

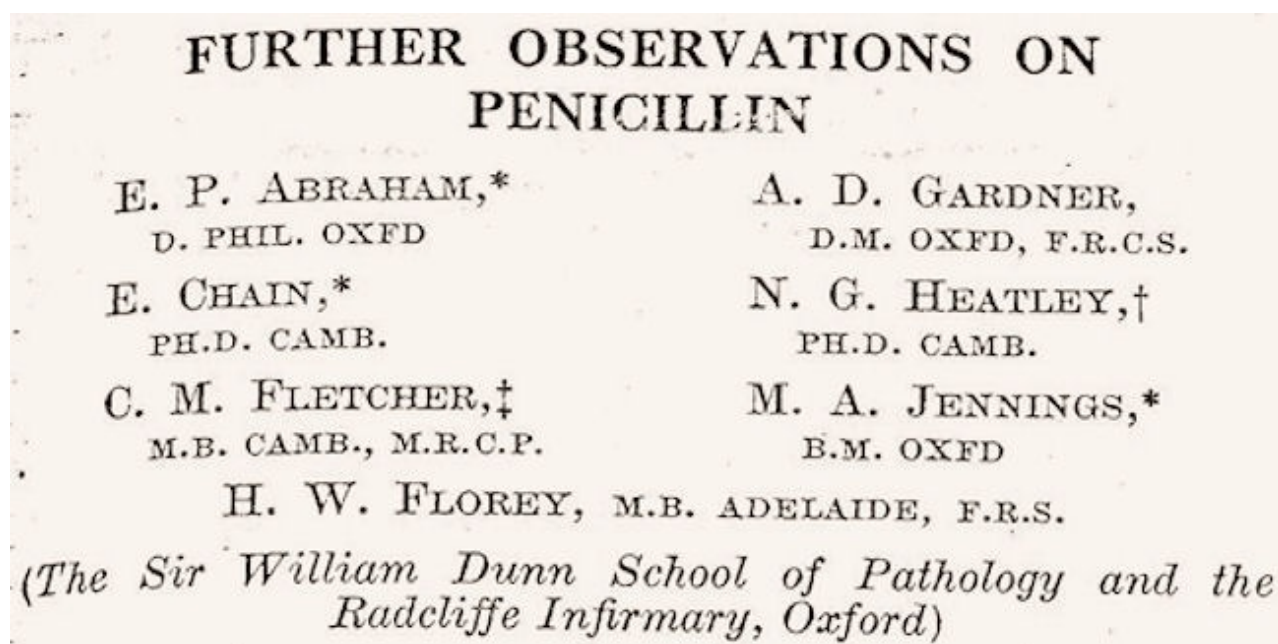
Records

Key Passage(s) Context

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[Abraham EP, Chain E, Fletcher CM, Gardner AD, Heatley NG, Jennings AM, Florey HW \(1941\)](#). Further observations on penicillin. *Lancet* 2:177-189.

Key passages



THERAPEUTIC TRIAL OF PENICILLIN

Methods of administration.—To avoid the uncertainties of intestinal absorption, the first cases were treated by penicillin given intravenously. Since it is rapidly eliminated by the kidneys and probably partially inactivated in the body, it was clear that frequent doses would be necessary. At the outset it was felt that intermittent administration might give the best diffusion into the tissues as a result of the repeated temporary raising of the concentration of the drug in the blood above the highest level that could be attained by continuous administration of the same total quantity. To facilitate frequent injections a cannula was tied or a needle inserted into a vein and connected to a slow drip apparatus (Marriott and Kekwick 1940) which delivered a steady flow of 500 c.c.m. of 1.05% sodium citrate and 0.8% sodium chloride in 24 hr. Each dose of penicillin was dissolved in about 2 c.c.m. of non-pyrogenic water, injected into the rubber tubing of the drip apparatus and flushed in with a little of the citrate-saline solution. This method is admittedly inconvenient owing to the well-known difficulties of maintaining an intravenous infusion for more than two or three days, but it was thought that if the therapeutic efficacy of penicillin could be established by this method other ways of giving the drug could then be explored.

In case 5 the effect of running in a continuous supply of penicillin solution was tried. At first a dilution of 1/1000 in normal saline was used, and as this was found to be no more harmful to the vein than normal saline alone the concentration was raised to 1/500. The vein tolerated this concentration well. Higher concentrations have not been tried. It is probable that this method of intravenous medication is the simplest and most useful.

Administration by the mouth is complicated by the fact that penicillin is rapidly destroyed by acid and therefore serious losses are to be expected in the stomach. It may however be possible to carry the penicillin through the stomach by raising the pH of the gastric contents. Experiments with such substances as magnesium trisilicate or the recently described aluminium phosphate (Fauley et al. 1941) are clearly required. In case 6 a strongly antibacterial concentration of the drug was maintained in the urine for 7 days by giving it by mouth together with sodium bicarbonate. In this case however we were aiming at keeping up an antibacterial concentration only in the urinary tract, and not in the blood. The possibility of administration in capsules which will pass through the stomach has not been overlooked, but some tentative experiments with salol-coated capsules were discouraging. Moreover, Cook and LaWall (1936) stated that only 10% of such capsules passed through the stomach satisfactorily; we have therefore not thought it worth while to entrust a scarce and valuable substance to such unreliable vehicles. Rectal administration was tried in one subject, but very little active substance was recovered in the urine and it was afterwards found that faeces inactivate penicillin, probably by bacterial action. It was thought undesirable to introduce very strong solutions of penicillin subcutaneously or intramuscularly owing to uncertainty about the local effects. More dilute solutions, for example 1 in 500, which have been shown to be innocuous to leucocytes, would involve the use of excessive amounts of fluid. In case 1 the injection of 100 mg. in 2 c.c.m. of water intramuscularly caused some tenderness, though this cleared up quickly.

INTRAVENOUS ADMINISTRATION IN STAPHYLOCOCCAL AND STREPTOCOCCAL INFECTIONS

CASE 1.—Policeman, aged 43. Admitted Oct. 12, 1940. Suppuration of face, scalp and both orbits, starting from a sore at the corner of the mouth a month earlier. Primary infection *Staph. aureus*; secondary, *Strep. pyogenes*. Sulphapyridine 19 g. given from Dec. 12 to 19; no improvement; drug-rash. Jan. 19: incision of multiple abscesses on face and scalp. Osteomyelitis of right humeral head, proved by X rays, showed on Jan. 31, 1941, after 3 weeks of pain; a resulting arm-abscess, incised, gave *Staph. aureus* pus.

General infection of left eye; cornea perforated Jan. 21. Eye eviscerated Feb. 3. Blood-transfusion 2 pints Feb. 9. Fever intermittent all this time, 98°–101° F. Very ill and emaciated; tongue heavily furred. Feb. 11: right eye bulging and conjunctival chemosis, orbit incised, pus gave *Staph. aureus* and *Strep. pyogenes*.

Feb. 12: all incisions suppurating, in scalp, face, both orbits, and right arm. Lungs involved, with purulent expectoration containing both the pyogenic cocci. Hb 36%; red cells 1,800,000. Blood-culture sterile. Penicillin 200 mg. given intravenously; then 100 mg. 3-hourly, intravenous except for two intramuscular doses. Slight rigor after first dose, otherwise no reactions. Striking improvement after total of 800 mg. penicillin in 24 hours. Cessation of scalp-discharge, diminution of right-eye suppuration and conjunctivitis. Arm discharge seemed less. Blood-tests just before injections for penicillin: 7.30 A.M. faint trace; 11.30

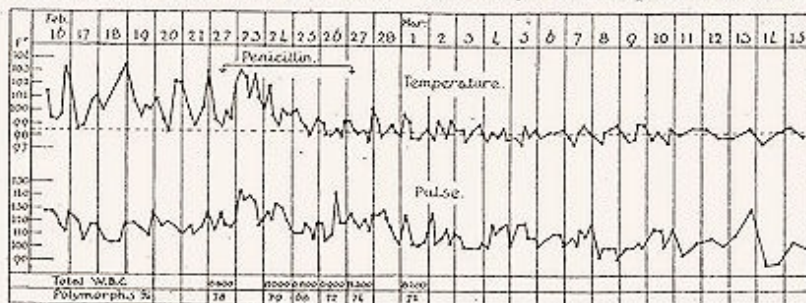


FIG. 5.—Chart and white-cell counts in case 2.

A.M. none. Feb. 13: penicillin 100 mg. intravenously 4-hourly. Feb. 14: condition much the same. Blood-transfusion 3 pints. Penicillin 100 mg. 2-hourly by injection into transfusion tube; total 1 g. in 24 hours. Feb. 15: 1 pint blood transfused and penicillin 100 mg. given 3-hourly, most of which had been recovered from previous urine. Feb. 16: much improvement; Hb. 74%. Right eye almost normal. Some discharge still from left eye and arm. Shortage of penicillin interrupted treatment from noon to 6 P.M.; then drip-infusion of sodium chloride and citrate, penicillin 200 mg. being injected into drip, then 100 mg. 3-hourly; no reaction. Feb. 17: penicillin supply exhausted. Total administered, 4.4 g. in 5 days. Patient felt much improved; no fever; appetite much better; resolution of infections in face, scalp and right orbit; still coughing; sputum contained *Strep. pyogenes* and *N. catarrhalis*. Left orbit and right humerus still suppurating. Blood-urea 30 mg. per 100 c.c.m., urine normal. Condition stationary for 10 days, then deteriorated, especially lungs. March 15: died. Autopsy showed typical picture of staphylococcal pyæmia with multiple abscesses.

White counts.—Feb. 12, 20,000 (polymorphs 88%); 13th, 19,000; 14th, 11,200; 15th, 16,800; 18th, 8,400; 19th, 7,600; 20th, 7,600 (polymorphs 84%); 25th, 8,000; March 5, 11,000 (polymorphs 88%).

The attempt to treat this forlorn case was chiefly valuable in that it showed that penicillin could be given over a period of 5 days without significant toxic effect. There was a fall in the total white count, but both granular and agranular cells were equally affected. Apart from this effect, which has not been seen in subsequent cases, and the slight rigor due to a pyrogenic impurity in the penicillin, no contra-indications to its use were observed. Assessment of its effect was difficult since a blood-transfusion was given at the same time, and later experience showed that the dose of penicillin employed was too small, and the period of administration too short. None the less the superficial sepsis responded well, and did not relapse after the penicillin was stopped.

CASE 2.—Boy, aged 15. Admitted Dec. 29, 1940, for slipped right femoral epiphysis. Open reduction with insertion of Smith-Petersen pin Jan. 24, 1941. Severe post-operative hæmorrhage followed by infection of wound with hæmolytic streptococcus (group A, type 13); positive blood-culture. Wound reopened and patient given Proseptasine from Jan. 25 to Feb. 3, two courses of 5 g. sulphapyridine soluble intravenously in 30 hours on Feb. 7th and 9th, and two blood-transfusions, but swinging temperature (99°–103° F.) continued (see fig. 5).

Feb. 22: looked ill, pale and wasted; two granulating areas over right hip, discharging sero-pus. Hb. 62%; red cells 3,000,000; white cells 8800 (polymorphs 78%). Blood-culture sterile. Blood-urea 32 mg. per 100 c.c.m. Urine normal. At noon 100 mg. penicillin injected into intravenous drip-infusion of citrate-saline; repeated 2-hourly for 8 hours. After interval of 3 hours given another 100 mg. producing

slight rigor; then 75 mg. 3-hourly. Feb. 24: general condition better, discharge less. By 9 p.m. had received 1.4 g. penicillin; dose raised to 100 mg. 3-hourly, using a purer penicillin; no reaction. Feb. 27: penicillin stopped; total 3.4 g. Three blood-examinations just before injections had only once shown slight antibacterial activity. Feeling better; local condition unchanged. Blood-urea 29 mg. per 100 c.cm. Urine normal. White cells 8300 (polymorphs 74%). Feb. 25: blood-transfusion 2 pints. Feb. 26: plaster spica applied. After 3-4 weeks of almost normal temperature pin removed. Again developed swinging temperature as before penicillin treatment.

Several different samples of penicillin were used in this case. The first five doses had been recovered from the urine of case 1 and caused no reaction. The next samples, which caused some shivers, were "third fraction," and although they had been passed through an absorption column again they still contained the pyrogen. The later doses were "second fraction" (our present "therapeutic penicillin"). Here there was a local infection by a haemolytic streptococcus which had proved resistant to sulphamamide in large doses and to moderate doses of sulphapyridine. Penicillin therapy was followed by a great improvement in the patient's general condition, in spite of the dose being insufficient to maintain a detectable concentration of penicillin continuously in the blood.

CASE 3.—Labourer, aged 48, of poor physique. Admitted May 2, 1941. Carbuncle 4 in. across over left scapula for 5 days; now discharging; pus grew pure *Staph. aureus*. History of chronic bronchial and nasal catarrh for 4 months. Left axillary adenitis. Hb. 106%; red cells 4,970,000; white cells 23,000. Blood-urea 31 mg. per 100 c.cm. Urine normal.

May 3: penicillin 200 mg. hourly for 5 doses by injection into intravenous drip as in case 2; then 100 mg. hourly. No reaction. Antibacterial activity continuously maintained in blood. May 7: carbuncle much improved; slight tenderness, only slight serous discharge. Dose dropped to 100 mg. 2-hourly and then 3-hourly. May 10: carbuncle almost completely resolved; no axillary adenitis; bronchial and nasal catarrh cleared; 100 mg. penicillin 6-hourly for 4 doses and then stopped. May 11: Hb. 90%; red cells 4,970,000; white cells 15,800. Blood-urea 37 mg. per 100 c.cm. Urine normal. Temperature, which had been swinging 97°-101° F. now normal and remained so. Local treatment had consisted in kaolin poultice for first 48 hours, sodium sulphate dressing for next 48 hours and subsequently dry dressing. May 15: discharged. Seen as outpatient on May 19 when skin over carbuncle almost normal and patient generally well; right ulnar neuritis which cleared quickly, possibly from splinting arm for several days during infusion.

White counts.—May 3, 23,000 (polymorphs 87%); 5th, 16,400; 6th, 15,200; 7th, 7800; 8th, 9200; 9th, 19,200; 10th, 19,800; 11th, 15,800.

In this case the supply of penicillin was sufficient to enable a detectable concentration of penicillin to be maintained continuously in the blood for the first 4 days. There was no toxic effect from the larger dosage. The result was a rapid resolution of the carbuncle without its discharging and without scar formation. In addition the chronic nasal and bronchial catarrh were cleared. The white count was temporarily depressed on the 4th and 5th days but rose again in spite of the drug being continued.

CASE 4.—Boy, aged 4½ years. Admitted May 13, 1941. Cavernous-sinus thrombosis from septic spots on left eyelid and face following measles 5 weeks before. Had received 30 g. sulphapyridine in 14 days before admission. Semi-comatose, incontinent of urine and faeces. Gross oedema both eyelids (fig. 6a), especially left, with bilateral proptosis. Complete bilateral external ophthalmoplegia and 2 dioptres of papilloedema; neck rigidity; bilateral Kernig's sign and extensor plantar responses. Moist sounds both bases. Liver edge two finger-breadths below costal margin. Blood-culture sterile. Lumbar puncture gave a faintly yellow cloudy fluid under high pressure (see table III).

May 13: intravenous infusion of citrate saline at 10 c.cm. an hour (rate maintained with slight variations for 9 days, the site of infusion being changed 4 times). Penicillin injected into infusion; dose 100 mg. hourly for two doses, 50 mg. hourly for four doses, then 25 mg. hourly. May 14: pus from incision made into left eyelid and swab from nose grew

Staph. aureus. X ray: opacity of left antrum, ethmoids clear. May 15: blood sample an hour after dose of penicillin showed no antibacterial activity; dose increased to 50 mg. hourly. General improvement. May 16: obviously better; swelling of eyelids largely subsided. Blood taken just before injection showed trace of antibacterial activity. May 19:

TABLE III—CEREBROSPINAL FLUID OF CASE 4

Date	Pressure	Protein (mg. per 100c.cm.)	Red cells per c.mm.	White cells per c.mm.	Culture
May 13*	Raised	110	v. few	109	<i>Staph. aureus</i>
.. 14	Normal	100	v. few	372	<i>Staph. aureus</i>
.. 19	Normal	60	v. few	110	<i>Staph. aur. and alb.</i>
.. 22	Normal	95	v. few	45	Sterile
.. 27*	Raised	120	14,600	56	Sterile
.. 28	Raised	140	21,800	276	Sterile
.. 29	Raised	95	12,500	920	Sterile
.. 30	Raised	90	840	2120	Sterile

* Cell-count done after fluid had stood for several hours.

general and local condition vastly improved (see fig. 6b); bilateral 6th nerve palsy and extensor plantar responses remained. Penicillin reduced to 50 mg. 3-hourly. Small corneal ulcer left eye treated with penicillin 1 in 5000, which caused no discomfort. May 22: improvement maintained, patient talking and playing with toys. Chest clinically normal. Slight pyrexia still thought to be due to pyrogen in penicillin or to reaction from thromboses in veins used for injections (see fig. 7). Penicillin stopped. May 26: progress good. Temperature normal. General condition excellent. Eye movements returning. X ray of sinuses: only slight clouding left antrum; chest; patch of consolidation left apex and small ring shadow right mid-zone. These thought to be embolic signs but general condition so good that no further penicillin needed. May 27: 1 a.m. vomited and had general convulsions. Lumbar puncture gave uniformly blood-stained fluid under high pressure. Became comatose with neck rigidity, positive Kernig's sign and spastic limbs. May 28: temperature began to rise again. May 29: appearance much as on admission. Penicillin 2 g. given in next 36 hours, but died May 31.

Autopsy (Dr. A. H. T. Robb-Smith).—Brain showed no thrombosis of main venous sinuses; adhesions and old haemorrhage in hypophysial region. Considerable old and recent haemorrhage in region of pons and cerebellum due to rupture of aneurysm on left vertebral artery. Cavernous-sinus region and left orbit occupied by oedematous granulation tissue; left carotid artery partially occluded by thrombus in its cavernous course and completely occluded in its bony course. Both lungs showed scattered abscess cavities, larger ones being air-containing cysts lined by yellowish membrane; smaller ones containing yellowish material not exactly resembling pus. Other organs not remarkable.

Histologically granulation tissue is essentially similar whether in lung abscesses, orbital tissues or cavernous regions (fig. 8). There is a small central area of necrosis sometimes containing a few gram-positive cocci; around this is an oedematous exudate with lipid-containing histiocytes; surrounding this is a granulation tissue formed largely of histiocytes containing lipid and blood-pigment, lymphocytes and plasma cells with a very occasional neutrophil



FIG. 6—Case 4: (a) at beginning of treatment; (b) on 11th day of treatment.

leucocyte; this tissue is well vascularised and there is some fibroblastic proliferation, greatest in the periphery. In the cavernous region some of the veins contain organising thrombus; the left carotid and vertebral arteries show organising thrombi which do not appear to be infected, but as there are large breaks in the media and elastica of the walls of both these vessels it must be presumed that they are the late results of an acute arteritis probably of bacterial origin. The other organs show no significant change.

The autopsy showed that the infection in the cavernous sinus, orbits and in the lungs had been almost entirely overcome, and that healing processes were well advanced. Death was due to the ruptured mycotic aneurysm and not to a recrudescence of the infection. Before this vascular accident the patient had been restored from a moribund condition to apparent convalescence. No toxic effects from the penicillin were noticed.

CASE 5.—Boy, aged 14½. Admitted May 6, 1941. Staphylococcal septicæmia with early osteomyelitis of left femur following fall 6 days before. Blood-culture grew *Staph. aureus*. Given sulphathiazole 64 g. between May 7 and 12 with little benefit. May 17: left hip-joint explored, no abscess found, joint contained little sterile fluid with polymorphs in it. May 22: blood and albumin in urine. Embolic pustular rash. Extension by skin traction applied to left leg. May 30: X rays showed osteitis left femoral neck with involvement of joint and destruction of alveolar walls. Discharge from wound grew *Staph. aureus*.

June 6: still extremely ill, with temperature rising to 101° F., much pain in left hip and thigh; urine still contained blood and albumin. Hb. 74%; red cells 4,290,000. Blood-urea 23 mg. per 100 c.cm. Intravenous infusion of 500 mg.

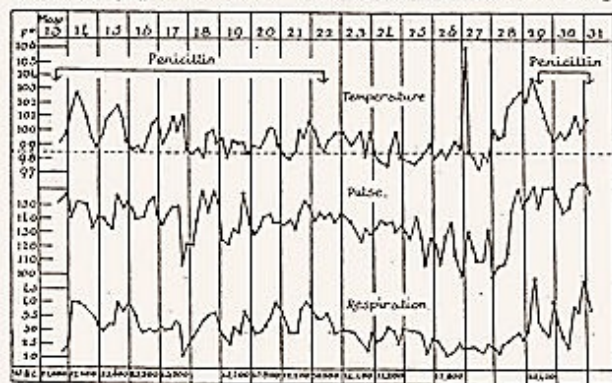


FIG. 7.—Chart and white-cell counts in case 4.

penicillin in 540 c.cm. normal saline started at 45 c.cm. an hour. Infusion continued for 90 hours during which time 3.5 g. penicillin given. No reaction. Daily tests showed constant bacteriostatic concentration in blood. General condition much improved. By June 10 had lost almost all pain and tenderness. Cannula transferred to another vein and infusion continued at half rate with double strength of penicillin (1 g. in 500 c.cm.). On June 11 and 13 sudden rises of temperature without apparent cause; traced to use of penicillin prepared 2 months previously and containing pyrogenic impurity. June 14: cannula transferred to another vein and penicillin recovered from boy's urine used. No further rise of temperature. Steady improvement. On June 16 continuous administration stopped. Given another 50 mg. 3-hourly for 12 doses and then 4-hourly for 12 more doses. Stopped June 20; total dosage 17.2 g. Urine then normal. Blood-urea 29 mg. per 100 c.cm. June 21: Hb. 64%; red cells 3,750,000. June 23: radiograms of hip showed no extension of destructive process; boy felt quite well. July 9: extension removed. July 11: had been afebrile for 3½ weeks. No pain in leg. Passive hip movements, flexion 80°. Other movements almost full.

White counts.—June 6, 9400; 8th, 9700; 9th, 11,800; 10th, 13,800; 11th, 11,400; 12th, 7500; 13th, 9400; 14th, 16,400; 15th, 10,400; 16th, 8400; 17th, 7600; 18th, 6200; 20th, 11,800; 21st, 12,400.

This was a case of staphylococcal septicæmia, localising in the left hip-joint, which had been uninfluenced by large doses of sulphathiazole in the early stages. When penicillin was started the boy was extremely ill, in great pain, and had an active nephritis. As in the other cases there was a striking improvement in the general condition

during the period of therapy. All pain in the region of the left hip disappeared, the nephritis cleared and his temperature fell to normal. At the time of writing it had remained normal for 3½ weeks and there was good function in the hip.

ORAL ADMINISTRATION IN URINARY INFECTION

CASE 6.—Boy, aged 6 months. Admitted April 8, 1941. Ill a fortnight with diarrhoea and vomiting, melæna and generalised convulsions. Dehydrated, few petechiæ in skin. Red

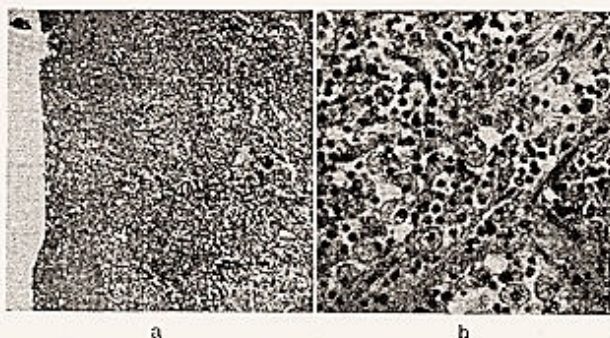


FIG. 8.—(a) Low-power view (×40). Wall of "abscess cavity" in the lung showing the oedema fluid rich in lipid-containing histiocytes, and the wall made up of a vascular granulation tissue in which there are large numbers of lipid-containing histiocytes, lymphocytes and plasma-cells and only a few neutrophil leucocytes. At the extreme right of the section the normal lung parenchyma can be seen.

(b) High-power view (×180). Granulation tissue from the left orbital region showing the characteristics of the cellular reaction, a mixture of lipoid-containing histiocytes, lymphocytes and plasma-cells, and a moderate fibroblastic proliferation.

cells 1,560,000; white cells 28,000 (atypical lymphocytes 50%, many primitive cells). Blood-urea 60 mg. per 100 c.cm. Urine contained albumin and pus; grew *Staph. aureus* and *Eact. coli*. Sulphapyridine tried but stopped because polymorphs full to 400 per c.mm. After fortnight's course of ammonium mandelate urinary infection remained. June 3: urine grew pure *Staph. aureus*. Hb. 62%; red cells 3,200,000; white cells 5000 (polymorphs 600). Blood-urea 66 mg. per 100 c.cm. June 5: attempts to pass duodenal tube failed, so penicillin given by mouth; 20 mg. with 2 g. sodium bicarbonate given hourly for 3 doses and then 3-hourly. No toxic signs. Vomited once, which was not unusual. All specimens of urine contained strongly bacteriostatic concentration of penicillin. June 7: urine contained no pus cells; penicillin reduced to 10 mg. 3-hourly. Vomited 2-3 times daily. Steady general improvement. June 9: polymorphs up to 1000 per c.mm.; blood-urea 46 mg. per 100 c.cm. June 12: penicillin stopped. June 17: blood-urea 39 mg. per 100 c.cm.; Hb. 70%; white cells 4000 (polymorphs 440). June 19: urine sterile though still containing heavy cloud of albumin and occasional casts and red cells. General condition continued to improve. June 26: urine still free from *Staph. aureus*.

This case demonstrates that it is possible to maintain a bacteriostatic concentration of penicillin in the urine with small doses given by mouth. Although the diagnosis was obscure there was no doubt of the urinary infection by *Staph. aureus*, and the administration of penicillin overcame this infection.

LOCAL APPLICATION TO THE EYE

In case 4 a 1/5000 solution of penicillin in normal saline was applied to a corneal ulcer. It caused no irritation and the condition of the eye improved. The local application of penicillin in other eye infections was therefore tried on patients in the Oxford Eye Hospital.

CASE 7.—Married woman, aged 32. Had a corneal ulcer of the left eye 4 months previously, treated successively by instillation of Collosal Argentum, boracic lotion and mercurochrome, and ultraviolet light. In 6 weeks ulcer resolved completely, but 3 weeks later similar ulcer developed in right eye. Treated on similar lines, for 6 weeks as outpatient and then for fortnight as inpatient, but without improvement. May 26, 1941: infiltrating ulcers in inner and upper quadrants of limbus, gross injection of conjunctiva and considerable corneal opacity. Swab from eye grew *Staph. aureus*.

May 30: treatment with penicillin begun; 1/5000 solution in normal saline dropped into eye hourly by day and 2-hourly

by night. After 2 days little progress had been made and continuous application considered necessary. Modification of Bunyan-Stannard bag (Bunyan 1940) made to fit eye and 1/5000 solution penicillin run into it. New bag applied each day, and remained full for about 8 hours, after which began to leak and needed refilling occasionally. After one day of continuous application less injection of conjunctiva and patient free from pain for first time. Treatment given for 4 days; on second day concentration of penicillin raised to 1/1000 but this caused slight irritation and for last 2 days solution of 1/2500 used. By end of fourth day eye greatly improved; conjunctiva only slightly injected and corneal opacity almost disappeared; deeper ulcer remained, but considerably smaller. Treatment continued with hourly drops of 1/2500 penicillin and after one day strength increased to 1/500 "therapeutic penicillin," which caused no discomfort. June 9 (8 days after bag had first been applied): ulcer no longer stained with fluorescein, but still slight injection. Treatment continued with drops of 1/500 penicillin, 2-hourly by day, 4-hourly by night, but further improvement slow. June 20: patient discharged, ulcer healed, leaving only slight residual infiltration of conjunctiva, which had cleared a week later.

CASE 8.—Girl, aged 19.—Burnt her face with cigarette end 6 weeks before admission; burn became infected and from this a septic rash spread over face. Week before admission left eye became red, swollen and painful. On admission on June 9, 1941, many small crusted impetigo-like spots on both sides of face. Left conjunctiva inflamed and showed thick mesh of fine vessels; cornea clear, lids slightly swollen. Eye-bath as in case 7 applied and filled with 1/2500 penicillin. Next day less injection and eye not painful. After 3 days eye almost normal; treatment continued with drops of 1/500 penicillin 2-hourly by day and 4-hourly by night. June 13: eye normal. On and after June 10 ointment consisting of 1/500 penicillin in hydrated lanoline applied to rash on face twice daily. When patient was discharged on June 15 rash had healed completely with only slight residual erythema.

While the treatment of these 2 cases was in progress, some 1/2500 penicillin solution was given to 2 outpatients who were told to apply drops of the solution hourly by day.

CASE 9.—Man, aged 24. Foreign body in left eye May 28, 1941; developed acute conjunctivitis treated with boracic acid and zinc lotion, collosol argentum, and painting lids with silver nitrate. Only slight improvement by June 7, when given penicillin drops; in next 2 days rapid improvement, with complete relief of pain. Slight residual conjunctival infiltration, so treatment continued until June 19, when healing complete.

CASE 10.—Woman, aged 20. Developed acute mucopurulent conjunctivitis on June 5, 1941; treated for 2 days with boracic acid and zinc lotion and by painting lids with silver nitrate. Penicillin drops given on June 7, and 5 days later the eye was almost normal.

In these 4 eye cases, 2 of which had proved resistant to routine therapeutic measures, penicillin application resulted in rapid relief from pain and resolution of the inflammation. In none was there any ill effect.

Discussion

From experiments in vivo and in vitro much evidence has now been assembled that penicillin combines to a striking degree two most desirable qualities of a chemotherapeutic agent—low toxicity to tissue cells and powerful bacteriostatic action. Its capacity to prevent multiplication covers a wide range of bacterial species, including some of the most common and destructive organisms with which man may be infected, and this bacteriostatic action is in no way interfered with by body fluids or pus, and only to a limited extent by very large numbers of organisms.

The crucial test, however, of the efficacy of any chemotherapeutic agent is whether it can favourably influence a natural infection. In spite of the difficulties of large-scale production in the laboratory, we have collected enough material to try penicillin in a few cases. Cases 1, 2, 4, 5 and 6 had previously been treated with various forms of chemotherapy and some also by surgery. They were, in fact, patients for whom no further treatment likely to be of benefit could be proposed. Case 3 had had no previous treatment. In all patients the temperature fell and the general and local condition improved. Where there was a recrudescence of infection it could in

each case be attributed to insufficient administration of penicillin. The only toxic effect of any importance so far seen was due to a pyrogenic impurity, which could be removed; and it is worth noting that an improvement in the spirits and appetite of the patient during treatment was remarked on in all the cases. Where local application has been tried, it has given equally promising results.

Methods of administration and dosage have necessarily been tentative, but the many points which still need investigation await an adequate supply of penicillin. Enough evidence, we consider, has now been assembled to show that penicillin is a new and effective type of chemotherapeutic agent, and possesses some properties unknown in any antibacterial substance hitherto described.

Summary

A description is given of the cultural and other conditions required for the effective production of penicillin by *Penicillium notatum*; and of methods of small-scale mass production and assay of material suitable for therapeutic use in man.

Observations on the absorption and excretion of the drug have been made on the rabbit, the cat and man. The material is excreted in high concentration in the urine of all three species. There is a high concentration in cats' and less in rabbits' bile (that of man has not yet been investigated).

Evidence is produced of the low toxicity of the substance when applied directly to body tissues.

No toxic effects attributable to "therapeutic penicillin" injected intravenously have so far been observed, though crude penicillin products contain a pyrogenic substance which can be removed by suitable treatment.

It is shown that the growth in vitro of many pathogenic bacteria is prevented by purified penicillin at a dilution of one in a million or more, and that others possess diminishing degrees of sensitiveness, some being quite resistant.

Proof is given of the inability of blood, pus and tissue derivatives to prevent the action of penicillin.

Adaptation of *Staph. aureus* to high concentrations of the substance has been demonstrated, and this has been shown not to be due to the development of a penicillin-destroying enzyme.

A comparison is made between the antibacterial activity of penicillin and the sulphonamides, and reasons are adduced why penicillin can be expected to operate when the sulphonamides are ineffective.

During the course of some therapeutic trials in human infections it has proved possible to secure and maintain a bacteriostatic concentration of penicillin in the blood without causing any toxic symptoms. After intravenous administration a large proportion of the active substance can be recovered from the urine and used again.

Penicillin was given intravenously to five patients with staphylococcal and streptococcal infections and by mouth to one baby with a persistent staphylococcal urinary infection. It was also applied locally to four cases of eye infection. In all these cases a favourable therapeutic response was obtained.

The work was planned and started by E. Chain and H. W. Florey. The chemical and biochemical part of the work was carried out in the main by E. Chain and E. P. Abraham. N. G. Heatley devised the assay method and developed and supervised the production of penicillin. M. A. Jennings and H. W. Florey have conducted the biological tests except those especially mentioned in the text. A. D. Gardner has conducted the bacteriological investigations and made some special observations on the growth of the mould. C. M. Fletcher (of the Nuffield Department of Medicine) has been in charge of the administration to man. The successful conduct of the work to its present stage has only been made possible by the closest collaboration of all concerned. We wish to thank the physicians and surgeons who placed their cases at our disposal.

We wish also to acknowledge the work of the following technicians, without whose efforts adequate supplies of penicillin could not have been produced: D. Callow, R. Callow, E. Cooke, S. A. Cresswell, G. Glister, C. Inayat, J. Kent, M. Lancaster, P. McKegney, E. Vincent.

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