stallworth.) Female, age 37, weight in health about 120 lb. After a delivery with considerable haemorrhage given blood-transfusion intravenously. R. saphenous vein; 4 days later temperature rose to 102°F. and felt pain behind R. knee. On 7th day signs of lung involvement. Temperature remained between 102° and 105°F. and pulse after 140 until 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 voice 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 interosseous tissues along thigh side of leg. Well-marked oedema of dependent parts of body.

Previous treatment.—Sulphonamides given but frequently vomiting 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.mm. and 4 days later 70 colonies per c.mm.), and from sputum before penicillin started, and later from abscesses were grown in pure culture.

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 dyspnoea accompanied by pain in chest started, with clinical signs of multiple emboli; cough looser. On 4th day kient began to look better and blood culture sterile. After 6th day attacks of dyspnoea 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 used during the illness. On 17th day 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 opacification 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 embolic. 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 an uninterrupted recovery. Cough completely gone 3 days after penicillin stopped.

Patient was losing profuse bright red lochia throughout treatment.

Blood examinations

<table>
<thead>
<tr>
<th>Red cells per c.mm.</th>
<th>White cells per c.mm.</th>
<th>Blood-urea</th>
<th>mg. per 100 c.c.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>At beginning of Tt.</td>
<td>38</td>
<td>5000</td>
<td>46</td>
</tr>
<tr>
<td>2nd day of Tt.</td>
<td>3,700,000</td>
<td>40</td>
<td>16,000</td>
</tr>
<tr>
<td>10th</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14th</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At end of Tt. (20th)</td>
<td>7,200,000</td>
<td>28</td>
<td>6000</td>
</tr>
</tbody>
</table>

* Before transfusion of cells from 1 pint of blood.

Blood examinations

| At beginning of Tt. | 38 | 5000 | 46 |
| 2nd day of Tt. | 7000,000 | 35 | 9000 |
| 14th | | | |

Comment.—In spite of the patient's very low haemoglobin no transfusion was given after the initial print of packed cells for the first 10 days. With the mastery of the infection the haemoglobin rose although a profuse lochia continued. Only after the disappearance of the signs of emboli and after 12 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 not to attribute the very satisfactory clinical result to the penicillin treatment alone.

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

* This case was treated with penicillin supplied from Oxford. We are indebted to Prof. Robert Parker Fildes 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 wound incised in both 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 98° 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 in both lungs. 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 joints; thick blood-stained pus aspirated from R. fibula. Tenderness and tenderness of L. joint; pssos spasm and tenderness under L. ischiium; 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 Orthopedic Hospital.

Bacteriology.—Heavy growth of Staph. aureus (coagulase +ve) obtained from sinuses of abscesses asystole 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 overcame continued pssos 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, infection asyptote 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. Respirograph showed earliest definite improvement; regular between 20 and 25 by 9th day. Temperature finally remained normal 26 days after treatment began. Anemia 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 lesion not complete by close of treatment. Elbow swollen and painful on movement on 6th day, but subsided. Sinuses dry by 9th day. L. ankle swollen more during second week; aspiration produced no fluid. R. fibula abscess aspirated several times and showed signs of discrete abscess in Staph. aureus; both this abscess and some fluid which had collected in old R. tibial abscess cavity sterile at end of 3 weeks.

Radiograms, as in other cases, showed progressive rarefaction of affected bones at first (fig. 2a 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, skipping 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 asymptomatic. Movement in all joints except L. ankle became full and free. Leuко very well and had returned to same weight as before illness.

Blood examinations Red cells White cells

<table>
<thead>
<tr>
<th>Day</th>
<th>Doce (per c.mm.)</th>
<th>Hb. %</th>
<th>White cells (per c.mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6</td>
<td>1,900,000</td>
<td>35</td>
<td>22,000</td>
</tr>
<tr>
<td>7-13</td>
<td>1,900,000</td>
<td>35</td>
<td>22,000</td>
</tr>
<tr>
<td>14th</td>
<td>1,900,000</td>
<td>35</td>
<td>22,000</td>
</tr>
<tr>
<td>6 weeks later</td>
<td>3,000,000</td>
<td>74</td>
<td>10,000</td>
</tr>
</tbody>
</table>

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

INTRANUSCULAR AND INTRAVENOUS

Case 15.—Subacute bacterial endocarditis. (Radcliffe Infirmary. Dr. Cooke.) Male, age 24, weight about 98 lb. (135 cm.); health apparently normal. Admitted for treatments 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. sulphamamide in a week and later 'Solusetamine,' 4 ampoules daily for 3 days. None of these drugs affected TPR or symptoms.

Bacteriology.—Month after illness begun Strep. viridans cultivated from blood. Positive blood-culture also obtained before beginning of penicillin administration. Streptococci 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 Doce and route of penicillin

<table>
<thead>
<tr>
<th>Day</th>
<th>Doce (mg.)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>25,000</td>
<td>intra.</td>
</tr>
<tr>
<td>4-55</td>
<td>25,000</td>
<td>intra.</td>
</tr>
<tr>
<td>6-75</td>
<td>25,000</td>
<td>intra.</td>
</tr>
<tr>
<td>8-95</td>
<td>25,000</td>
<td>intra.</td>
</tr>
</tbody>
</table>

Progress.—During first week appetite improved rapidly and remained of surprising proportions throughout treatment; temperature dropped steadily till between 95° and 99°F., pulse-rate fell a little and respiratory-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 from 10,000,000 to 22,000,000 units, transitory improvement and rose again after 2 days. On further raising dose temperature again dropped; blood-culture at this stage negative.

Pre- and post-treatment 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 the effect was remarkable. An impression that a condition had been reversed, and that the blood-urea level was lower than before. Little change in heart signs; some indefinite abdominal pain and tension sensation across chest; no other added symptoms and no embolic phenomena. Three weeks after admittance fever had stopped; he seemed better; blood transfusion and blood-culture were again positive; he was sent home, and died 3 weeks later.

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 case 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 not infrequent. A dose of at least 60,000 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 it must be attempted 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 something new. Other aids 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 a period as long as 14–20 days. Penicillin should be continued until this result has been obtained and for a few days longer.

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Sensitivity of Organism to Penicillin Before Treatment Compared with That During or After Treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Organism</th>
<th>Source of organism</th>
<th>Involvement, start of treatment, when culture taken</th>
<th>Comparative amounts of penicillin necessary for complete inactivation of culture at 2nd and 1st culture</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Staph. aureus</td>
<td>Wound</td>
<td>10</td>
<td>No change</td>
<td>None with culture from original wound</td>
</tr>
<tr>
<td>11</td>
<td>Carbanue</td>
<td>13</td>
<td>4 times as much</td>
<td>Both compared with original culture from carbanue</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Sputum</td>
<td>15</td>
<td>No change</td>
<td>Organism from the original blood-culture had the same titre</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Abscess, L. ankle</td>
<td>7</td>
<td>No change</td>
<td>Abscesses stimulated during treatment compared with original blood-culture</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Blood-culture: abscess</td>
<td>12</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Staph. viridans</td>
<td>Blood-culture</td>
<td>51</td>
<td>4 times as much</td>
<td>Same blood-culture taken 21 days after end of treatment</td>
</tr>
</tbody>
</table>

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. The possibility of local use must be considered—for instance, its unimpaired activity in the presence of pus and autolytic products, and its low count and hemoglobin 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. This fact that in certain cases blood-transfusion was witheld does not mean that it is undesirable. Improvement in the haemoglobin 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 bone lesions were particularly interesting, for rarefaction of the bone increased simultaneously with the general improvement, so that at the end of the treatment the bones looked a good deal worse radiologically than at the beginning. Nevertheless, when left alone they gradually recalculated. 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 (7 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 arthritis 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.
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. In the present paper, it is assumed that the hygroscopic calcium 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 on account of the calcium ion entering in no circumstances, however, be injected in strong solutions intramuscularly or intravenously.

In essence, the problem of using penicillin locally is that the sodium salt is the 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 order it is best to establish a closed cavity when possible and let the penicillin be in situ, for 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 technique so as to be able to fulfill 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. Cases was found in 18, mucoid or mucopurulent material in the ear.

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

Bacteriology.—Hemolytic streptococci were found in 8 cases, pneumococci in 6 and Staph. aureus in 2; 4 cases were sterile. No pathogenic hemococcoids were isolated.

Method of treatment.—After an orthodox Schwartzte 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 for 5 days, then 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.c.m. The amount used for one case varied from 5000 to 35,000 units; average 17,500 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 of penicillin was sometimes found to be in the serum of infected patients—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, as some cases in the present series were treated for 14 days, 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 reported by E. R. Hobbs for her 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 hydropnyp 1), 19 of chronic conjunctivitis, and 6 of dacrocystitis.

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 in 35 cases; 34 grew 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 35 cases no cultures were made.

Treatment 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 eye-lids with the vaseline for a few seconds 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 allow their eyes to be swabbed. 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 remission was noted in 13 cases, 2 of which were later cured, 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, and their treatment was activity at the infectious 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. In 4 cases reporting no improvement, one of which we had a chemical blepharitis, a lid 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.

In the 4 cases of conjunctivitis infected with Staph. aureus, 1 growing a hemolytic streptococcus as well; 6 cases with corneal ulcers, 4 being infected with Staph. aureus and 1 each with Staph. albus and Baciliiarium coli; 1 case with hydropnyp which gave a growth of non-pathogens only; 1 case with management cyst, infected with Staph. aureus and a hemolytic streptococcus; 1 case of infected eye-socket, in which an achromobacterium only was found; and 5 cases of ophthalmia neonatorum, 2 again with Staph. albus and 3 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.c.m. The ointment was preferred as ensuring less waste, but when patients, as they occasionally did, complained that too much vaseline had been left on the lid, 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 treatments before penicillin. 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 hydropnyp 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 hydropnyp, in a woman of 80, had cleared completely in a month. Treatment was continued for 6-8 weeks after they had been made sterile 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 34 weeks' sulphadiazine and irrigation. The discharge was profuse even under 4-hourly irrigations. Penicillin (1200 units/c.c.m.) 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 conjunctive white, no gonococcus 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.c.m.) and all cleared within a week. A mild recurrence which occurred in one was easily dealt with.

The infected eye had been treated by various local applications for 2 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 sinuses.—There were 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), Strep. haemolyticus (2), Strep. pyogenes (1), 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 and Neisseria catarrhalis.

Penicillin drops or ointment, 400–800 units per g. or c.c.m., 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. Laceration 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 of a typical “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.

Dacrocystitis.—All except one of these 6 cases were of several years’ duration. The organisms grown were: Staph. aureus 2 cases, Staph. albus 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.c.m.) five times in a week. Cultures were taken on the 8th day. Where probing of the duct was necessary, penicillin in vial 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. Whitecock, Mr. Livingstone or Dr. Findlay at either the Wingfield-Morris Orthopedic 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 epymomas, 4 cases (duration 3 months to 1 year).

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old osteomyelitis</td>
<td>Staph. aureus 1</td>
</tr>
<tr>
<td>Nephrectomy</td>
<td>Staph. albus and albus 2</td>
</tr>
<tr>
<td>Ear and mastoid</td>
<td>Strep. hemolyticus 2</td>
</tr>
<tr>
<td>Epymemas</td>
<td>Staph. aureus and 1</td>
</tr>
<tr>
<td>Staph. albus 2</td>
<td></td>
</tr>
<tr>
<td>Strep. hemolyticus 1</td>
<td></td>
</tr>
<tr>
<td>Staph. albus 1</td>
<td></td>
</tr>
</tbody>
</table>

Method of treatment.—(a) For long and tortuous sinuses, injection of penicillin solution (200–500 units/c.c.m.) 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 epymemas, injection of solution, 5–20 c.c.m., twice daily with closure of the opening for all but an hour before the next injection.

Results.—Apart from 2 epymemas, 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, Pseudomomas pyogenes and Bacit. 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 epymemas where healing was delayed a rib sequestrum and thickened pleura in the first and an epithelialised bronchopneumonic 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, empyemas, 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.

The case of staphylococcal infection in the terminal phalanx of the right thumb and then the left thumb provided an unplanned controlled experiment. Fig. 3a shows the condition of the right thumb 6 weeks after the onset of infection and before penicillin treatment was started. Fig. 3b is 18 days later, at the end of a course of local applications of penicillin; note the increase in bone absorption. Fig. 3c 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. 3d shows the right thumb 6 weeks after the onset of infection; penicillin was not used in this case, and fig. 3e 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 24-hour 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 example the apparent clinical relief 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 anti-septic 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, 12 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 streptobacillus plus an anaerobic streptococcus, and in 1 a subacute bacterial endocarditis. The streptococcal cases comprised 1 of orbital infection, 4 of acute or subacute osteomyelitis, 3 of pyemia or septicemia, 1 of fulminating cavernous sinus thrombosis and 1 of chronic osteomyelitis. All recovered as also did the cases 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 bone lesions is particularly startling. 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 mouth due to the rapidity of its effect; in 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 is about 15,000,000 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 clinical knowledge.

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

Local penicillin treatment has been used in 179 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 toICI (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.

REFERENCES


Wright, A. E. and Colebrook, L. (1921), Technique of the test and capsular glass tube, London.

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, 21, Portland Place, London, W.1, or to the Manager, 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

C. C. UNGLEY, M.D. DURR, F.R.C.P.

J. S. F. HORTON, M.D.

(From a Naval Auxiliary Hospital)

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 examined and treated. From trawler-mine-sweepers and other small vessels, 2 from land-based, 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 has been deficient during the past, and whether 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 victualing and cooking in small ships. Typical values were derived from those of raw, cooked and canned foods were adopted from food tables (Fixinson and Roscoe 1938 and 1940, Fixisen 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 daily average intake in 49 cases ranged from 10 to 80 mg., as follows: 10-19 mg. (14 cases), 20-30 mg. (12 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. Leaves 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. Cabbage was a useful source of vitamin C. Canned vegetables 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 and added just before serving. Although plentiful, turnips were seldom used 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 of vitamin C, were rarely eaten. 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., a cup of milk from a milk bottle, a receptacle of butter from Royal Infirmary, Edinburgh. In the case of potatoes and other vegetables the amount customarily served was estimated with quantities they normally consumed aboard ship and these amounts were weighed.
† Trays were kept in nitric acid for 4 hour periods in dark bottles kept cool and containing concentrated glacial acetic acid, was tested by rapid titration against 2: 6 dichlorophenolphthalein. Results checked well with those of C. P. Stewart, and of McNees and Reid.