LOCAL THERAPY OF WAR WOUNDS

I. WITH PENICILLIN *

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SAMPLES of the sodium and calcium salts of penicillin were sent to the Central Pathological Laboratory, Middle East Forces, by courtesy of Prof. H. W. Florey. A number of battle casualties at a Scottish general hospital were treated with these reagents, with satisfactory results, which are here described.

As a preliminary the wounds were dressed by an aspirating device.

In the treatment of wounds with various reagents locally applied, the presence of pus in large amounts or of necrotic material and deep pockets made it impossible to get the wound really clean by ordinary dressing methods. Moreover, the wounds were often exquisitely tender and became more so as healing proceeded.

In order to obtain a really clean surface for local applications, the apparatus here illustrated was set up (see figure). A is a stand, 7 ft. high with two arms. B is a reservoir of fluid with a drip feed, thumb screw to adjust drip. C is a glass nozzle to apply fluid to wound. In these experiments, normal saline alone has been used, so as not to confuse the issue; but 0·1% electrolytic hypochlorite would probably be better. D is an aspirator; as fluid drips away from E a negative pressure is created in flask F, and thus applied to a curved applicator G.

Results have been excellent, deep pockets are readily explored, and surfaces quickly cleansed; the process is relatively painless, and painful points can be avoided. The method is similar to that of Tudor Edwards in empyema drainage; it is hoped to develop it further in general hygiene of wounds.

As an irrigating fluid normal saline at 37° C. was found to be simple and painless, and deep pockets could be readily cleaned by its use. In fact, employed by itself without any other reagent, the control of smell, and of the soiling of the bed and dressings, as well as the relief given to the patient, were of definite value. It seems essential that some such device should be used in conjunction with any local therapeutic agents, since it is of little use to float these on a sea of pus.

The first supply of penicillin was the sodium, the second the calcium, salt. In-vitro tests confirmed statements that the drug was highly bacteriostatic to gram-positive organisms, inhibiting *Staphylococcus aureus* in dilutions up to 1 in 1,000,000 or more; and that it was not bactericidal. Further it was found to be non-irritant to the rabbit's eye. It was poorly bacteriostatic when tested on *Ps. pyocyanea*, *P. proteus*, and *S. typhi*.

One ampoule of the sodium salt was found to be inert. The rest was employed in various ways, as a powder, as a spray, and as a wet dressing covered with soft-paraffin gauze. The liquid was always painless; the powder in one case caused pain for 30 minutes, radiating down the leg; in other cases the powder was painless. No deleterious effect was noted on wounds; but in 2 cases, when the calcium salt was injected intrathecally, severe reactions were noted. Professor Florey had warned against such use, but it was employed because the cases were resistant to all other methods of treatment. The "standard solution" referred to in the text contained 100 mg. of penicillin in 16 c.cm. of saline.

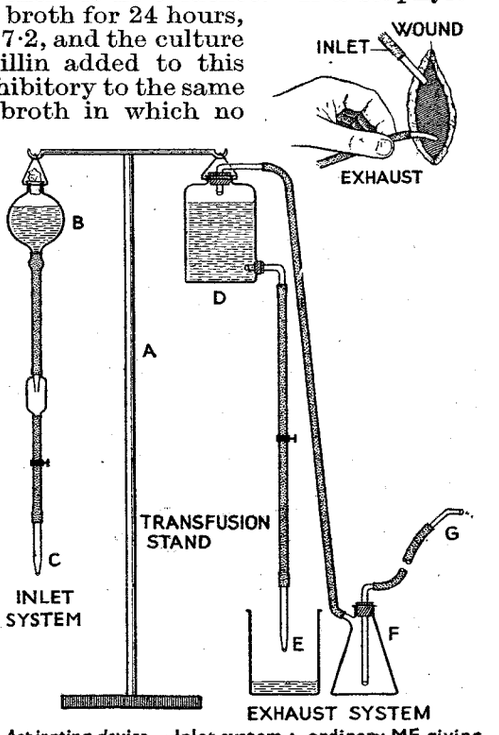
The effects of treatment are given in the table. In most cases there was a rapid and progressive diminution of gram-positive organisms, and much clinical improvement, in some cases dramatic. Gram-negative organisms, far from disappearing, often appeared when previously absent: the drug in fact appeared to encourage their presence. A similar result was noted with other drugs. However, gram-negative organisms in wounds, without pyogenic cocci, do not seem to be of much account. A wound with such organisms gives few of the cardinal signs of inflammation.

Some experiments, whose results were negative, were performed to investigate the nature of its action. Unlike that of the sulphonamides, the inhibitory action of penicillin is not neutralised by paraminobenzoic acid. At some concentrations it is not inhibitory to pyocyaneus. If pyocyaneus is cultured in broth containing that concentration, and the culture is then adjusted to a pH of 7·2 and filtered, this filtrate is still inhibitory to *Staph. aureus*; there is no evidence therefore that there is any breakdown of the drug by this common wound organism. A medium in which pyocyaneus has grown is not inhibitory to *Staph. aureus*.

When *S. typhi* is cultured in a medium containing penicillin, the organisms are found to grow in filamentous forms, but growth is poor. Therefore the effect of the drug appears to be in inhibiting bacterial fission, but not the metabolism and growth of individual organisms; and films from wounds indicate that these organisms are phagocytised, and in this state are not culturable.

It was thought possible that a growing and subdividing organism might manufacture a substance stimulating further division, and that this hypothetical substance might overcome the inhibitory action of penicillin; of this there is no evidence. If a staphylococcus is grown in broth for 24 hours, the pH adjusted to 7·2, and the culture filtered, then penicillin added to this filtrate is just as inhibitory to the same strain as it is in broth in which no previous growth has occurred.

No drug effective against gram-negative organisms was found; 1% acetic acid, often advised, was not found to be effective; neither was sodium mandelate, applied locally. Even succinyl sulphathiazole (sulphasuxidine), so effective by mouth in eliminating gram-negative organisms from fæces, was ineffective when applied to wounds of this group.



Aspirating device.—Inlet system: ordinary ME giving set will do with glass connexion. Exhaust system: all-rubber tubing is best used with ¼ in. internal diameter (pressure tubing).

COMMENT

Since this series was completed, several other cases have been treated, most of them with the same results. Gram-positive organisms have quickly disappeared, and clinical improvement has been considerable. On the other hand, in 2 cases of late and severe sepsis in compound fractures, an early disappearance of such flora was followed by a clinical relapse, and the organisms returned to the wound. It is true that the calcium salt of penicillin used, which was forwarded in bulk, may perhaps not have been equally potent throughout. On two occasions in-vitro tests of bacteriostatic value seemed to show a drop in titre, but the organisms isolated from these wounds were fully susceptible to the action of the drug in vitro.

A third case—of compound fracture of femur with sinus, infected with hæmolytic streptococci—showed no response whatever to penicillin injected thrice daily through a catheter tied into the sinus. A number of other drugs were also tried locally without effect. Eventually a large sequestrum was removed and the wound healed.

The opinion was formed that penicillin is of real value in the control of infection by gram-positive organisms. It must be applied repeatedly, and those cases in which it was most often applied did best. It does not always eliminate organisms, perhaps because it cannot always get to their hiding places when externally applied.

The war wounds which are most dangerous, from the point of view of later infection, are those of large muscle groups—e.g., buttock wounds. Anaerobic infection here is most dangerous, and penicillin appears to be effective in this group. It is suggested that in this class of

* The second part of this paper, including the discussion, will appear in a forthcoming issue.

CASE REPORTS

Case and date	Age, state of wound and progress	Treatment	Smear (S) and Culture (C)
CASE 1	Aged 23. Wounds of both thighs; lt. fractured femur	..	Not done
Aug. 30, 1942	Suppurating. Temp. 99–104° F.	Sulphanilamide 2 g. daily	,, ,,
Aug. 31	,, ,,	Sulphanilamide 3 g. daily	,, ,,
Sept. 1	,, ,,	Discontinued drug	,, ,,
Oct. 16	Copious creamy discharge; bed and dressings soaked in pus; foul smell. Bedsores; septic fever; gross cachexia; poor appetite; severe anæmia	Catheter inserted into sinus in lt. thigh; 4 c.cm. of penicillin (standard strength) inserted thrice daily	S: vast nos. extra-cell. streps. C: hæm. streps. *C. hofmanni*, pyocyaneus
Oct. 17	Discharge less	Same; produced no symptoms	S: no cocci seen. C: pyocyaneus only
Oct. 19	Discharge less. Temp. settling	Same	No change
Oct. 20	Discharge less	Sinus in right thigh similarly irrigated	S: streps. +++. C: hæm. streps., pyocyaneus
Oct. 23	Rt. thigh, swelling much diminished. Lt. thigh, little suppuration. Temp. settling rapidly; gen. condition much improved	Same; pressure-sore treated with penicillin: rapid healing	S: rt. and lt. gram-neg. bacilli only. C: rt. thigh, pyocyaneus; lt. thigh, proteus and pyocyaneus
Oct. 27	Catheters removed. Lt. thigh, almost healed. Rt. thigh, little discharge. Temp. settled; pt. comfortable; appetite good	No treatment	S: no cocci seen. C: no change
Oct. 30	Rt. thigh, much swelling. Loculated pus; discharged by pressure	2 c.cm. penicillin	S: streps. +++; few cells. C: hæm. streps.
Nov. 3	Both healed; no discharge. Complete recovery. Streps. disappeared from both wounds 24 hr. after start of treatment; gram-neg. bacilli unaffected, but did not prevent healing	No treatment	S: nil. C: nil
CASE 2 Sept. 1, 1942	Aged 33. Multiple bomb wounds; penetrating wound rt. parietal lobe of brain	Sulphonamide pack	Not done
Sept. 2–11	Infected. CSF: white cells 6270 per c.mm.; polys. 95%, Hb. 40%	Sulphadiazine 55 g.; sulphapyridine 31 g.	,, ,,
Sept. 21	Brain abscess opened; 8 c.cm. pus removed. Penicillin produced no symptoms	Sulphadiazine 50 mg. Penicillin to abscess cavity (solid); 50 mg. in solution injected into cavity through catheter	S: staphs., streps. gram-neg. bacilli. C: hæm. *Staph. aureus*; hæm. strep.; unrecognised gram-pos. coccus; *B. mesentericus*
Sept. 23	Wound healthy; 2 c.cm. of pus aspirated. CSF contains no penicillin. Pt. fit, talking coherently	2 c.cm. of standard penicillin injected through catheter; sulphadiazine contd.	S: few organisms; intracell. staphs. only. C: hæm. *Staph. aureus*, scanty growth; unidentified gram-pos. coccus
Sept. 24	Wound healthy; 0·2 c.cm. pus aspirated. Catheter came out; treatment stopped. Pt. was recovering well but died on Oct. 29 from intercurrent extradural abscess, lumbar region. Autopsy: brain, no sign of recent damage or infection; no meningitis, considerable loss of tissue; defect sealed off by meninges.	2 c.cm. standard penicillin injected. Sulphadiazine contd.	S: no organisms seen. C: 2 colonies *Staph. aureus*; unidentified gram-pos. coccus
CASE 3	Aged 31. Gunshot wound of sacrum	..	..
Aug. 17, 1942	Vast tissue defect over sacrum; shell fragments in wound; copious stinking discharge. Not suitable for treatment, since probable duration of illness would absorb all available penicillin; case used as test of action on organisms	Penicillin standard solution, 100 mg.	S: many staphs., streps., diphtheroids, coliforms; few cells. C: overgrown with pyocyaneus
Sept. 18	Discharge much less; smell less offensive. Pt. and his friends commented on alteration of smell	Penicillin, 100 mg.	S: organisms greatly reduced; few staphs., diphtheroids or coliforms present. C: pyocyaneus
Sept. 19	ISQ	Treatment discontinued as test	No change
Sept. 21	Immediate return of organisms. Wound stinking; profuse discharge	Penicillin, 100 mg.	S: staphs. ++++. C: not done
Sept. 22	Much less pus; wound cleaner. Experiment shows control of flora by penicillin	End of test	S: staphs. much diminished. C: not done
CASE 4	Aged 24. Thigh wound, chipping of femur	..	..
Oct. 27, 1942	Much pus, œdema	Penicillin, 50% standard, injected into sinus (ampoule tested in vitro and proved inert)	S: streps. +++; staphs. +; clostridia. C: hæm. strep.; hæm. *Staph. aureus*
Oct. 28	No effect on wound	Same	No change
Oct. 29	Foul profuse discharge. Treatment painful; shooting pain down leg: only case to react like this— ? nerve injury	Solid penicillin, 100 mg. active sample inserted into wound	No change
Oct. 30	Remarkable change; no œdema; little pus; no smell. Immediate effect when active drug applied	Same	S: few organisms seen. C: hæm. streps., proteus
Nov. 4	Improved	Irrigated with standard penicillin thrice daily	No change

CASE REPORTS—(*continued*)

Case and date	Age, state of wound and progress	Treatment	Smear (S) and Culture (C)
(*Case 4 contd.*) Nov. 5	Healing well. Nov. 7: treatment stopped; wound well advanced towards healing; evacuated soon after for convalescence	Irrigated with standard penicillin thrice daily	S: no cocci seen. C: 3 colonies hæm. streps., pyocyaneus
CASE 5	Aged 36. Multiple penetrating wounds, most severe in lt. calf muscles. Bare area 4 × 3 in.; deep pocket	..	..
Nov. 10, 1942	Foul-smelling, slimy wound; looked "dead"; little discharge; did not bleed on touching; gas in tissues. Pt. delirious, almost maniacal. Clinical gas gangrene; amputation considered. Psychiatrist attributed mental state to clostridial infection	Standard penicillin spray, after irrigation and cleaning	S: bacteria only; streps., staphs., clostridia; no cells. C: hæm. streps.; hæm. *Staph. aureus; Cl. ? welchii;* proteus
Nov. 11	Clean; no smell; little discharge; muscle red. Delirium much less	Same	S: few organisms. C: proteus; a few hæm. streps.
Nov. 12	Profuse suppuration; tender; bleeds readily. (Temporary suppuration in a non-reacting wound after penicillin: noted several times.)	,,	S: few intracellular cocci. C: no change
Nov. 13	Little discharge; pocket filling up. No delirium; pt. much better	,,	S: a few cocci only. C: 6 colonies of *Staph. albus*
Nov. 14	No change	,,	S: nil seen. C: sterile
Nov. 15	Granulation well advanced. No further infection. Traumatic aneurysm treated later. No treatment except penicillin and irrigation; recovery in clinical gas gangrene in which amputation was considered	Treatment stopped	S: nil. C: sterile
CASE 6 Oct. 24, 1942	Multiple wounds; severe comminuted fracture of humerus	..	..
Oct. 29	Much muscle loss; profuse foul stinking pus, much slough. Great pain; v. toxic; pt. crying and groaning	Penicillin spray; standard strength; irrigation of wound; penicillin, 100 mg. daily	S: extracellular streps. ++++. C: hæm. streps. ++++; pyocyaneus
Nov. 2	Discharge less	Same	S: no streps. seen; a few intracell. cocci. C: a few streps.; pyocyaneus
Nov. 3	Wound granulating, little smell. Gen. condition much improved	,,	No change
Nov. 4	Bleeds readily, swelling and pain much less	Penicillin 50 mg.	S: orgs. fewer. C: few streps.; pyocyaneus
Nov. 5	Wound improved. Almost free from pain	Same	S: phagocytised cocci only. C: pyocyaneus only
Nov. 6–10	Continuous improvement. Nov. 10 arm set up in closed plaster; recovery. Note relief of pain from treatment	Continuous irrigation with 1/1000 penicillin; continuous aspiration	No change
CASE 7	Aged 25. Extensive wound, lt. thigh. No excess discharge	..	Not sterile
April 16, 1943	Dull, lifeless-looking wound; no excess discharge	Gauze soaked in crude penicillin	S: pus cells ++, gram-pos. cocci in mod. nos. C: hæm. streps., free growth
April 17	Wound seemed more healthy; no excessive discharge	Same	S: still mod. nos. gram-pos. cocci
April 18	Fairly profuse discharge; healthy looking underneath	,,	Gram-pos. cocci, mod. nos., all intracell.
April 19	No change	Penicillin spray, on top of original dressing on surgeon's advice, to avoid discomfort to pt.	Gram-neg. bacilli
April 20	Pus collecting under dressing	Same treatment	No change
April 21	Dressing removed; little pus underneath	Penicillin gauze	,, ,,
April 22	No change	,, ,,	,, ,,
April 23	Slight serous discharge	,, ,,	,, ,,
April 24, 25	No change	,, ,,	,, ,,
April 26	No discharge; islands of epithelium forming in wound. April 29, pinch graft	,, ,,	,, ,,
CASE 8	Aged 34. Wound of spine with partial paralysis of lower limbs	..	..
April 7, 1943	Large unhealthy looking buttock bedsore, with sharp deep "cliff edges," covering about 14 sq. in.	Penicillin spray	S: gram-neg. orgs. in large nos. C: hæm. strep., free growth
April 9 16	All previous dressings done by ward staff; daily progress not recorded. Sharp edges lost; only sl. serous discharge	,, ,,	S: gram-neg. bacilli in large nos. C: no growth
April 17	Still only slight serous discharge	,, ,,	No change
April 18	No discharge; attempt to tan over surface	Proflavine powder; covered with wire cage	,, ,,
April 19	Slight tanning on lt. side; little change on rt.	Proflavine powder	Not done
April 20	Lt. side tanned over; rt. side filled with pus aspirated	Penicillin, 1% in cavity and *P. notatum* filtrate gauze	S: mod. nos. gram-neg. bacilli

CASE REPORTS—(*continued*)

Case and date	Age, state of wound and progress	Treatment	Smear (S) and Culture (C)
(*Case 8 contd.*)			
April 21	No change	Penicillin, 1% in cavity and *P. notatum* filtrate gauze	S: no change
April 22	More profuse discharge from rt. side; lt. side doing well	Same	,, ,,
April 23	Still less discharge. Pt. feels more comfortable	,,	,, ,,
April 24	Much less discharge; granulation over wound	,,	,, ,,
April 25	Only slight serous discharge. Patient has slight temperature; culture made from suprapubic drainage	UVL ½ in. at 8 in.; penicillin after	,, ,,
April 26	Sl. serous discharge; granulating well. Temperature still raised	Penicillin gauze	S: no change. Urine C: *B. coli*, free growth
April 27	No discharge. Attempt to tan over surface again. Pt. recovered feeling in hips	2:7 diamino-acridine monohydrochloride	S: no change. C: pyocyaneus
CASE 9	Aged 23. Amputation lower ⅓ lt. leg	Sulphonamide, soft paraff. gauze	..
Mar. 16, 1943	Little discharge, but wound unhealthy with little areas of slough over surface	Gauze soaked in standard penicillin	S: mod. nos. gram-pos. cocci; a few gram-neg. bacilli. C: hæm. *Staph. aureus*, hæm. streps., coliform orgs.
Mar. 17	Slightly more discharge; few sloughs came away with dressing	Gauze and penicillin	S: gram-pos. cocci, mostly intracellular
Mar. 18	Fairly profuse discharge; wound healthier	Same	S: gram-pos. cocci +, all intracell.; gram-neg. bacilli ++
Mar. 19	Only sl. serous discharge; all sloughs have come away; surface of wound clean	,,	S: gram-neg. bacilli in large nos.
Mar. 20	Still only sl. serous discharge. Leg strapped to splint after treatment to keep extension	Gauze and *P. notatum* filtrate	,, ,,
Mar. 21	No change	Same	,, ,,
Mar. 22	Pt. fell out of bed and bruised stump; sl. bleeding, several clots of blood removed	,,	,, ,,
Mar. 23	Wound healthy; no discharge. Splint left off	,,	S: only gram-neg. bacilli
Mar. 24	No change	,,	,, ,,
Mar. 25	Sl. serous discharge. Pt. up for 2 hr.	,,	,, ,,
Mar. 26	No discharge; wound healthy	Treatment stopped	,, ,,
CASE 10	Comminuted fracture of lt. femur; extensive wound 6 in. long on inside of thigh; much pus coming from sinus at top and passing upwards to groin	Sulphanilamide, plaster of paris, and later proflavine	..
Dec. 31, 1942	Much discharge	5 c.cm. of 1% penicillin injected into sinus, and remainder of wound sprayed; covered with paraff. gauze	S: pus cells; mod. nos. of short-chain gram-pos. cocci. C: hæm. strep.; hæm. *Staph. aureus*
Jan. 1 1943	Less discharge; no smell. Less painful	Same	S: pus cells; gram-neg. bacilli and mod. nos. intracell. gram-pos. cocci. C: hæm. *Staph. aureus*, proteus
Jan. 2	Still less discharge	,,	S: pus cells; gram-neg. bacilli. C: proteus, overgrowth
Jan. 3	Improvement maintained	,,	S: pus cells; a few intracellular gram-pos. cocci, and mod. nos. of gram-neg. bacilli. C: pyocyaneus
Jan. 4	Still improving. A similar wound on outside of thigh treated	Inside: same treatment. Outside: normal strength penicillin	S: inside, pus cells, gram-neg. bacilli; outside, pus cells; no orgs. seen. C: inside, pyocyaneus; outside, coliform bacilli, a few colonies
Jan. 5	Both wounds clean and healthy; no discharge		S: as before. C: coliform bacillus
Jan. 6	Healed without further incident	Treatment stopped	
CASE 11 Nov. 18, 1942	Tommy-gun bullet through lt. hand; fracture of metacarpus	Sulphanilamide and closed plaster	
Dec. 31	Two septic wounds on dorsum, one on palm. Hand much swollen; little finger movement	4 c.cm. of 1% penicillin injected into thenar space, and remainder of hand sprayed with normal strength penicillin	S: pus cells +++; gram-pos. cocci +. C: overgrowth of proteus
Jan. 1, 1943	Great improvement. Swelling less, and pt. had a little use in fingers	Same	S: pus cells +++; mod. nos. gram-pos. cocci and gram-neg. bacilli. C: *Staph. aureus*, proteus
Jan. 2	Improvement maintained	2% solution injected into thenar space	S: a few pus cells; gram-neg. bacilli ++. C: proteus, overgrowth
Jan. 3	Swelling gone	Same	S: pus cells +; mod. nos. of gram-neg. bacilli. C: proteus
Jan. 4	More movement in fingers. Sl. pain in hand	,,	S: scanty pus cells; no orgs. seen. C: few colonies of proteus
Jan. 5	Improvement maintained	,,	S: scanty pus cells; no orgs. seen. C: sterile

CASE REPORTS—(*continued*)

Case and date	Age, state of wound and progress	Treatment	Smear (S) and Culture (C)
(*Case 11 contd.*)			
Jan. 6	Finger movement still improving	3% penicillin injected	No change
Jan. 7	Wound clean and healthy	Treatment stopped	C: sterile
CASE 12	Multiple shell wounds, left upper arm. Indolent ulcers	Sulphanilamide and soft paraff. gauze	..
Dec. 31, 1942	No excessive discharge from ulcers, but all slow to heal	Sprayed with normal strength penicillin; paraff. gauze	S: pus cells + +; large nos. of gram-pos. cocci. C: hæm. streps.; hæm. *Staph. aureus*
Jan. 1, 1943	Vast change: edges of ulcers healthy looking; patient felt more comfortable; one ulcer had large "mushroom" growth	Same	S: scanty pus cells; mod. nos. gram-pos. cocci, mostly intracellular. C: hæm. streps.
Jan. 2	Improvement maintained	,,	S: scanty pus cells; a few gram-pos. cocci. C: hæm. streps., a few colonies
Jan. 3	,, ,,	,,	S: scanty pus cells. No orgs. seen. C: sterile
Jan. 5	,, ,,	,,	,, ,,
Jan. 7	All areas about to epithelialise	No further advantage from this treatment	..
CASE 13 Oct. 27, 1942	Multiple shell wounds, lt. thigh	Sulphonamide, paraff. gauze, later eusol for 2–3 days	..
Dec. 31	Dirty-looking ulcer, diameter 1½ in. lt. buttock; tender round edges, slightly undercut; foul smelling	Gauze soaked in normal strength penicillin applied	S: pus cells + + +; scanty gram-pos. cocci, all extracellular. C: hæm. *Staph. aureus*
Jan. 1, 1943	Much improved: edges flush with remaining tissue, surface healthier; little discharge; no smell	Same	S: scanty pus cells. Scanty gram-pos. cocci all intracellular. C: sterile
Jan. 2	Improvement maintained	,,	S: scanty pus cells; no orgs. seen. C: sterile
Jan. 3	No change	,,	,, ,,
Jan. 4	No change. Pt. felt much better; no pain on walking	,,	,, ,,
Jan. 7	Wound unhealthy looking again	Same treatment, every 24 hours	S: pus cells +; gram-neg. bacilli. C: coliform bacilli
Jan. 8	Healthy-looking except for small area of dark skin round the edges	,, ,,	S: pus cells +; no orgs. seen. C: sterile
Jan. 9	V. healthy-looking; some excess granulations	,, ,,	S: scanty pus cells; no orgs. seen. C: sterile
CASE 14	Gunshot wound, lt. thigh. Patella removed, fractured femur; large area of granulated flesh at top of thigh; small area of suppuration above knee	One skin graft	..
Dec. 31, 1942	Some discharge	Normal strength penicillin; paraff. gauze	S: pus cells; a few gram-pos. cocci. C: coliform bacilli
Jan. 1, 1943	Much less discharge; no other change	Same	S: pus cells; mod. nos. of gram-neg. bacilli. C: coliform bacilli
Jan. 2	Improvement maintained	,,	S: pus cells; gram-neg. bacilli. C: coliform bacilli
Jan. 4	No discharge; bleeds freely when dressing removed	,,	S: pus cells; no orgs. seen. C: pyocyaneus
Jan. 5	Still bleeds freely, but no actual discharge. Small area of mushroom growth forming at inner edge of wound	,,	S: pus cells; few gram-neg bacilli. C: pyocyaneus
Jan. 6	..	Not treated	..
Jan. 7	No effect after being left for 48 hr.; no discharge, no smell	Treatment resumed	S: few pus cells; few gram-neg. bacilli. C: pyocyaneus
Jan. 9	Wound surgically clean	Same	S: scanty pus cells; no orgs. C: sterile
Jan. 10	Wound v. healthy	No further advantage from this type of treatment; for further skin graft	
CASE 15 April 16, 1943	Empyema cavity discharging. Long drainage tube	*P. notatum* culture filtrates, 10 c.cm. injected into cavity for 2 hr. daily before water drainage	S: gram-pos. cocci in chains and pairs; pus cells + + +
April 17	Difficult to assess amount of discharge because of method of draining	Same	No change
April 18	Pt. felt no ill effects from penicillin	,,	Gram-pos. orgs. now mostly intracellular; gram-neg. bacilli numerous
April 19	Temp. slightly raised	,,	S: no gram-pos. orgs. left
April 23	Hardly any discharge. Long tube replaced by small tube, changed daily, draining directly into dressing	,,	..
April 24	V. little discharge	,,	..
April 25	..	Treatment finished	S: gram-neg. bacilli only

work, and in brain surgery, it may prove of particular value.

It has been thought wise to filter penicillin solutions through a Seitz filter, since the drug is not bactericidal, and there is a possibility of the bulk powder harbouring organisms if the container is often opened.

SUMMARY

A number of cases of infected war wounds have been treated with the calcium or sodium salts of penicillin (Florey), and 15 of these are recorded.

Within 24 hours there was a uniform and almost complete drop in the numbers of gram-positive organisms, including clostridia, staphylococci, streptoccoci and corynebacteria.

Gram-negative organisms were not affected. Therapeutic results were excellent.

The solid drug was introduced into a cerebral abscess cavity without deleterious effect.

A few experiments with *Penicillium notatum* culture filtrates, made locally, gave satisfactory results.

THERAPEUTIC USES OF THORIUM-X

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THORIUM-X is a short-lived radio-active metal (atomic weight 224). Its salts can be isolated by a complicated chemical process from thorium minerals. It is the second of a series of disintegrating elements beginning with thorium, thorium-X, thoron. The half-life period of thorium-X is 3·65 days. Thorium-X emits an alpha ray and then decays to thorium emanation (or thoron), a gas of atomic weight 220. Thoron in turn emits an alpha ray and its further decay products emit alpha, beta and gamma radiation. The insidious danger from radio-active substances giving off gamma rays is only too well known. But 99% of the total energy emitted by thorium-X is made up of alpha radiation. This will produce its effects long before any damage from gamma radiation can result, so that danger from the use of thorium-X can hardly exist theoretically; practically, freedom from danger has been established by Lomholt in experiments carried out on himself as long ago as 1920 (see Lomholt 1923 and 1936).

Compared with radium, whose half disintegration period is 1700 years, thorium-X is vastly more rich as a source of alpha rays. Alpha rays have a very feeble penetration—they are absorbed by a layer of paper of postcard thickness.

The metal thorium-X is an isotope of radium and belongs to the alkaline earth series. As one might expect, therefore, it is reasonably easy to manipulate chemically. The salts, as well as the element, are radio-active and are available in soluble and insoluble forms. Their richness in alpha rays is dependent on the rapid disintegration, which, however, is in some ways a therapeutic inconvenience. The power, in electrostatic units, of a solution containing thorium-X must be accurately predetermined for a given hour. It will be weakening all the time, so that therapeutic application must be made without too much delay.

Expense has also been advanced as an objection. The cost of 1 c.cm. of a solution containing 1000 electrostatic units is about ten shillings. But with this quantity several patients can be treated. The cost is thus not much greater than that of dispensing ointments to them all, and is incomparably less than X-ray treatment for them all, if capital outlay is included.

Thorium-X can be conveniently applied to the skin, either suspended in varnish dissolved in amyl acetate, or in solution in n-propyl alcohol. In the former instance the amyl acetate dries off and leaves the thorium-X contained in the varnish accurately applied to the area which it is desired to treat. The thorium-X will be more or less closely in contact with the skin, according to its distribution in the varnish and the thickness of the application. Where an alcoholic solution is used the alcohol dries off, leaving the thorium-X in contact with the skin, into the superficial layers of which some of the metal is possibly carried. Experiment on normal skin tends to show that a stronger effect is obtained when an alcoholic solution is used.

When thorium-X is applied to a square centimetre of surface of the front of the forearm, at a strength of 1000–2000 electrostatic units, a sharply defined square of erythema will appear after a day or two. The area is slightly œdematous and is hypersensitive. The reaction lasts for about a month and is succeeded by a deep pigmentation. The pigmentation may persist for a year or more. The intensity of the erythema and pigmentation varies greatly in different parts of the body. There is much less reaction on the extensor surfaces than the flexor, on parts such as hands and face normally exposed to the air, and on the scalp. This is therapeutically fortunate. It is also fortunate that when application is made, not to normal skin but to a dermatological lesion, pigmentation is relatively mild and of short duration.

Thorium-X was first used at St. Bartholomew's Hospital by Dr. F. Jacobson, who had it sent by airmail from Berlin at his own expense. Later in 1938, Dr. A. C. Roxburgh persuaded Messrs. Derby and Co., specialists in rare metals, to prepare and standardise solutions at their laboratories. Messrs. Derby and Co. placed a weekly supply of thorium-X at the disposal of the hospital free of charge, and this they continued to do for four years, in spite of several interruptions due to enemy action. The clinical investigation was conducted on the first fifty cases by Dr. Jacobson. The work unfortunately was interrupted by the outbreak of war for several months. Subsequently, Dr. Jacobson being engaged on other duties, the clinical investigation devolved on the writer. Over 250 cases in all have been treated, some at St. Bartholomew's Hospital, some at St. John's Hospital. In a number of instances results were inconclusive: patients ceased to attend, interfered with controls, or proved unsuitable for report for a variety of medical and non-medical reasons. In the following cases the facts ascertained appeared to be definite.

ALOPECIA AREATA

The first case of alopecia areata treated was a man aged 25, suffering from a circular bald patch the size of a two shilling piece. Half of the patch was painted with varnish three times at weekly intervals. A fortnight later, the area painted was covered with new hair, which soon after was fully grown. The other semicircle only became covered with hair after an interval of 2 months.

A woman of 47 had an oval patch of alopecia on the fronto-parietal region, 4 in. long by 2 in. wide. There were no exclamation-mark hairs. A cross ½ in. wide was painted on the area at weekly intervals. At the end of 6 weeks, new pigmented hair was growing in the area corresponding to the cross. It was many weeks before the remaining triangular areas filled in.

A man aged 26 was suffering from severe alopecia of the scalp: there were only a few hairs here and there; eyebrows, moustache and beard hairs were completely absent. Two squares on the parietal regions were painted with thorium-X in varnish, and in addition the inner half of the right eyebrow and the outer half of the left eyebrow were treated. At first there appeared to be no effect, but after some months hair grew on that half of each eyebrow which had been treated, and hair began to grow on the scalp. On the scalp, however, it was not possible to make out any relation between the areas which had been treated and the regions in which hair was growing. The scalp became extensively covered in the course of the next few months, though sparsely. Growth of eyebrows continues to be limited to the halves treated with thorium-X.

A girl aged 11, with almost total alopecia, including alopecia of the eyebrows, was treated. One inch squares were painted on the parietal and occipital areas at weekly intervals for 8 months. Hair finally began to grow in the areas painted, and later all the scalp became irrgularly and rather sparsely covered. The eyebrows had also been painted. Considerable erythema occurred on these, but there was no growth of hair. Erythema does not develop easily on the scalp, and pigmentation is correspondingly less than on the trunk and limbs.

Success was achieved in several other cases of alopecia areata. In all, 35 cases were treated and observed at length. There was no result whatever in 4 cases of total alopecia, cases with large irregular patches with numerous exclamation-mark hairs, and little if any

improvement in alopecia of beard and moustache areas. (New hair growing under thorium-X tends to grow pigmented at once.)

The conclusion arrived at is that thorium-X has a well-marked influence in those cases of alopecia areata where there is already some tendency to spontaneous recovery. There may yet be no external evidence that spontaneous recovery has started; in fact, such recovery may be still distant, or might even never start without the stimulus of the alpha rays. In those cases where the immediate prognosis is obviously bad, it is advisable to avoid using thorium-X: the patient might ascribe the unfavourable course of the disease to the treatment, and it is possible that he would be right.

CAVERNOUS NÆVI

A number of small cavernous nævi were painted with thorium-X in varnish weekly for several months. Some showed a superficial inflammation with a tendency to ulceration; when healed, a white scar remained, so that the bluish nævus was a little less obvious than before. But the main nævus was unaltered. It was concluded that the surface application of thorium-X has no value in the treatment of cavernous nævi. These nævi can be successfully dealt with by excision or by the application of radium (Finzi 1935 and 1936). In many spontaneous thrombosis and disappearance occurs.

NÆVUS FLAMMEUS

Thorium-X in varnish or alcohol will be successful in the treatment of selected cases of nævus flammeus, but it is necessary to make a clinical distinction in the main group.

Type I.—There is a bright red area, in most cases sharply defined. It is of variable size, but usually is rather extensive, covering a large part of one side of the face. One side of the nose is often affected and there is some tendency for the redness to extend across the middle line at some point. Eight such cases were treated. A square was painted with thorium-X in varnish or alcohol for many months with little noticeable effect. Treatment was ultimately abandoned in all cases.

Type II.—The nævus is more diffusely distributed on the face, some areas being perhaps quite separate from others. The nævus is bluish-red and the margins are not well defined. Three cases of this type were seen and treated. All three were in infants and all were much improved, if not completely cured.

Intermediate types.—Gradations exist between type I and type II. Success will be obtained in proportion as type II is approached.

A girl aged 12, suffering from a bluish-red nævus affecting the chin and lower lip and with moderately defined margins, has been under treatment weekly for 8 months. The nævus is still obvious, but has become a great deal paler. The serious cosmetic misfortune of such a lesion makes any treatment that helps at all of inestimable value.

In type II there is considerable tendency to spontaneous disappearance; in the intermediate type, less. In both, alpha radiation may make just the difference required to initiate absorption. Since no other satisfactory treatment is known, it is particularly fortunate that thorium-X therapy is available for the treatment of at least the milder types of these nævi. The results confirm the observations of Prosser Thomas (1939), who has treated a large number of cases of nævus flammeus at St. Thomas's Hospital.

TINEA OF THE NAILS

In 1939 a patient, in whom three finger nails on each hand were affected with ringworm, presented herself at St. Bartholomew's Hospital. Fungus was demonstrated microscopically. A nail was treated by Dr. Jacobson with thorium-X, 1000 units in alcohol weekly for 4 months. At the end of this time the nail seemed to be becoming normal. It finally became absolutely normal and has remained so since. In 1940, the patient returned to the hospital and wished to have the other nails cured. Fungus was found in one nail and treatment with thorium-X in varnish was instituted. After fourteen applications the nails were unaltered. A change was made to thorium-X in alcohol, but again without effect. Treatment was abandoned after 5 months of weekly applications.

In a second patient treated by Dr. Jacobson, five out of ten fingers were affected. Complete success was obtained in all.

These two examples show that thorium-X in alcohol will cure at any rate some cases of ringworm of the nails. The following instances show that only some respond to treatment, and these are not very many.

A patient has attended St. John's Hospital for 15 years. Fungus was found in the finger nails originally by Dr. Knowsley Sibley and its presence was confirmed in later years by Dr. I. Muende and Dr. Bernard Green. The patient was treated first with fourteen weekly applications of 2000 units of thorium-X in varnish. This had no effect. It was followed by twenty applications of thorium-X in alcohol, the finger nails being covered with strapping for two or three days after each treatment with the alcoholic solution. There has been no result whatever from all this treatment, and after 16 years' regular attendance at St. John's Hospital, the patient has finally made up her mind to seek specialist advice elsewhere.

Two more patients have been treated for tinea of the nails at St. John's Hospital, both with thorium-X 2000 units in 1 c.cm. of alcohol. In one patient there was no effect, but in the other, a man, who has been under treatment for 4 months, the nails appear to be growing up normal at the time of writing.

At present, the conclusion to be drawn is that treatment of tinea of the nails with thorium-X should be tried, but that success is uncertain. It seems reasonable to hope that only a modification in technique is required to produce completely satisfactory results.

LICHENIFICATION

The treatment of patches of lichenified skin by means of thorium-X in varnish immediately gave encouraging results and over fifty patients were treated. As in alopecia areata, a treated area can readily be compared with another area either not treated or treated by other means on the patient himself; in most instances in one and the same patch of lichenification.

A woman had a patch of lichenified skin on the inside of her thigh. It was about 4 in. × 3 in., the edges rather sharply defined, the surface uniformly thickened and greyish in colour. Treatment was instituted by painting on thorium-X 1000 units in varnish as a band an inch wide across the patch. Improvement occurred after two or three weekly applications, as regards both symptoms and physical signs. After further applications the band became a deep plum colour. On palpation, it was obvious that the darkened area was depressed below the untreated lichenified areas, so that a shallow valley ran transversely across the patch. Paroxysms of pruritus continued in the untreated areas but had almost ceased in the thinning area. To some extent, itching had been relieved on the whole patch. Treatment with thorium-X on the transverse band was suspended and transferred to one of the untreated semicircles left; this now followed the same course that the transverse band had done. The remaining semicircle was given a few doses of X rays, to which it readily responded.

Observations such as this were repeated with variations in numerous cases of lichenification of skin. The lichenification was in some instances localised and heavy—typical lichen simplex of Vidal such as that described. In others it was mild, more diffuse, and a consequence of a recent seborrhœic, occupational or other dermatitis. In the latter type, progress to normality was relatively more rapid. In some instances, relief of itching was almost inmediate, as sometimes follows X-ray treatment. Generally speaking, X rays in doses of $\frac{1}{4}$–$\frac{1}{2}$ Sabouraud Noiré pastille work a good deal more rapidly than alpha rays, but not always.

A woman of 60 had a patch of lichenification in the occipital area, just inside the hair margin. The area was 3 in. across by $1\frac{1}{2}$ in. vertically. It was as heavy a lichenification as one can meet with. Beneath the psoriasiform, scaly surface was a deep thickening, producing a cartilage-like plaque, scarcely movable on the underlying ligamentous tissues. This was treated for a year by X-ray treatments varying from $\frac{1}{3}$ to $\frac{3}{4}$ pastille, the whole totalling up to over 6 pastilles. There had been improvement and at times complete relief of itching. But pruritus continued to recur; cumulative X-ray dosage was becoming dangerous; it was decided to try the effects of thorium-X 2000 units in varnish. Relief from symptoms

was immediate and has been maintained. After five weekly applications, there was a greater change in the physical signs than had ever been seen in any period of X-ray treatment. With further fortnightly applications, the skin has become nearly if not quite normal.

Lichenification in the suboccipital region in women of middle-age is a common and obstinate condition. X rays almost always relieve symptoms for a time, but relapses or incomplete cures are frequent in spite of repeated applications of X rays. Thorium-X is therefore a valuable addition to the therapeutic agents at one's disposal.

In most cases of chronic dermatitis, the chief physical abnormality of the skin which develops is lichenification. Thorium-X may thus be expected to be of use in at least some stage of most cases of chronic dermatitis.

LICHEN PLANUS

The success obtained in lichen simplex suggested the trial of thorium-X in lichen planus. A patient was selected in whom the disease was neither acute nor chronic but of intermediate type, and in whom there were patches on each wrist of similar appearance, and therefore suitable for a controlled test. The result was disappointing. Treatment in a few other cases also failed or produced improvement of little practical value.

PSORIASIS

The successful treatment of psoriasis has been recorded by almost all writers on thorium-X, so that it seemed unnecessary to put it to the test very extensively. But some ten cases were treated and some facts were noted. Most important of all, it was found that applied over the white scales of the patches, thorium-X was without effect of any kind. This might be expected, for alpha rays have so feeble a power of penetration that they are almost completely absorbed in the scales themselves.

The following ointment was prescribed.

℞ Hydrarg. ammon.	..	..	gr. 10
Acid salicyl.	..	..	gr. 10
Liq. picis carbonis	..	..	min. 60
Paraffinum molle	..	ad	1 oz.

This was to be rubbed well in to all patches every night for a week and washed off in the morning. At the end of the week, scales were absent or nearly so. Thorium-X in varnish was then applied to, say, one arm, and selected patches were treated with thorium-X in alcohol. Patches elsewhere continued to be treated by ointment and bathing. Thorium-X was applied once a week for a few weeks. It soon became obvious that places treated with thorium-X were doing better than those to which ointment only was being applied. Where ointment only was used, scale formation was kept down, but scales re-formed as soon as the inunction was given up. Where thorium-X was used, erythema disappeared, the patches became whiter than the surrounding skin, and scales ceased to form at all. Allowances had to be made for the variable course of psoriasis in different patients and at different times in the same patient. Taken as a whole, the claim made by Nagelschmidt (1932), Scholtz (1937) and Prosser-Thomas (1939), that thorium-X has considerable value in the treatment of psoriasis, was confirmed. The alcoholic solution gave better results than the varnish.

SYCOSIS BARBÆ

Sycosis in all its forms is notoriously resistant to treatment, and is a severe test for any therapy. It is usually symmetrically distributed on the beard area; the conditions are therefore ideal for comparing the side treated with the other side not treated or treated by other means. The patients lend themselves well to experiment, being young and interested as well as disappointed with previous efforts to get cured. Fourteen patients chosen as suitable for trial attended regularly till a decision was reached. Thorium-X in alcohol or in varnish was applied to one side of the chin or jaw or moustache area once a week or once a fortnight for several months. In every case there was improvement, which could be ascribed without hesitation to the thorium-X. Where there had been erythema this was reduced and where there had been follicular pustules these diminished in number and in some instances disappeared. But in scarcely any case could there be confidence that the condition was cured. At best there remained some degree of erythema or an appearance of instability of the skin suggesting that a relapse was not unlikely at some future date.

When one side treated with thorium-X was compared with the other side treated with X rays, the latter won easily: the side treated with X rays tended towards normality faster than that treated with thorium-X. But relapses after X-ray therapy when all physical signs have disappeared are well known, and X-ray treatment cannot be continued for long without danger, whereas thorium-X appears to be harmless.

CONCLUSION

Thorium-X is a valuable agent in the treatment of alopecia areata and psoriasis.

It is likely to be useful at some stage in all forms of subacute and chronic dermatitis, particularly where there is lichenification. It sometimes proves superior to X rays in such cases.

Encouraging results were obtained in the treatment of ringworm of the nails and sycosis.

Thorium-X appeared to be without effect on any but purely capillary nævi. In these good results were obtained, provided the nævus was not too dense. There being no other good treatment available in this serious disfigurement, thorium-X may justly be said to be invaluable in selected cases of capillary nævus.

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ACTION OF NICOTINIC ACID ON CARBOHYDRATE METABOLISM

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THE influence of a vitamin-free diet on carbohydrate metabolism was already suspected by Funk and von Schönborn in 1914. In 1937 Martin found a high degree of insulin insensitivity in depancreatised dogs deprived of the vitamin-B complex. Despite previously adequate amounts of insulin, their blood-sugar became elevated after 5–7 weeks, and intense glycosuria developed. Increasing doses of insulin corrected this state for a time, but later even eight times the dose proved insufficient to control the glycosuria. In two of these experiments the disturbances could be overcome by injections of vitamin B_1 and B_2. Vitamin B_1 alone was ineffective, but vitamin B_1 and lactoflavin were effective; lactoflavin alone was not tried. Martin refers to the observations of Schroeder, that in diabetics generally the vitamin requirement is greater than normal. He also cites the observations of Collazo and Pi-Suner Bayo, which indicate that in normal animals deficiency of vitamin B leads to disturbances of carbohydrate metabolism and diminished insulin activity. Martin concludes that the action of insulin apparently depends on the presence of factors comprising the vitamin-B complex. At present the evidence of the therapeutic value of the vitamin-B complex, or any of its constituents, in diabetes is conflicting, though it suggests that the diabetic organism may require more of these vitamins than is obtained in a mixed diet. These and similar observations form the basis of the present investigations, which were begun because of reactions after the administration of nicotinic acid.

In treating a large series of cases of arterial disease of the heart and lower limbs with intravenous injections of 0·05% nicotinic acid in saline no reactions were seen at first, when a solution containing 5% or 10% of dextrose was used, but when the dextrose was omitted a violent and long-lasting rigor occurred during or after the